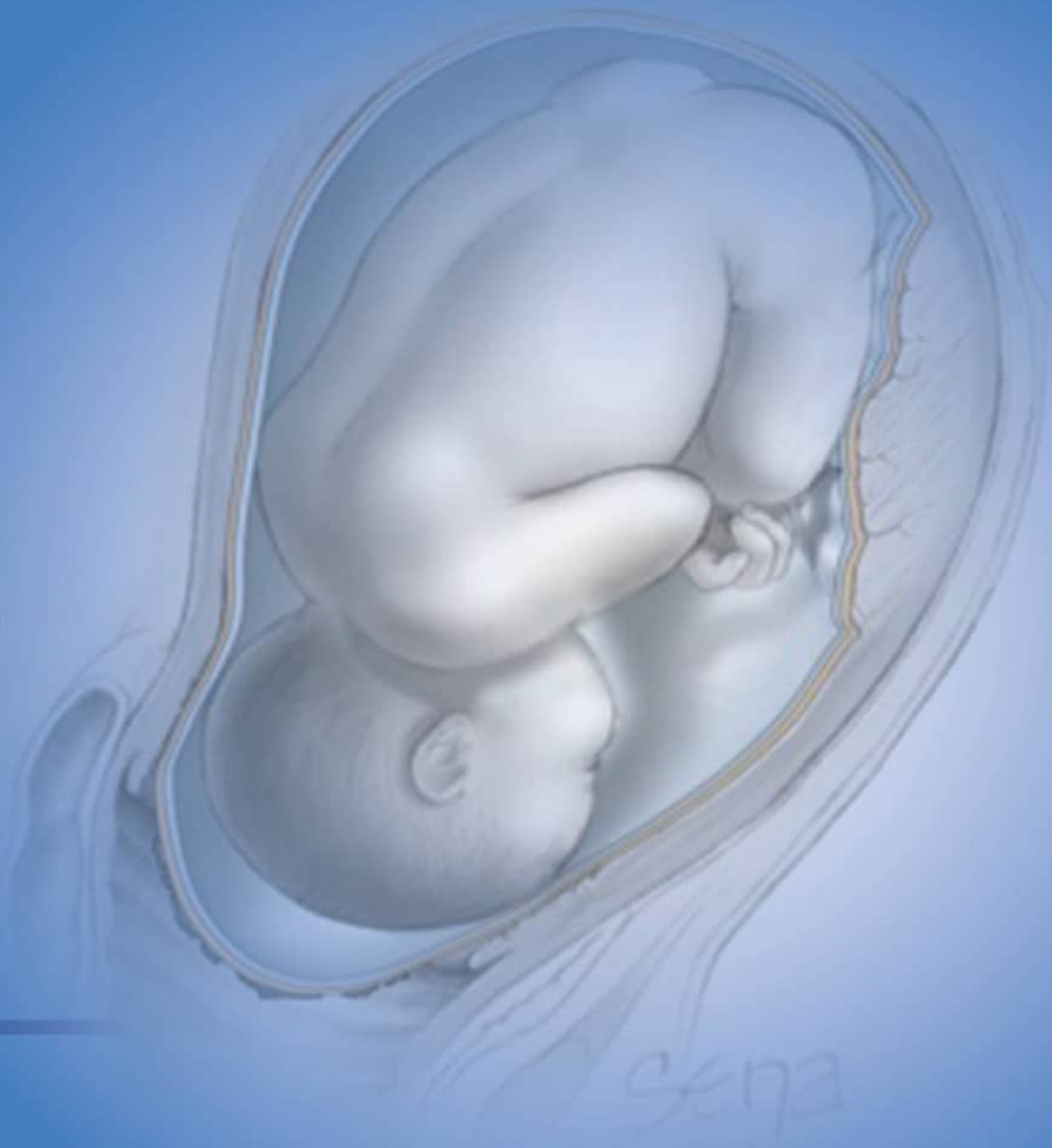
26TH EDITION

Williams OBSTETRICS



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Williams OBSTETRICS

26TH EDITION

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Editor of *Williams Obstetrics*
18th through 26th Editions

In the early 1970s, as I was finishing my residency at Charity Hospital of New Orleans, the 14th edition of *Williams Obstetrics* was published. The residents in our program were totally enamored with the textbook because it was a clinical manual derived from the editors' personal experiences and from contemporary, evidence-based literature.

During my last year, my chairman, Dr. Abe Mickal, invited me to attend a national meeting where I first met four obstetricians who would have an immeasurable impact on my life—Drs. Jack Pritchard, Paul MacDonald, Norman Gant, and Peggy Whalley. Following that, I was invited to Dallas to spend time at the University of Texas Southwestern and Parkland Hospital. As I followed Dr. Pritchard through Labor & Delivery and his clinical research laboratory, I became hooked on "Parkland Obstetrics" and later that year began a fellowship that was the nascent subspecialty of Maternal–Fetal Medicine. It also began a lifelong friendship with Jack Pritchard that I will always treasure.

Beginning with the 15th edition of *Williams Obstetrics*, the author-editors were Drs. Pritchard, MacDonald, and Gant. After publication of the 17th edition, these mentors asked me to assume the senior editor role. I was immediately struck by the awesome responsibility of shepherding the book that many people called "the bible of obstetrics."

Over the years, and now as we publish this 26th edition, I reflect on the evolution of obstetrics, and hence the complexity of sustaining a textbook designed to cover the breadth of obstetrics. As essential fields such as sonography, genetics, and fetal medicine were developed, we enlisted the help of extremely talented leaders in their respective fields to ensure that the book adequately presented these innovations. As for my role in this and other editions, I can only promise the readers that the quality of the book has been foremost in my mind and led me to spend literally tens of thousands of hours to help prepare the past nine editions. To this end, the editors have always strived to put the best product forward because of the tremendous responsibility that we shoulder regarding the care of women and their unborn children. The textbook has been one of the great passions in my life, and I will miss the challenge.

DEDICATION

KENNETH LEVENO, MD
1941–2020

Dr. Kenneth Leveno was a vocal and stalwart defender of evidence-based obstetrics. Sadly, he passed away in May 2020. Ken joined the Department of Obstetrics & Gynecology at the University of Texas Southwestern after completing a Maternal–Fetal Medicine fellowship in 1978. In 1984, he was appointed Chief of Obstetrics at Parkland Memorial Hospital—a role in which he served for the next 20 years. During that time and afterwards, he worked tirelessly to achieve a level of excellence in obstetrical care for indigent women of Dallas County. His inspiring leadership and innovations raised the quality of care at the community obstetrics clinics, the high-risk prenatal clinics at Parkland, and the inpatient units, which include the Obstetrical Triage Unit, Labor & Delivery, postpartum wards, and the High-Risk Pregnancy Unit. Early on, he also designed a computerized database to measure quality indicators and provide an underpinning for clinical research. Indeed, his contributions to these programs were reverently referred to by us as *Parkland Obstetrics.*

Ken Leveno's leadership extended well beyond the hospital that he loved. He was a leader in American obstetrics by his defining of clinical research. Through his hundreds of peer-reviewed publications, his clinical opinions, and his willingness to engage in national debates, he helped shape obstetrical practices worldwide. In 1993, Ken began serving as an editor for *Williams Obstetrics*—a task that he regarded as a privilege and a responsibility. He co-authored the 19th through the current 26th editions. Last and importantly, he mentored the careers of many Maternal–Fetal Medicine fellows and young faculty who have gone on to achieve national reputations in the care of women. Ken will be greatly missed.

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PREFACE

Over its 26 editions, *Williams Obstetrics* has aimed to serve practicing obstetricians and midwives in the bedside care of their patients. With its detailed explanations of disease pathophysiology and treatment fundamentals, it provides a bedrock text for residents who are training in Obstetrics or in Family Medicine specialties. Fellows in Maternal–Fetal Medicine will benefit from its additional discussions of complicated pathology and management. Last, *Williams Obstetrics* can aid specialists who act as consultants for gravidas with non-pregnancy-related disorders. Specifically, each chapter in Section 12 focuses on a specific organ system, the normal physiological changes and frequent disorders of that system in pregnancy, and suitable treatment options.

For this 26th edition, we continue to present the detailed staples of basic obstetrics such as maternal anatomy and physiology, preconceptional and prenatal care, labor, delivery, and the puerperium. These accompany detailed discussions of obstetrical complications exemplified by preterm labor, hemorrhage, hypertension, and many more. To emphasize the "M" in Maternal–Fetal Medicine, we continue to instruct on the many medical and surgical disorders that can complicate pregnancy. And, our second patient—the fetus—has accrued especial attention with an entire section devoted to diagnosis and treatment of fetal disorders. For all of these, we once again emphasize the science-based practice of clinical obstetrics. Expert clinical pearls add depth to these discussions and are written for busy practitioners—those "in the trenches." To integrate all our content, the reader of one chapter may be referred to a different chapter that contains complementary content. This offers a more global understanding of a given topic.

To accomplish our teaching goals, the text has been updated with more than 3000 new literature citations through 2021. Many of the nearly 900 figures are new, and these graphs, sonograms, magnetic resonance images, photographs, photomicrographs, and data graphs are all in vivid color. Much of the original artwork was rendered by our own medical illustrators.

As before, we continue to incorporate contemporaneous guidelines from professional and academic organizations such as the American College of Obstetricians and Gynecologists, the Society for Maternal–Fetal Medicine, the Centers for Disease Control and Prevention, the National Institutes of Health, and other authoritative sources. Many of these data are distilled into nearly 100 tables, in which information has been arranged in an easy read-and-use format. In addition, several diagnostic and management algorithms are available to quickly guide practitioners. Although we strive to cite numerous sources and provide multiple evidence-based options for such management schemes, we also include our own clinical experiences drawn from the large obstetrical service at Parkland Hospital. We are convinced that these are disciplined examples of evidence-based obstetrics but quickly acknowledge that they do not constitute the sole method of management.

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ACKNOWLEDGMENTS

In the creation and production of this textbook, we were fortunate to have the assistance and support of countless talented professionals both within and outside the Department of Obstetrics and Gynecology. To begin, we acknowledge that an undertaking of this magnitude would not be possible without the unwavering support provided by our recent Chairman Dr. Steven Bloom and Vice-Chairman Dr. Barry Schwarz, whose financial and academic endorsement has been essential. Dr. Bloom has served as an editor for the 22nd through 25th editions but now has assumed the important role of Associate Dean of Clinical Sciences at the University of Texas Southwestern Medical Center.

In constructing such an expansive academic compilation, the expertise of many colleagues was needed to add vital, evidence-based content. It was indeed fortuitous for us to have access to a trove of collaborators from our medical center. From our own Department of Obstetrics and Gynecology, Dr. Shivani Patel was essential to the production of our book and is an invaluable addition to our team. We benefitted from her obstetrical expertise, writing talent, and ability to translate difficult concepts into teaching pearls. Faculty with specific expertise included Dr. Claudia Werner, who lent valuable insight into the management of cervical dysplasia. Our nationally known pelvic anatomist, Dr. Marlene Corton, prepared graphic masterpieces for the anatomy chapter with artist Lew Calver. We also are grateful to the numerous faculty and residents who added seminal clinical photographs to our text.

In addition to these contributors, we relied heavily on our colleagues in the Division of Maternal–Fetal Medicine. These professionals, in addition to providing expert consultation, graciously assisted us by covering clinical duties when writing and editing were especially time consuming. These include Drs. Scott Roberts, Oscar Andujo, Vanessa Rogers, Charles Brown, Julie Lo, Robyn Horsager, Patricia Santiago-Muñoz, Mark Peters, Elaine Duryea, Jamie Morgan, Morris Bryant, Shena Dillon, Anne Ambia, Robert Martin, Robert Stewart, Stephan Shivvers, Ashley Zink, Sarah Happe, and Christina Herrera.

We also emphasize that production of *Williams Obstetrics* would not be feasible without the help of our Maternal–Fetal Medicine fellows and our residents in Obstetrics and Gynecology. Their insatiable curiosity serves to energize us to find new and effective ways to convey age-old truths, new data, and cutting-edge concepts. Their logical and critical questions lead us to weaknesses in the text, and thereby always help us to improve our work. In addition, we sincerely thank them for their vigilance in capturing photographs of spectacular examples of both obstetrical pathology and normal findings.

This edition is heavily populated with seminal examples of sonographic findings. We are grateful for the efforts of Mary Gibbs, RDMS; Rafael Levy, RDMS; Michael Davidson, RDMS; and the many talented sonographers at Parkland Hospital.

Thanks to generous funding from the McGraw-Hill Companies, this 26th edition now contains more than 200 color illustrations. Most of these were crafted by several skilled medical illustrators who include Ms. Marie Sena, Ms. Erin Frederickson, and Ms. SangEun Cha. All of these talented artists trained here at UT Southwestern under the instruction of Mr. Lewis Calver. Additional artistic support came from Mr. Joseph Varghese, Ms. Shreya Tiwari, Dr. Sudhi Singh, and Mr. Manoj Kumar Choudhry. Their work at Thomson Digital provided the full-color graphs and line art used to enhance this edition. Their team tirelessly coordinated efforts between author and artist and graciously accommodated our numerous changes and tweaks.

Production of the 5000-page manuscript would not have been possible without a dedicated team. Once again, we are deeply indebted to Ms. Dawn Wilson and Ms. Melinda Epstein for their untiring efforts with manuscript production. Ms. Regina Williams also provided excellent, cheerful, conscientious manuscript assistance. Mr. Charles Richards offered knowledgeable and responsive information technology support. For these and many more that go unnamed, we could not have done our job without their expertise.

It again has been a privilege to work with the dedicated professionals from McGraw-Hill Education. We have had the pleasure to work with Executive Editor Mr. Jason Malley in production of our textbook and are grateful for his support of *Williams Obstetrics*. Senior Project Development Editor Ms. Christie Naglieri has again brought her considerable knowledge to this edition of our book. Her dedication to creating the best textbook supported our efforts, and we appreciate her productive, gracious style. We thank Ms. Leah Carton, who provided professional, timely, and ever-sunny aid. Mr. Richard Ruzycka served as production supervisor for this edition of the textbook, and our book benefits from his years of experience.

Our text took its final shape under the watchful care of our compositors at Aptara, Inc. We thank Ms. Indu Jawwad for her talents in graciously and masterfully coordinating and overseeing composition. Her dedicated attention to detail and organization were vital to completion of our project. She has created many editions with us, and we consider her an essential team member. At Aptara, Mr. Mahender Singh carried out the crucial task of quality control. He also assisted, along with Mr. Rajesh Chander, Mr. Kamlesh Bhatt, and Mr. Anil Varghese, in creating beautiful chapter layouts to highlight our content aesthetically and informatively. This edition's chapters were also posted and available online for use prior to print publication. We thank Mr. Braj Bhushan and Mr. Ashish Kumar Sharma for preparing this content so brilliantly. Special thanks go to Mr. Greg Feldman. As copyeditor, Greg added

precision and clarity to our efforts. His endurance and pleasant professionalism through many challenging chapters has made our text better.

Last, we acknowledge our significant debt to the women who have entrusted themselves and their unborn children to us for obstetrical care. The clinical expertise and many images provided in this text would not have been possible without their collaborative spirit to help us advance obstetrical knowledge. We also offer enthusiastic and heartfelt appreciation to our families and friends. Without their patience, generosity, love, and encouragement, this task would have been impossible.

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Williams OBSTETRICS

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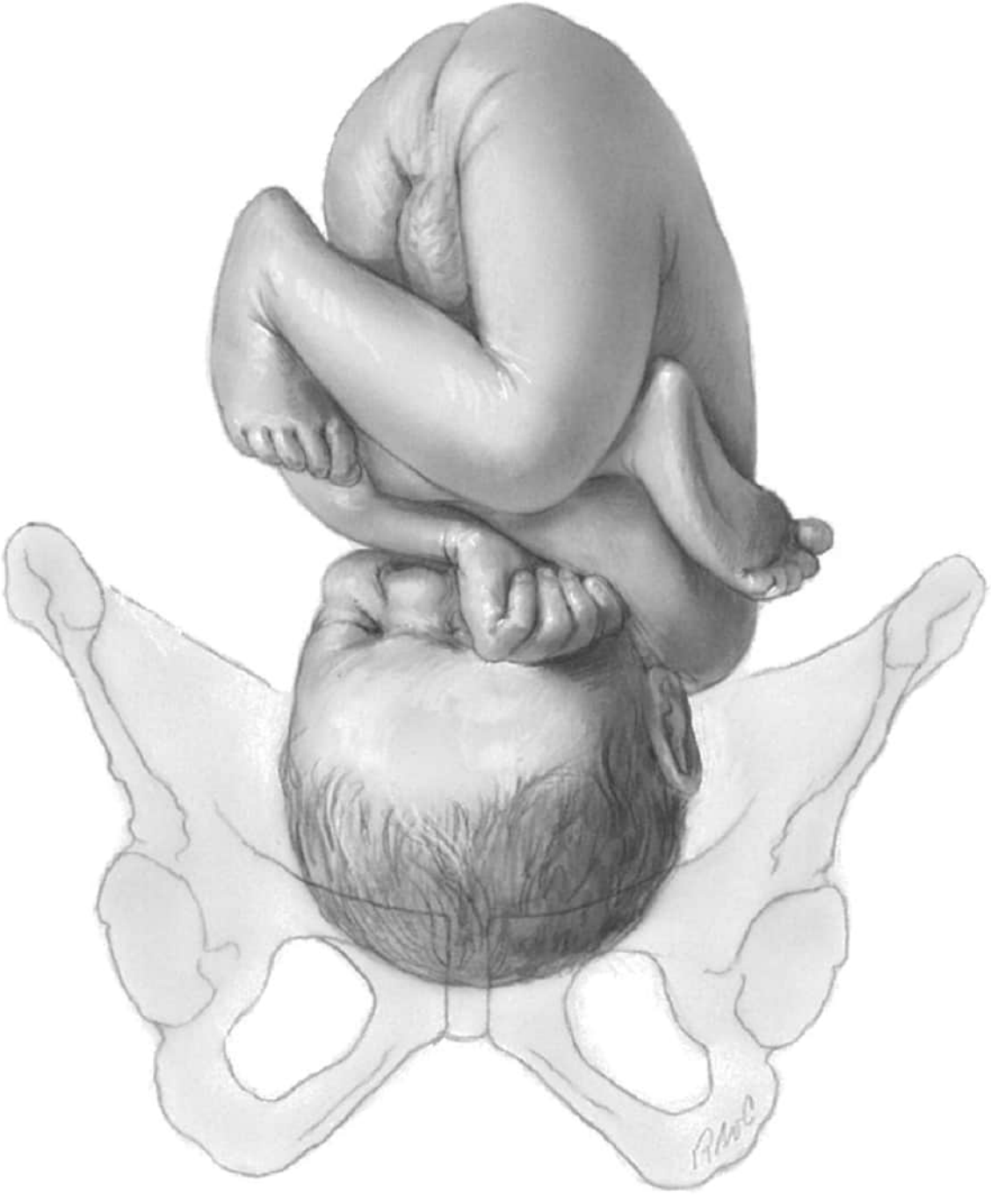
SECTION 1

OVERVIEW



CHAPTER 1

Overview of Obstetrics

The science and clinical practice of obstetrics focuses on human reproduction. The specialty promotes the health and well-being of the pregnant woman and her fetus through quality perinatal care. Such care entails recognition and treatment of complications, supervision of labor and delivery, initial care of the newborn, and management of the puerperium. Postpartum care promotes health and provides family planning options.

Evidence-based medicine dominates the modern practice of obstetrics. As described by Williams in this textbook's first edition, we too strive to present the scientific evidence for current obstetrical care. Still, high-quality data do not support most recommendations (Brock, 2021). Thus, much of our practice stems from expert-based opinions and historical experiences (Society for Maternal-Fetal Medicine, 2021). To help bridge knowledge gaps, we also rely on authoritative sources such as the American College of Obstetricians and Gynecologists and the Society for Maternal-Fetal Medicine, as well as agencies such as the Centers for Disease Control and Prevention (CDC) and National Institutes of Health (NIH).

VITAL STATISTICS

The importance of obstetrics is demonstrated by the use of maternal and neonatal outcomes as an index of health and life quality among nations. Intuitively, indices showing poor obstetrical and perinatal outcomes could be assumed to reflect medical care deficiencies for the entire population.

The National Vital Statistics System of the United States collects statistics on births and deaths, including fetal deaths. Legal authority for collection resides individually with the 50 states; two regions—the District of Columbia and New York City; and five territories—American Samoa, Guam, the Northern Mariana Islands, Puerto Rico, and the Virgin Islands. The standard birth certificate includes information on medical and lifestyle risks, labor and delivery factors, and newborn characteristics. Importantly, the current death certificate contains a pregnancy checkbox (Hoyert, 2020).

Definitions

Standard definitions are encouraged by the World Health Organization as well as the American Academy of Pediatrics and the American College of Obstetricians and Gynecologists (2019a). Uniformity allows data comparison between states or regions and between countries. Still, not all definitions are uniformly applied. For example, uniformity is incomplete among states regarding birthweight and gestational age criteria for reporting fetal deaths (American College of Obstetricians and Gynecologists, 2020a). Not all states follow this recommendation. Specifically, 28 states stipulate that losses beginning at 20 weeks' gestation should be recorded as fetal deaths; eight states report all products of conception as fetal deaths; and still others use a minimum birthweight of 350 g, 400 g, or 500 g to define fetal death. To further the confusion, the National Vital Statistics Reports tabulates fetal deaths from pregnancies that are 20 weeks' gestation or older (Centers for Disease Control and Prevention, 2020a). This is problematic because the 50th percentile for fetal weight at 20 weeks approximates 325 to 350 g—considerably less than the 500-g definition. In fact, a birthweight of 500 g corresponds closely with the 50th percentile for 22 weeks' gestation.

Definitions recommended by the National Center for Health Statistics and the CDC are as follows:

Perinatal period. The interval between the birth of a neonate born after 20 weeks' gestation and the 28 completed days after that birth. When perinatal rates are based on birthweight, rather than gestational age, recommendations define the perinatal period as commencing at the birth of a 500-g neonate.

Birth. The complete expulsion or extraction from the mother of a fetus after 20 weeks' gestation. As described above, in the absence of accurate dating criteria, fetuses weighing <500 g are usually not considered births but rather are termed *abortuses* for purposes of vital statistics.

Birthweight. Neonatal weight determined immediately after delivery or as soon thereafter as feasible. It should be expressed to the nearest gram.

Birth rate. The number of live births per 1000 population.

Fertility rate. The number of live births per 1000 females aged 15 through 44 years.

Live birth. The term used to record a birth whenever the newborn at or sometime after birth breathes spontaneously or shows any other sign of life such as a heartbeat or definite spontaneous movement of voluntary muscles. Heartbeats are distinguished from transient cardiac contractions, and respirations are differentiated from fleeting respiratory efforts or gasps.

Stillbirth or fetal death. The absence of signs of life at birth.

Early neonatal death. Death of a liveborn neonate during the first 7 days after birth.

Late neonatal death. Death after 7 days but before 29 days.

Stillbirth rate or fetal death rate. The number of stillborn neonates per 1000 neonates born, including live births and stillbirths.

Neonatal mortality rate. The number of neonatal deaths per 1000 live births.

Perinatal mortality rate. The number of stillbirths plus neonatal deaths per 1000 total births.

Infant death. All deaths of liveborn infants from birth through 12 months of age.

Infant mortality rate. The number of infant deaths per 1000 live births.

Low birthweight. A newborn whose weight is <2500 g.

Very low birthweight. A newborn whose weight is <1500 g.

Extremely low birthweight. A newborn whose weight is <1000 g.

Term neonate. A neonate born any time after 37 completed weeks' gestation and up until 42 completed weeks' gestation (260 to 294 days). The American College of Obstetricians and Gynecologists and Society for Maternal-Fetal Medicine encourage specific gestational age designations (2019a). *Early term* refers to neonates born at 37 completed weeks up to $38^{6/7}$ weeks. *Full term* denotes those born at 39 completed weeks up to $40^{6/7}$ weeks. Last, *late term* describes neonates born at 41 completed weeks up to $41^{6/7}$ weeks.

Preterm neonate. A neonate born before 37 completed weeks (the 259^{th} day). A neonate born before 34 completed weeks is early preterm, whereas a neonate born between 34 and 36 completed weeks is late preterm.

Postterm neonate. A neonate born any time after completion of the 42nd week, beginning with day 295.

Abortus. A fetus or embryo removed or expelled from the uterus in the first half of gestation—20 weeks or less, or in the absence of accurate dating criteria, born weighing <500 g.

Induced termination of pregnancy. The purposeful interruption of an intrauterine pregnancy that has the intention other than to produce a liveborn neonate and that does not result in a live birth. This definition excludes retention of products of conception following fetal death.

Direct maternal death. The death of the mother that results from obstetrical complications of pregnancy, labor, or the puerperium and from interventions, omissions, incorrect treatment, or a chain of events resulting from any of these factors. An example is maternal death from exsanguination after uterine rupture.

Indirect maternal death. A maternal death that is not directly due to an obstetrical cause. Death results from previously existing disease or a disease developing during pregnancy, labor, or the puerperium that was aggravated by maternal physiological adaptation to pregnancy. An example is maternal death from complications of mitral valve stenosis.

Late maternal death. Death of a woman from direct or indirect obstetrical causes more than 42 days but less than 1 year after the pregnancy's end.

Nonmaternal death. Death of the mother that results from accidental or incidental causes not related to pregnancy. An example is death from an automobile accident or concurrent malignancy.

Pregnancy-associated death. The death of a woman, from any cause, while pregnant or within 1 calendar year of termination of pregnancy, regardless of the duration and the site of pregnancy.

Pregnancy-related death. A pregnancy-associated death that results from: (1) complications of pregnancy itself, (2) the chain of events initiated by pregnancy that led to death, or (3) aggravation of an unrelated condition by the physiological or pharmacological effects of pregnancy and that subsequently caused death.

Maternal mortality ratio. The number of maternal deaths that result from the reproductive process per 100,000 live births. Used more commonly, but less accurately, are the terms *maternal mortality rate* or *maternal death rate*. The term *ratio* is more accurate because it includes in the numerator the number of deaths regardless of pregnancy outcome—for example, live births, stillbirths, and ectopic pregnancies—whereas the denominator includes the number of live births.

PREGNANCY RATES IN THE UNITED STATES

According to the CDC, the fertility rate of women aged 15 to 44 years in the United States in 2019 was 58 live births per 1000 women. This rate began slowly trending downward in 1990 and has now dropped below that for replacement births to sustain the population level. This indicates a population decline. The birth rate decreased for all major ethnic and racial groups, for adolescents and unmarried women, and for

TABLE 1-1. Total Pregnancies and Outcomes in the United States in 2019

Outcome	Number or Percent
Total births	3,747,540
Cesarean deliveries	31.7%
Primary cesarean delivery	21.6%
Vaginal birth after cesarean	13.8%
Preterm births (<37 weeks)	10.0%
Low birthweight (<2500 g)	8.0%
Very low birthweight (<1500 g)	1.4%
Induced abortions	862,320

Data from Guttmacher 2019b; Martin, 2021.

those aged 20 to 24 years. For women older than 30 years, the birth rate rose slightly. Almost half of newborns in 2019 in the United States were minorities: Hispanic—25 percent; African-American—15 percent; and Asian—4 percent (Martin, 2021).

The total number of pregnancies and their outcomes in 2019 are shown in Table 1-1. According to the Guttmacher Institute (2019b), 45 percent of births in the United States are unintended at the time of conception. But, the overall proportion of unintended births has declined since 2008. Unmarried women, black women, and women with less education or income are more likely to have an unplanned pregnancy.

OBSTETRICAL CARE MEASURES

Several indices are used to assess obstetrical and perinatal outcomes as measures of medical care quality. As noted, the *perinatal mortality rate* includes the number of stillbirths and neonatal deaths per 1000 total births. In 2016, this rate was 6 deaths per 1000 births (Fig. 1-1). This rate has been unchanged for several years (Gregory, 2018). Rates of fetal death at 28 weeks' gestational age or more have declined since 1990, whereas rates for those between 20 and 27 weeks are static.

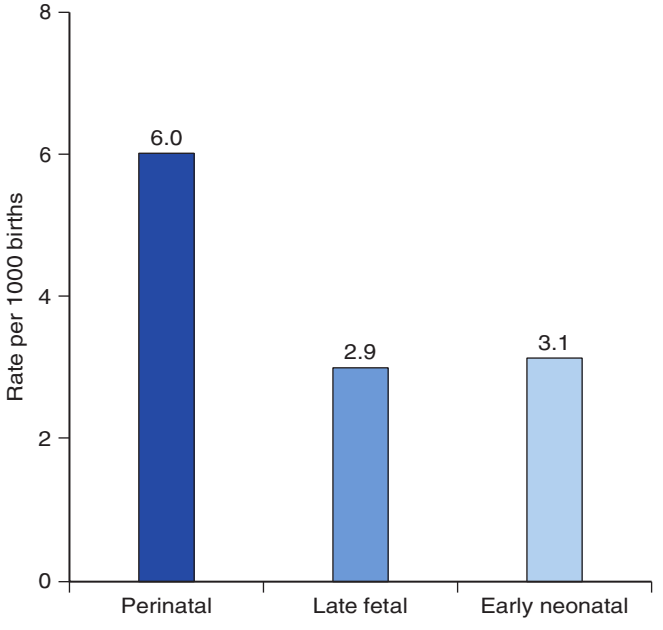


FIGURE 1-1 Perinatal, late-fetal, and early-neonatal mortality rates per 1000 births in the United States in 2016. (Data from Gregory, 2018).

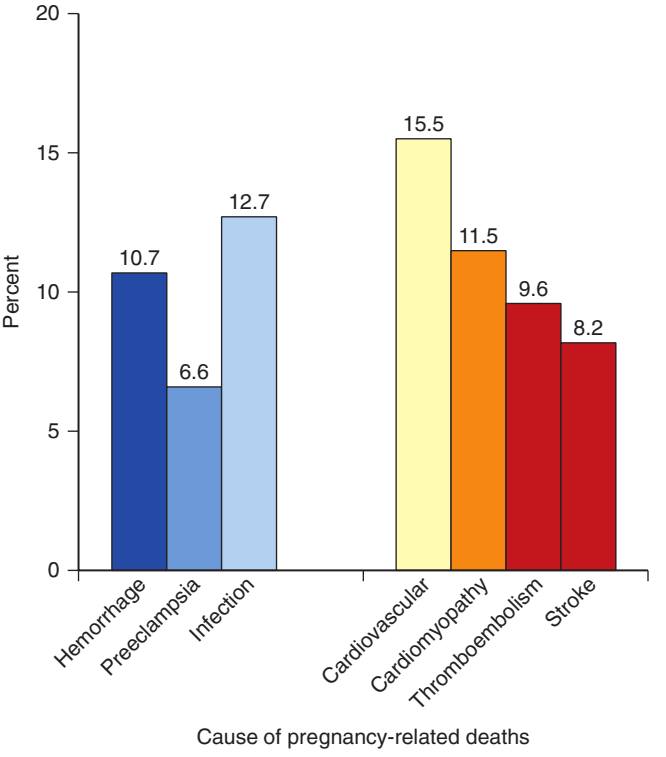


FIGURE 1-2 Some causes of and their contributions to pregnancy-related maternal deaths in the United States from 2014–2017. (Data from Centers for Disease Control and Prevention, 2020c).

Of *infant deaths*, the rate approximated 6 deaths per 1000 live births in 2018 compared with nearly 7 in 2001 (Centers for Disease Control and Prevention, 2020b). The four leading causes—congenital malformations, preterm birth, low birthweight, and maternal pregnancy complications—accounted for almost half of all infant deaths. Neonates born at the lowest gestational ages and birthweights add substantively to these mortality rates. For example, 17 percent of all infant deaths in 2018 were in those born preterm and with a low birthweight (Centers for Disease Control and Prevention, 2020d). Of particular interest are neonates with birthweights <500 g, for whom neonatal intensive care can now be offered (Chap. 45, p. 785).

Of *maternal deaths*, rates dropped precipitously in the United States during the 20th century. Pregnancy-related deaths are so uncommon as to be measured per 100,000 births. The CDC maintains data on pregnancy-related maternal deaths in its Pregnancy Mortality Surveillance System (PMSS). Its latest report described 3410 pregnancy-related deaths between 2011 and 2015 (Petersen, 2019b). Approximately 5 percent were early-pregnancy maternal deaths due to ectopic gestation or abortive outcomes. The deadly obstetrical triad of hemorrhage, preeclampsia, and infection accounted for a third of all deaths (Fig. 1-2). Thromboembolism, cardiomyopathy, and other cardiovascular disease together accounted for another third. Other significant contributors were amniotic fluid embolism (5.5 percent) and cerebrovascular accidents (8.2 percent). Anesthesia-related deaths were at an all time low—only 0.4 percent. Similar

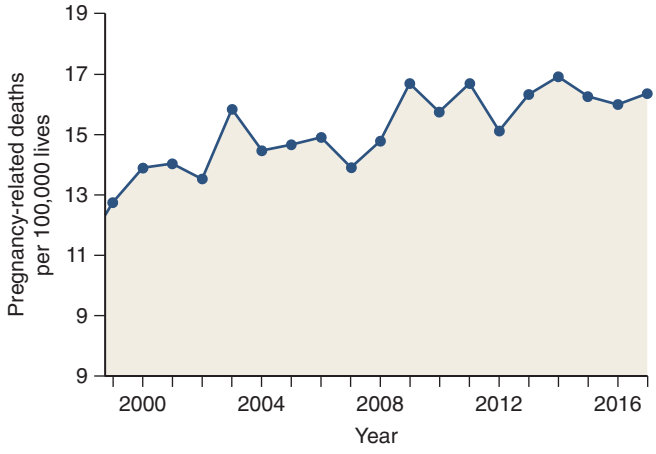


FIGURE 1-3 Trends in pregnancy-related maternal mortality in the United States from 1999–2017. (Data from Centers for Disease Control and Prevention, 2020c).

causes were reported for selected cohorts by MacDorman and associates (2017).

The pregnancy-related maternal mortality ratio was 17 deaths per 100,000 live births in 2017 (Fig. 1-3). The cause of this rise during the last 30 years may simply be that more women are dying, however, other factors explain this increase (Joseph, 2017). First, the number of pregnant women with severe chronic health conditions, which place women at higher risk, is greater (Centers for Disease Control and Prevention, 2020c). Second, the increased proportion of births to women older than 40 years contributes to higher mortality rates (Petersen, 2019b). Another is an artificial elevation caused by the International Statistical Classification of Diseases, 10th Revision (ICD-10), implemented in 1999. Additionally, improved reporting of maternal mortality contributes to the rise (MacDorman, 2016, 2017). Last, implementation of the pregnancy checkbox on the death certificate was associated with an increased identification of maternal deaths (Rossen, 2020). Thus, after accounting for the checkbox, predicted maternal mortality rates did not change significantly from 1999 through 2017.

Another consideration is the obvious disparity of higher mortality rates among black, Hispanic, and white women as shown in Figure 1-4. Racial disparities stem from health-care

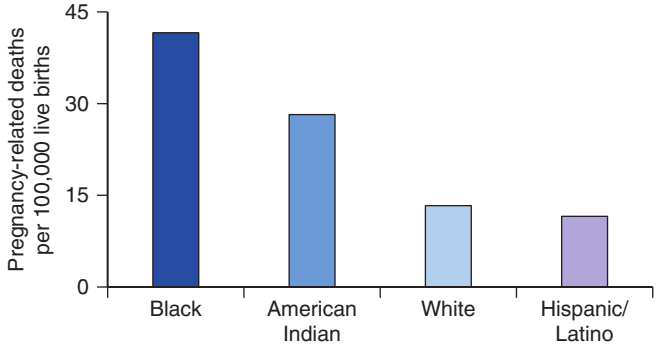


FIGURE 1-4 Pregnancy-related mortality ratio by race/ethnicity in the United States from 2014–2017. (Data from Centers for Disease Control and Prevention, 2020c).

availability, access, or use (Petersen, 2019a). The maternal mortality rate is also disparately high in rural compared with metropolitan areas (Maron, 2017).

Importantly, many maternal deaths are considered preventable. In one report, up to a third of pregnancy-related deaths in white women and up to half of those in black women were deemed preventable (Berg, 2005). One evaluation of an insured cohort reported that 28 percent of 98 maternal deaths were preventable (Clark, 2008). Thus, further efforts are imperative for obstetrics and described on page 6.

Severe Maternal Morbidity

This is defined as unintended events of labor and delivery resulting in serious short- or long-term consequences to a woman. Indicators serve as one measure to guide prevention (Table 1-2). The American College of Obstetricians and Gynecologists and the Society for Maternal-Fetal Medicine (2016) have provided lists of suggested screening topics for this purpose.

To study severe maternal morbidity (SMM), the CDC analyzed more than 50 million maternity records from 1998 to 2009 (Callaghan, 2012). They reported that 129 per 10,000 women had at least one indicator for SMM (Table 1-2). Thus, for every maternal death, approximately 200 women experience severe morbidity. As shown in Figure 1-5, SMM rates have increased during the past 15 years, and this trend is attributed to better documentation and a rise the blood transfusion rate. These numbers are greatest in smaller hospitals with <1000 deliveries annually (Hehir, 2017). Last, as with mortality rates,

TABLE 1-2. Severe Maternal Morbidity Indicators

Acute myocardial infarction
Acute renal failure
Adult respiratory distress syndrome
Amnionic fluid embolism
Cardiac arrest/ventricular fibrillation
Cardiac monitoring
Cardiac surgery
Conversion of cardiac rhythm
Disseminated intravascular coagulation
Eclampsia
Heart failure during procedure
Hysterectomy
Injuries of thorax, abdomen, and pelvis
Intracranial injuries
Puerperal cerebrovascular disorders
Pulmonary edema
Severe anesthesia complications
Sepsis
Shock
Sickle-cell crisis
Thrombotic embolism
Tracheostomy
Ventilation

Summarized from the Centers for Disease Control and Prevention, 2021.

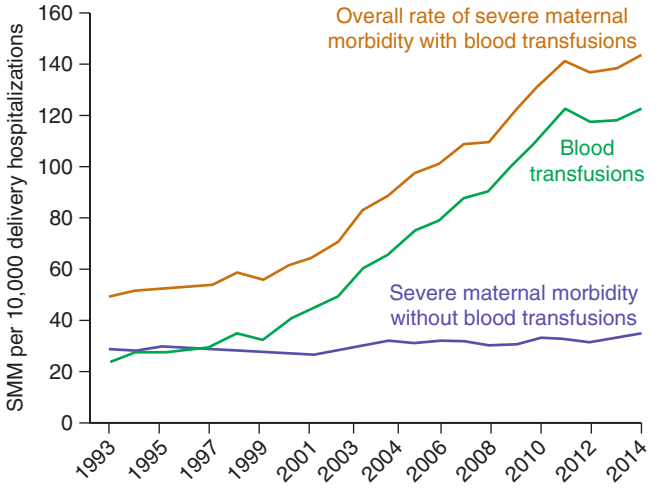


FIGURE 1-5 Rates of severe maternal morbidity (SMM) per 10,000 delivery hospitalizations. Women who received blood transfusions account for the greatest fraction of SMM. (Data from Centers for Disease Control and Prevention, 2021).

there are serious racial and ethnic disparities for SMM, and black women are disproportionately affected (Creanga, 2014).

Near Misses

Lowering medical error rates serves to diminish risks for maternal death and SMM. The terms *near misses* or *close calls* were introduced and defined as unplanned events caused by error that do not result in patient injury but have this potential (Institute for Safe Medication Practices, 2009). These are more common than injury events, but for obvious reasons, they are more difficult to identify and quantify. Systems designed to encourage reporting have been installed in various institutions and allow focused safety efforts (Clark, 2012; King, 2012; Shields, 2017). The World Health Organization (WHO) also implemented such a system. It has been validated in Brazil and accurately correlates with maternal death rates (Souza, 2012). A similar system in Britain is the *UK Obstetric Surveillance System—UKOSS* (Knight, 2005, 2008). In the United States, one is the *National Partnership for Maternal Safety* (D'Alton, 2016; Main, 2015).

TIMELY TOPICS IN OBSTETRICS

Various topics have been in the forefront since the 25th edition of this textbook. Here, we discuss several of these.

COVID-19 Pandemic

In early 2020, the severe acute respiratory syndrome (SARS)-CoV-2 virus spread rapidly around the globe, creating the greatest public health crisis since the influenza pandemic of 1918 (Chap. 67, p. 1187). As of early 2021, the disease caused by this virus and commonly known as COVID-19 is estimated to have infected more than 181 million people and caused nearly 4 million deaths (World Health Organization, 2021). Expectedly, the healthcare and political landscapes in the United States changed dramatically because of the pandemic.

Following the January 2020 declaration of a Global Health Emergency by the WHO, citywide lockdowns, state-mandated shelter-in-place orders, and public mask mandates were all implemented to help control early viral spread. Healthcare systems scrambled to acquire COVID-19 tests and personal protective equipment for staff. Wards dedicated solely to COVID-19 care opened in hospitals throughout the nation to handle substantial patient volume. Despite these measures, more than 500,000 individuals—including more than 3000 healthcare workers—died in the United States in 2020 from the infection.

Maternity wards were not spared, and traditional models of prenatal care were transformed. Namely, virtual care and drive-through prenatal care models aimed to reduce exposure risk to patients and staff (Holcomb, 2020; Turrentine, 2020). Asymptomatic or mild infections were common in pregnancy (Adhikari, 2020). Still, the effects of COVID-19 on pregnancy are not completely understood, and the effect of pregnancy on disease course is controversial. Management of severe COVID-19 infection in pregnancy requires interdisciplinary care and an understanding of pregnancy physiology and viral pathophysiology.

Preventive measures—including mRNA vaccines—have been shown to be safe and highly effective in disease prevention. However, this critical information was delayed following exclusion of pregnant individuals from initial clinical trials (Adhikari, 2021; Polack, 2020). In a report describing over 800,000 pregnancies, Chinn and colleagues (2021) found that 2.2 percent (18,715) of these women had COVID-19. When compared with women without such infections, these women had significantly increased adverse outcomes to include preterm birth, ICU admissions, intubations and mechanical ventilation, and maternal deaths. In 2021 the FDA approved COVID-19 vaccines for pregnant women.

Knowledge gained during the SARS-CoV-2 pandemic will undoubtedly shape healthcare moving forward (Cook, 2021). Indeed, a combined in-person plus audio-only virtual prenatal care model may most effectively provide services to vulnerable patients who lack internet access (Duryea, 2021).

Maternal Mortality—a Call to Arms

Almost 700 women in the United States die each year from pregnancy or its complications, and many deaths are deemed preventable. As a result, obstetricians and other stakeholders have united to address these tragedies (Chescheir, 2015). Because maternal deaths are inextricably linked to SMM indicators (see Table 1-2), several programs have been designed by national organization to avoid these events. Noted earlier, the Pregnancy Mortality Surveillance System (PMSS) collects national pregnancy-related death data to guide prevention efforts. Another, the Alliance for Innovation on Maternal Health (AIM) program, creates patient *safety bundles*, which describe evidence-based best practices for various obstetrical settings. The Joint Commission recommends that birthing centers establish protocols and implement simulation efforts (Barbieri, 2015). Moreover, national working groups target specific risks, such as thromboembolism (D'Alton, 2016).

In addition to pregnancy, the puerperium is a vulnerable period as well. One specific national effort is to establish

dedicated 1-year postpartum follow-up to ensure ongoing care. Important targets are medical disorders such as hypertension, diabetes, other cardiovascular diseases, and their consequences. To emphasize puerperal care, the concept of a "fourth trimester" has been introduced (Chap. 36, p. 634). Moreover, legislation—the MOMMA's Act—aims to expand Medicaid postpartum coverage from 60 days to 12 months (Bailey, 2021). As stated by Surgeon General Jerome Adams, "We must act now; our nation and our mothers deserve better." (Frieden, 2020).

Opioid Use Disorder

During 1999 to 2014, the national prevalence of opioid use disorder in pregnant women rose 333 percent from 1.5 to 6.5 cases per 1000 deliveries (Centers for Disease Control and Prevention, 2018). In addition to the complexities of maternal addiction, opioid use has led to an unprecedented increase in the incidence of the *neonatal opioid withdrawal syndrome* (Chap. 33, p. 605). To combat the associated adverse effects on women and their pregnancies, the American College of Obstetricians and Gynecologists (2019b) has stressed an active role by obstetricians. The College recommends universal screening by questionnaire, as well as care given to affected women by a multidisciplinary team. Therapeutic use of opioids is curtailed as best possible. Treatment of opioid use disorder with methadone or buprenorphine is challenging and discussed in Chapter 64 (p. 1150). Despite efforts, a significant decline in the prevalence of these disorders in gravidas is not in sight.

Advances in Prenatal Genetics

Several technologies help detect fetal genetic abnormalities. Since the last edition, noninvasive prenatal screening that uses cell-free DNA (cfDNA) has become commonplace in prenatal care (Zhang, 2019). Another promising technique is chromosomal microarray analysis (CMA) performed on samples of chorionic villi or amnionic fluid. These tests provide sophisticated information about gains and losses of DNA segments as small as 50 to 100 kilobases. However, although the yield with CMA is superior to that with fetal karyotyping, *most* birth defects occur in the setting of normal CMA and karyotype results.

As knowledge of the human genome has expanded, the role of specific DNA sequence abnormalities has gained attention. As an example, evaluation of fetal skeletal dysplasia may include panels of tests in which next-generation sequencing is used to identify mutations in specific genes. Whole exome sequencing (WES) analyzes all coding regions of DNA, which together account for 1.5 percent of the genome. In pregnancies with structural fetal abnormalities, and in which CMA and karyotype results are normal, WES has identified clinically significant abnormalities in approximately 10 percent of fetuses (Lord, 2019; Petrovski, 2019). In one series of fetuses with unexplained nonimmune hydrops, WES detected diagnostic genetic variants in nearly 30 percent (Sparks, 2020).

Although promising, WES technology at this time is not recommended for routine use in prenatal diagnosis (American College of Obstetricians and Gynecologists, 2020b). Limitations include high rates of genetic variants of uncertain significance, long turnaround times, and high costs. Comprehensive counseling is needed because WES may detect or suspect a finding that is unrelated but medically actionable. Genomic tests are reviewed in Chapter 16 (p. 324), and elements of counseling are discussed in Chapter 17 (p. 334).

Placenta Accreta Spectrum

Since our last edition, the cesarean delivery rate has been static and approximates 32 percent. However, rates of pregnancies complicated by placenta accreta spectrum (PAS) have grown substantially. An incidence as high as 1 case in 300 deliveries has been cited (American College of Obstetricians and Gynecologists, 2018). Sequelae of these dangerous syndromes are discussed in Chapter 43 (p. 765). To address these risks, specialized accreta surgical teams at tertiary care centers and greater antepartum transfer to these centers are both on the rise. As one prevention, national efforts have worked to avoid the *primary* cesarean delivery. However, despite these efforts, PAS will likely continue as a significant risk for SMM.

Progestogens to Prevent Preterm Birth

Progesterone derivatives to forestall preterm birth have been studied for decades. One—intramuscular 17-alpha-hydroxyprogesterone caproate (17-OHPC)—was approved by the U.S. Food and Drug Administration (FDA) under the accelerated approval process and contingent on demonstration of efficacy in a second trial. The drug is marketed as *Makena*, and subsequent, observational studies, described in Chapter 45 (p. 795), have led to questions of its efficacy (Nelson, 2021).

In 2019, results of the confirmatory trial of *Makena* efficacy—the PROLONG trial—failed to show its benefits compared with placebo for prevention of birth before 35 weeks (Blackwell, 2020). Later in 2019, an FDA Advisory Committee voted 9 to 7 to withdraw interim accelerated approval. Analyses by the committee included cross-study comparisons and subgroup analyses that did not show 17-OHPC benefits (Fig. 45-6, p. 796). In late 2020, the FDA Center for Drug Evaluation and Research (CDER) recommended drug withdrawal from the market.

Subsequently, obstetricians became polarized regarding "off label" use of the drug because it *appears safe* (Chang, 2020; Greene, 2020; Sibai, 2020). Despite findings from the PROLONG trial and the FDA's CDER, both the American College of Obstetricians and Gynecologists (2021) and the Society for Maternal-Fetal Medicine (2020) continued to endorse 17-OHPC use. This, however, is with the proviso that "uncertainty regarding benefit" be shared with the patient during decision-making. Last, the EPPPIC Group (2021) performed a metaanalysis of randomized trials evaluating progestogens for preterm birth prevention. Although not statistically significant, they concluded progestogens, which include 17-OHPC, reduced births at less than 34 weeks. The FDA's CDER (2021) continues to recommend withdrawal of 17-OHPC from the market. At this time, however, thousands of women continue to receive 17-OHPC despite its questionable efficacy.

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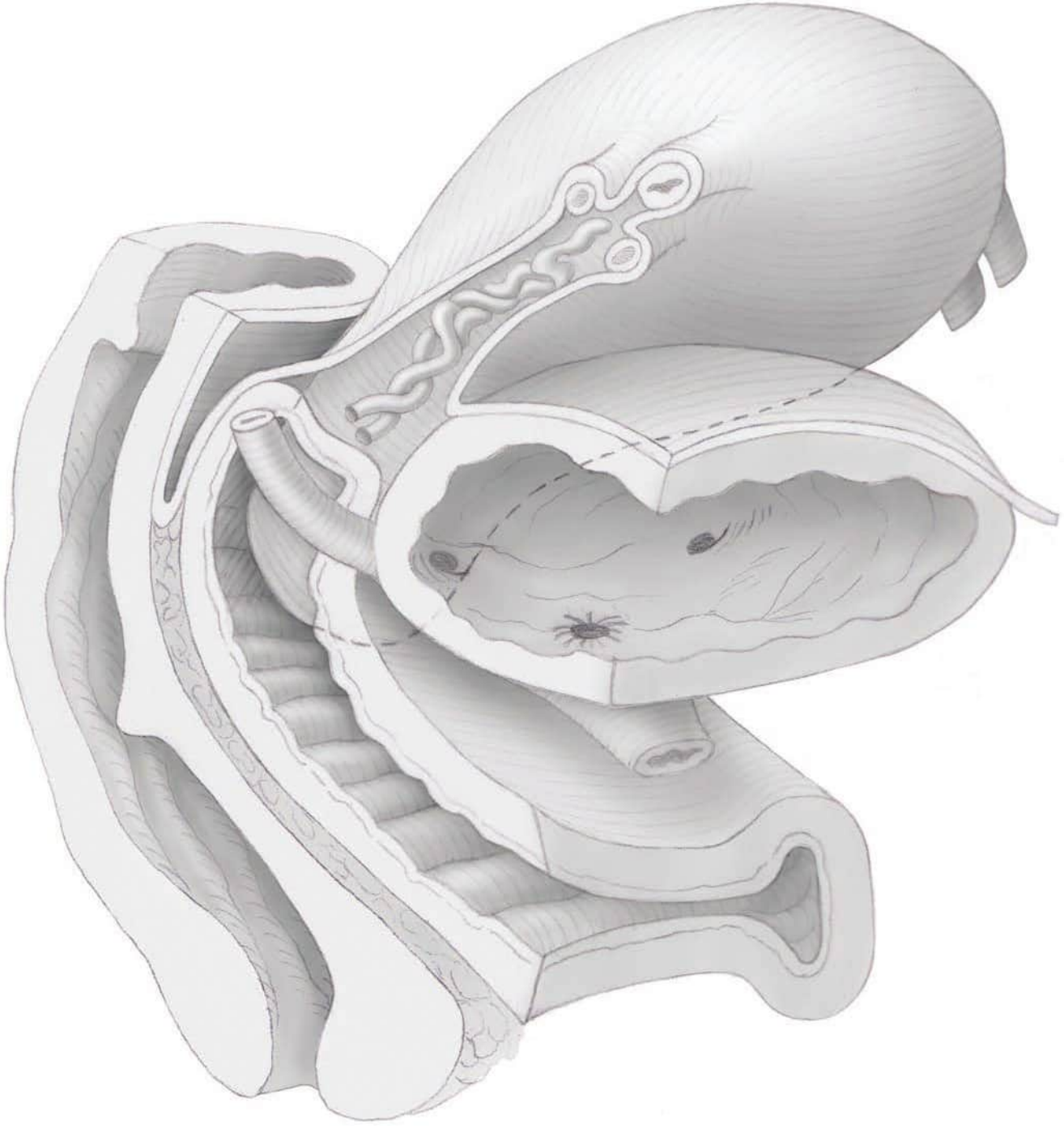
SECTION 2

MATERNAL ANATOMY AND PHYSIOLOGY



CHAPTER 2

Maternal Anatomy

ANTERIOR ABDOMINAL WALL

Skin, Subcutaneous Layer, and Fascia

The anterior abdominal wall confines abdominal viscera, stretches to accommodate the expanding uterus, and provides surgical access to the internal reproductive organs. Thus, a comprehensive knowledge of its layered structure is required to surgically enter the peritoneal cavity.

Langer lines describe the orientation of dermal fibers within the skin. In the anterior abdominal wall, they lie transversely. As a result, vertical skin incisions sustain greater lateral tension and in general develop wider scars. In contrast, low transverse incisions, such as the Pfannenstiel, follow Langer lines and lead to superior cosmetic results.

The subcutaneous layer can be separated into a superficial, predominantly fatty layer—Camper fascia—and a deeper membranous layer—Scarpa fascia. Camper fascia continues onto the perineum to provide fatty substance to the mons pubis and labia majora and then to blend with the fat of the ischioanal fossa. Scarpa fascia continues inferiorly onto the perineum as Colles fascia, (p. 18).

Beneath the subcutaneous layer, the anterior abdominal wall muscles are the midline *rectus abdominis* and *pyramidalis muscles* as well as the *external oblique*, *internal oblique*, and *transversus abdominis muscles*, which extend across the entire wall (Fig. 2-1). The fibrous aponeuroses of these three latter muscles form the primary fascia of the anterior abdominal wall. These fuse in the midline at the linea alba, which normally sonographically measures ≤15 mm wide below the umbilicus in nongravid women (Beer, 2009; Mota, 2018). An abnormally wide separation may reflect diastasis recti or ventral hernia.

These three aponeuroses also invest the rectus abdominis muscle as the rectus sheath. The construction of this sheath varies above and below a boundary, termed the arcuate line (see Fig. 2-1). Cephalad to this border, the aponeuroses invest the rectus abdominis bellies on both dorsal and ventral surfaces. Caudal to this line, all aponeuroses lie ventral or superficial to the rectus abdominis muscle, and only the thin transversalis fascia and peritoneum lie deep to the rectus (Loukas, 2008). This transition of rectus sheath composition can be seen best in the upper third of a midline vertical abdominal incision.

The paired small triangular pyramidalis muscles originate from the pubic crest and insert into the linea alba. These muscles lie atop the rectus abdominis muscle but beneath the anterior rectus sheath.

The umbilicus is covered by peritoneum, transversalis fascia, and skin and contains the umbilical ring. The ring is a defect in the linea alba through which the fetal umbilical vessels previously passed. The round ligament of the liver and the median umbilical and medial umbilical ligaments variably attach to the ring.

Transversalis Fascia and Peritoneum

Transversalis fascia is the thin fibrous tissue layer between the inner surface of the transversus abdominis muscle and the

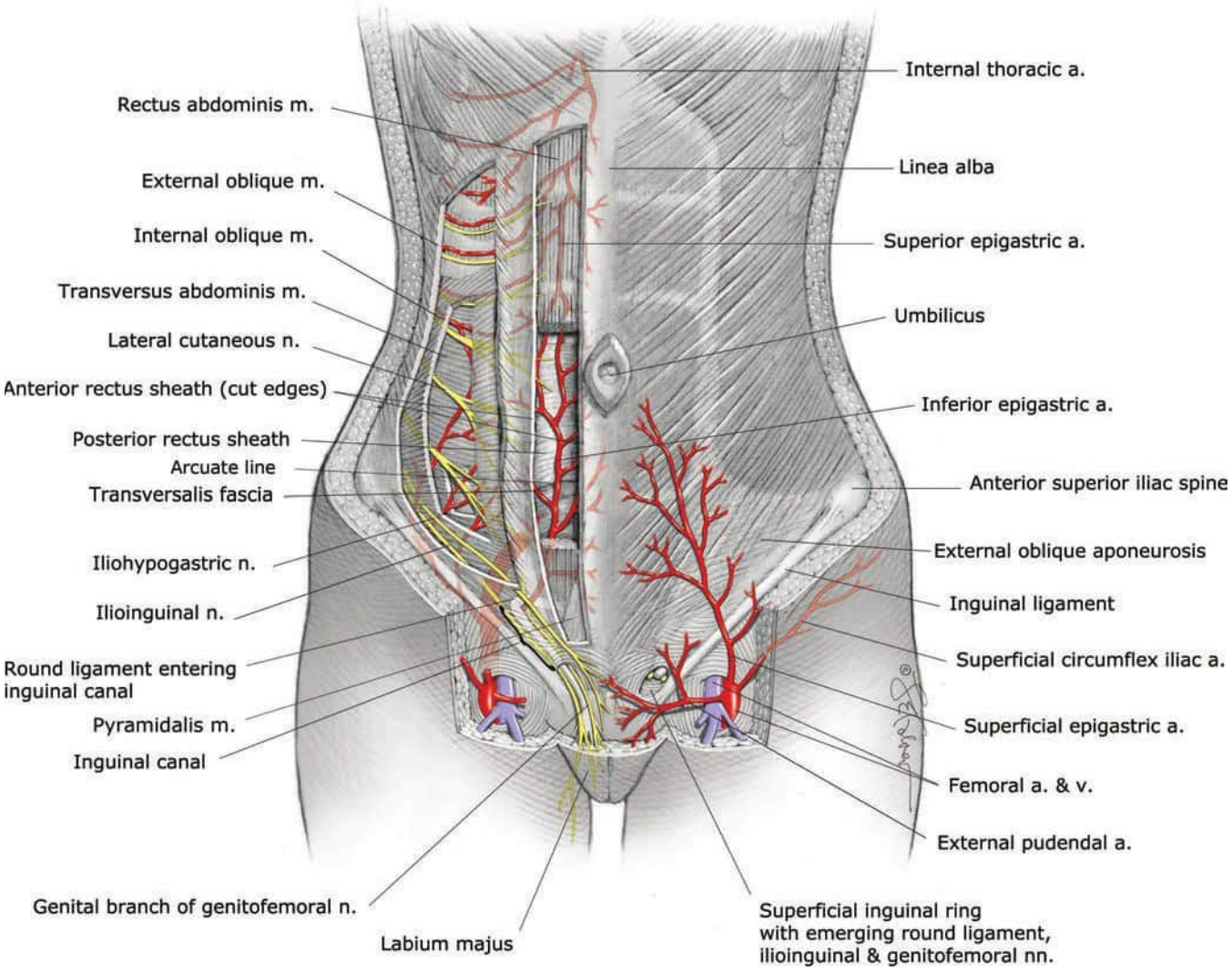


FIGURE 2-1 Anterior abdominal wall anatomy. (Modified with permission from Corton MM: Anatomy. In Hoffman BL, Schorge JO, Halvorson LM, et al (eds): Williams Gynecology, 4th ed. New York, NY: McGraw Hill; 2020.)

preperitoneal fat. Inferiorly, the transversalis fascia blends with the periosteum of the pubic bones.

The peritoneum contains a single layer of epithelial cells and a supporting connective tissue. The visceral peritoneum densely wraps around the abdominopelvic viscera, whereas the parietal peritoneum lines the inner surface of the abdominal walls. In the anterior abdominal wall, five elevations of parietal peritoneum converge toward the umbilicus and are known as umbilical ligaments.

The single *median umbilical ligament* is formed by the urachus, a fibrous fetal remnant that extends from the bladder apex to the umbilicus. Clinically, this ligament may be seen at laparotomy during peritoneal incision as a white, midline, fibrous cord. The paired *medial umbilical ligaments* are formed by the obliterated fetal umbilical arteries. The paired *lateral umbilical ligaments* contain the patent inferior epigastric vessels (see Fig. 2-1).

■ Blood Supply and Lymphatics

The *superficial epigastric*, *superficial circumflex iliac*, and *superficial external pudendal arteries* arise from the femoral artery just below the inguinal ligament within the femoral triangle (see Fig. 2-1). These vessels supply the skin and subcutaneous layers of the anterior abdominal wall and mons pubis. The superficial epigastric vessels are surgically important and course diagonally from their origin toward the umbilicus. With a low transverse skin incision, these vessels can usually be identified at a depth halfway between the skin and the anterior rectus sheath. They lie above the Scarpa fascia and several centimeters from the midline. Ideally, these vessels are identified and surgically occluded. Lymphatics run cephalad–caudad on the lower abdomen (Tourani, 2015). Most channels lie in the dermis, and a smaller density is found between the Camper and Scarpa fascias (Friedman, 2015).

More deeply, the bilateral *inferior epigastric artery* and vein are respective branches of the external iliac vessels and supply anterior abdominal wall muscles, nerves, and fascia. Of surgical relevance, the inferior epigastric vessels initially course lateral to and then posterior to the rectus abdominis muscles, which they supply. A deep system of lymphatics follows these arteries (Tourani, 2015).

Clinically, when a Maylard incision is used for cesarean delivery, the inferior epigastric vessels may be lacerated during muscle transection. Preventively, identification and surgical

occlusion are preferable. These vessels rarely may rupture spontaneously or traumatically during pregnancy to create a rectus sheath hematoma (Eckhoff, 2016; Gibbs, 2016).

On each side of the lower anterior abdominal wall, the Hesselbach triangle is the region bounded laterally by the inferior epigastric vessels, inferiorly by the inguinal ligament, and medially by the lateral border of the rectus abdominis muscle. Hernias that protrude through the abdominal wall in the boundaries of the Hesselbach triangle are termed direct inguinal hernias. In contrast, indirect inguinal hernias bulge through the deep inguinal ring, which lies lateral to this triangle, and enter the inguinal canal. Here, contents may exit out the superficial inguinal ring.

Innervation

The entire anterior abdominal wall is innervated by intercostal nerves ($T_{7–11}$), the subcostal nerve (T_{12}), and the iliohypogastric and the ilioinguinal nerves (L_1). The intercostal and subcostal nerves are anterior rami of the thoracic spinal nerves and run along the lateral and then anterior abdominal wall between the transversus abdominis and internal oblique muscles (Fig. 2-2). This space, termed the transversus abdominis plane, can be used for postcesarean analgesia blockade (Chap. 25, p. 480) (Ng, 2018).

Near the rectus abdominis lateral borders, anterior branches of the intercostal and subcostal nerves travel superficially to pierce the posterior sheath, rectus muscle, and then anterior sheath to reach the skin. Thus, these nerve branches may be severed during a Pfannenstiel incision creation during the step in which the overlying anterior rectus sheath is separated from the rectus abdominis muscle (Chap. 30, p. 552).

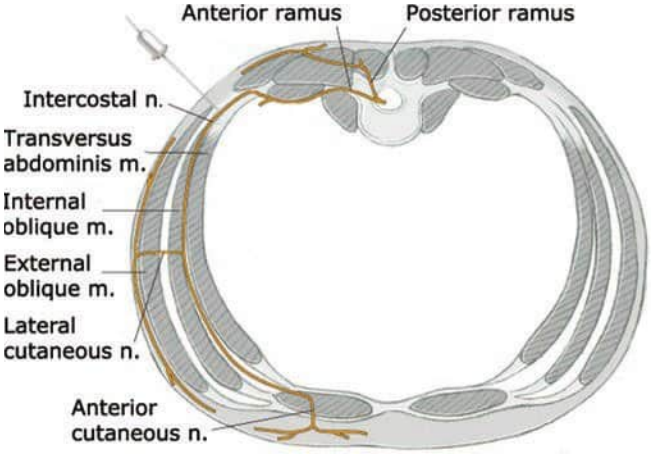


FIGURE 2-2 Intercostal and subcostal nerves are the anterior rami of spinal nerves. In this figure, an intercostal nerve extends ventrally between the transversus abdominis and internal oblique muscles. During this path, the nerve gives rise to lateral and anterior cutaneous branches, which innervate the anterior abdominal wall. As shown by the inserted needle, the transversus abdominis plane (TAP) block takes advantage of this anatomy. (Modified with permission from Hawkins JL: Anesthesia for the pregnant woman. In Yeomans ER, Hoffman BL, Gilstrap LC III, et al: Cunningham and Gilstraps's Operative Obstetrics, 3rd ed. New York, NY: McGraw Hill; 2017.)

The iliohypogastric and ilioinguinal nerves originate from the anterior ramus of the first lumbar spinal nerve. They emerge lateral to the psoas major muscle and travel across the quadratus lumborum in the retroperitoneum and toward the iliac crest. Near this crest, both nerves pierce the transversus abdominis muscle and course ventromedially. At a site 2 to 3 cm medial to the anterior superior iliac spine, the nerves then pierce the internal oblique muscle and course superficial to it toward the midline (Whiteside, 2003). The iliohypogastric nerve perforates the external oblique aponeurosis near the lateral rectus border to provide sensation to the suprapubic skin (see Fig. 2-1). The ilioinguinal nerve in its course medially travels through the inguinal canal and exits through the superficial inguinal ring, which forms by splitting of external abdominal oblique aponeurosis fibers. This nerve supplies the skin of the mons pubis, upper labia majora, and medial upper thighs.

The ilioinguinal and iliohypogastric nerves can be severed during a low transverse incision or entrapped during closure, especially if incisions extend beyond the lateral borders of the rectus abdominis muscle (Rahn, 2010). These nerves carry sensory information only, and injury leads to loss of sensation within the areas supplied. Rarely, chronic pain may develop (Verhagen, 2018).

The T_{10} dermatome approximates the level of the umbilicus. Analgesia to this level is suitable for labor and vaginal birth. Regional analgesia for cesarean delivery or for puerperal sterilization ideally extends to T_4.

PERINEUM

This diamond-shaped area has boundaries that mirror those of the bony pelvic outlet (p. 28). These are the pubic symphysis anteriorly, ischiopubic rami and ischial tuberosities anterolaterally, sacrotuberous ligaments posterolaterally, and coccyx posteriorly. An arbitrary line joining the ischial tuberosities divides the perineum into an anterior triangle, also called the urogenital triangle, and a posterior triangle, termed the anal triangle (Fig. 2-3).

Vulva

Mons Pubis, Labia, and Clitoris

The vulva includes all structures visible externally in the urogenital triangle. These are the mons pubis, labia majora, labia minora, clitoris, hymen, vestibule, urethral opening, greater vestibular (Bartholin) glands, minor vestibular glands, and paraurethral glands (see Fig. 2-3). The vulva receives innervations and vascular support from the pudendal nerve (p. 22).

The mons pubis is a fat-filled cushion overlying the symphysis pubis. After puberty, the mons pubis skin is covered by hair that forms the triangular escutcheon, whose base aligns with the upper margin of the symphysis pubis. In men and some hirsute women, the escutcheon extends farther onto the anterior abdominal wall toward the umbilicus and thus is diamond shaped.

Labia majora usually are 7 to 8 cm long, 2 to 3 cm wide, and 1 to 1.5 cm thick. They are continuous directly with the

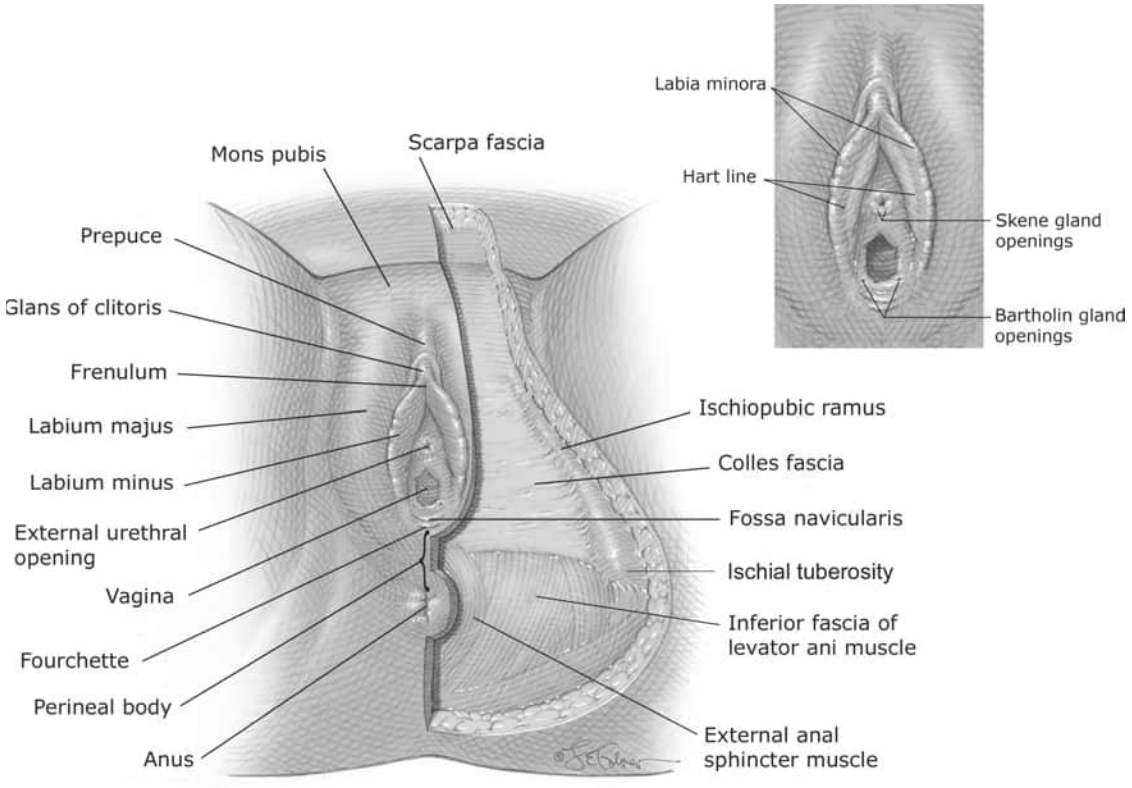


FIGURE 2-3 Vulvar structures and subcutaneous layer of urogenital triangle. **Inset:** Vestibule boundaries and openings onto the vestibule. (Modified with permission from Corton MM: Anatomy. In Hoffman BL, Schorge JO, Halvorson LM, et al (eds): Williams Gynecology, 4th ed. New York, NY: McGraw Hill; 2020.)

mons pubis superiorly, and the round ligaments terminate at their upper borders. Hair covers the labia majora, and apocrine, eccrine, and sebaceous glands are abundant. Beneath the skin, a dense connective tissue layer is nearly void of muscular elements but is rich in elastic fibers and fat. This fat mass provides bulk to the labia majora and is supplied with a rich venous plexus. During pregnancy, this plexus may develop varicosities from pressure created by the growing uterus.

Each labium minus is a thin tissue fold that lies medial to each labium majus. The labia minora begin at the fourchette and extend superiorly, where each divides into two lamellae. From each side, the lower lamellae fuse to form the frenulum of the clitoris, and the upper lamellae merge to form the prepuce (see Fig. 2-3). The labia minora dimensions vary greatly among reproductive-aged women (Cao, 2015; Lykkebo, 2017). In one large study, the mean length was 4 cm (range 0.5 to 10 cm) and mean lateral span was 1.5 (range 0.1 to 6 cm) (Kreklau, 2018).

Structurally, the labia minora are composed of connective tissue with many small vessels, elastin fibers, but very little smooth muscle. Nerve fibers are numerous (Ginger, 2011a; Schober, 2015). The epithelia of the labia minora differ by location. Thinly keratinized stratified squamous epithelium covers the outer surface of each labium. On their inner surface, the lateral portion is covered by this same epithelium up to a demarcating line, termed the Hart line. Medial to this line, each labium is covered by squamous epithelium that is nonkeratinized. Labia minora lack hair follicles, eccrine glands, and apocrine glands but have many sebaceous glands (Wilkinson, 2011).

The clitoris is the principal female erogenous organ (Fig. 2-4). It is located beneath the prepuce, above the frenulum and urethra, and projects downward toward the vaginal opening. The clitoris rarely exceeds 2 cm in length and is composed of a glans, a corpus or body, and two crura. The glans is usually less than 0.5 cm in diameter and is covered by stratified squamous epithelium. Nerve bundles are prominent and correspond to the paired dorsal nerves of the clitoris (Jackson, 2019). The clitoral body contains two corpora cavernosa. Extending from the clitoral body, each corpus cavernosum diverges laterally to form a long, narrow crus. Each crus lies along the inferior surface of its respective ischiopubic ramus and deep to the ischiocavernosus muscle. The clitoral blood supply stems from branches of the internal pudendal artery. Specifically, the *deep artery of the clitoris* supplies the clitoral body, whereas the *dorsal artery of the clitoris* supplies the glans and prepuce.

Vestibule

In adult women, the vestibule is an almond-shaped area that is enclosed by the Hart line laterally, the hymen medially, the clitoral frenulum anteriorly, and the fourchette posteriorly (see Fig. 2-3). The vestibule is usually perforated by six openings: the urethra, the vagina, two greater vestibular (Bartholin) gland ducts, and ducts of the two largest paraurethral glands—the Skene glands. The posterior portion of the vestibule between the fourchette and the vaginal opening is called the vestibular fossa (Hill, 2021). It is usually observed only in nulliparas.

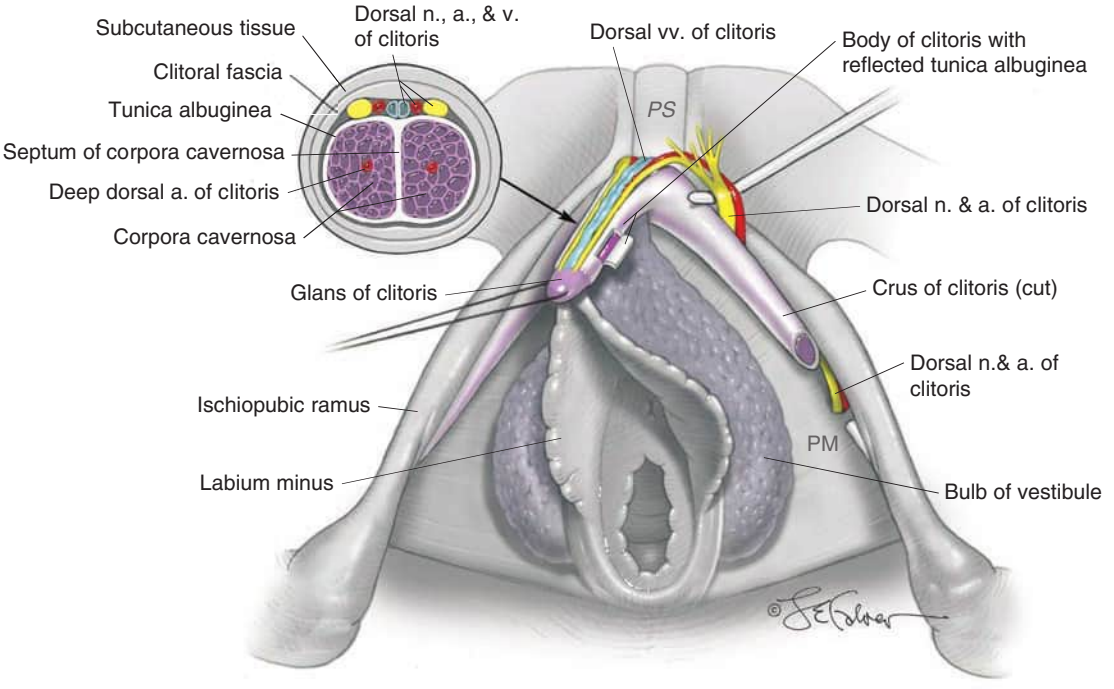


FIGURE 2-4 Clitoris and associated vulvar structures in superficial space of urogenital triangle. Inset: cross section through proximal body of clitoris. PM = perineal membrane; PS = pubic symphysis. (Modified with permission from Corton MM: Anatomy. In Hoffman BL, Schorge JO, Halvorson LM, et al (eds): Williams Gynecology, 4th ed. New York, NY: McGraw Hill; 2020.)

The bilateral Bartholin glands are 0.5 to 1 cm in diameter. On their respective side, each lies inferior to the vestibular bulb (bulb of vestibule) and deep to the inferior end of the bulbospongiosus muscle (former bulbocavernosus muscle). A duct extends medially from each gland, measures 1.5 to 2 cm long, and opens distal to the hymeneal ring. One duct opens at 5 and the other at 7 o'clock on the vestibule. Following trauma or infection, either duct may swell and obstruct to form a cyst or, if infected, an abscess. In contrast, the minor vestibular glands are shallow glands lined by simple mucin-secreting epithelium and open along the Hart line.

The paraurethral glands are a collective arborization of glands whose numerous small ducts open into the urethra and predominantly along its entire inferior aspect (Costa, 2016; Huffman, 1948). The two largest are called Skene glands, and their ducts typically lie distally and near the urethral meatus. Clinically, inflammation and duct obstruction of any of the paraurethral glands can lead to urethral diverticulum formation (Chap 56, p. 1007). The urethral opening or meatus is in the midline of the vestibule, 1 to 1.5 cm below the pubic arch, and a short distance above the vaginal opening.

■ Vagina and Hymen

In adult women, the hymen is a thin membrane that surrounds all or much of the vaginal opening in an annular or crescent form. Mainly elastic fibers, collagen, and fine vessels compose the hymen. Nerve fibers are few and localize to its base. Both outer and inner hymeneal surfaces are covered by nonkeratinized stratified squamous epithelium (Mahran, 1964). The aperture of the intact hymen ranges in diameter from pinpoint to one that admits one or even two fingertips. As a rule, the hymen is torn at several sites during first coitus. However, identical tears may form by other penetration, for example, by tampons used during menstruation. The torn edges soon reepithelialize.

Proximal to the hymen, the vagina is a muscular tube that extends to the uterus and is interposed lengthwise between the bladder and the rectum (Fig. 2-5). Total vaginal length is 9 to 10 cm (Collins, 2017; Patnam, 2019). Anteriorly, the vagina is separated from the bladder and urethra by connective tissue—the vesicovaginal septum. Posteriorly, between the lower portion of the vagina and the rectum, similar tissues together form the rectovaginal septum. The upper fourth of the vagina is separated from the rectum by the rectouterine pouch, also called the cul-de-sac or pouch of Douglas (Balgobin, 2020).

Normally, the anterior and posterior walls of the vaginal lumen lie in contact. The vaginal apex is subdivided by the cervix into anterior, posterior, and two lateral fornices. Clinically, the internal pelvic organs usually can be palpated through the thin walls of these fornices.

The vaginal lining is composed of nonkeratinized stratified squamous epithelium and underlying lamina propria. In premenopausal women, this lining is thrown into numerous thin transverse ridges, known as rugae. Deep to this, a muscular layer contains smooth muscle, collagen, and elastin. Beneath this, an adventitial layer consists of collagen and elastin (Maldonado, 2020; Mazloomdoost, 2017). No true fascia separates the vagina from the bladder or from the rectum.

The vagina lacks glands. Instead, it is lubricated by a transudate that originates from the vaginal subepithelial capillary

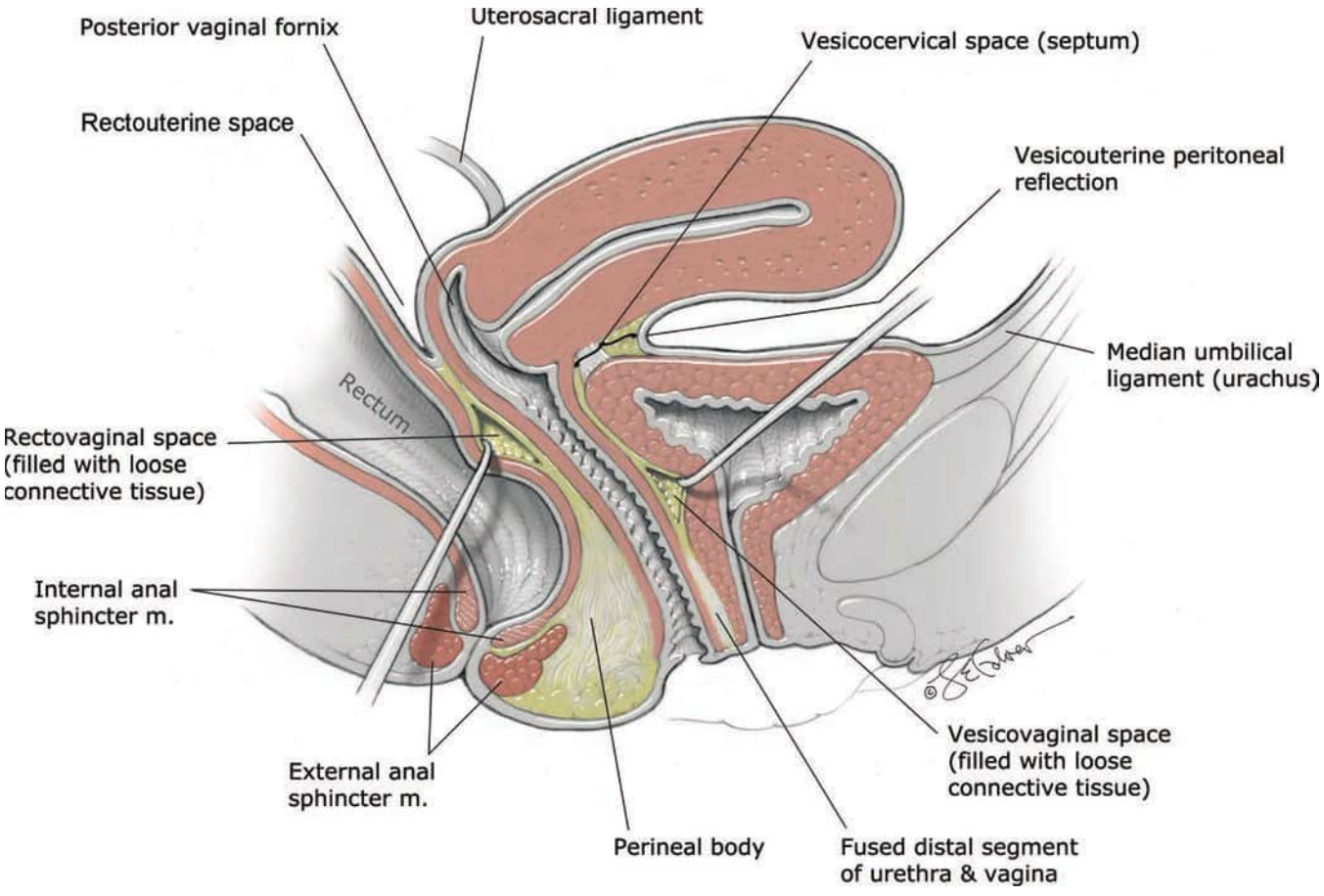


FIGURE 2-5 Vagina and surrounding anatomy. (Modified with permission from Corton MM: Anatomy. In Hoffman BL, Schorge JO, Halvorson LM, et al (eds): Williams Gynecology, 4th ed. New York, NY: McGraw Hill; 2020.)

plexus and crosses the permeable epithelium (Kim, 2011). Due to increased vascularity during pregnancy, vaginal secretions are notably increased. At times, this may be confused with amniotic fluid leakage, and clinical differentiation of these two is described in Chapter 22 (p. 426).

After birth-related epithelial trauma and healing, fragments of stratified epithelium occasionally are embedded beneath the vaginal surface. Similar to its native tissue, this buried epithelium continues to shed degenerated cells. As a result, epidermal inclusion cysts, which are filled with debris, may commonly form.

The vagina has an abundant vascular supply. The proximal portion is supplied by the cervical branch of the uterine artery and by the vaginal artery. The latter may variably arise from the uterine or inferior vesical artery or directly from the internal iliac artery. The middle rectal artery contributes supply to the posterior vaginal wall, whereas the distal walls receive contributions from the internal pudendal artery. At each level, vessels supplying each side of the vagina course medially across the anterior or posterior vaginal wall and form midline anastomoses.

An extensive venous plexus also surrounds the vagina and follows the course of the arteries. Lymphatics from the lower third, along with those of the vulva, drain primarily into the inguinal lymph nodes. Those from the remainder drain into the pelvic lymph nodes.

Perineal Body

This fibromuscular pyramidal mass lies in the midline at the junction between the urogenital and anal triangles (Figs. 2-3 and 2-5) (Oh, 1973; Soga, 2007). Clinically, it measures 3.5 to 5 cm in nulliparas from the posterior midline hymen to the mid-anal opening, which are standard pelvic organ prolapse-quantification (POP-Q) landmarks (Komorowski, 2014; Reimers, 2016). It lengthens slightly during pregnancy, and during second-stage labor, one study showed that it stretches >65 percent (Meriwether, 2016). It serves as the junction for several structures and provides significant perineal support (Shafik, 2007). Superficially, the bulbospongiosus, superficial transverse perineal, and external anal sphincter muscles converge on the perineal body. More deeply, the perineal membrane, portions of the pubococcygeus muscle, and internal anal sphincter contribute (Larson, 2010).

The perineal body is incised during episiotomy incision and is torn with second-, third-, and fourth-degree lacerations. Data conflict as to whether a shorter perineal body length predisposes to higher-order lacerations (Deering, 2004; Dua, 2009; Hokenstad, 2015; Meriwether, 2016).

Urogenital Triangle

Superficial Space

The urogenital triangle is bounded by the pubic rami superiorly, the ischial tuberosities laterally, and the superficial

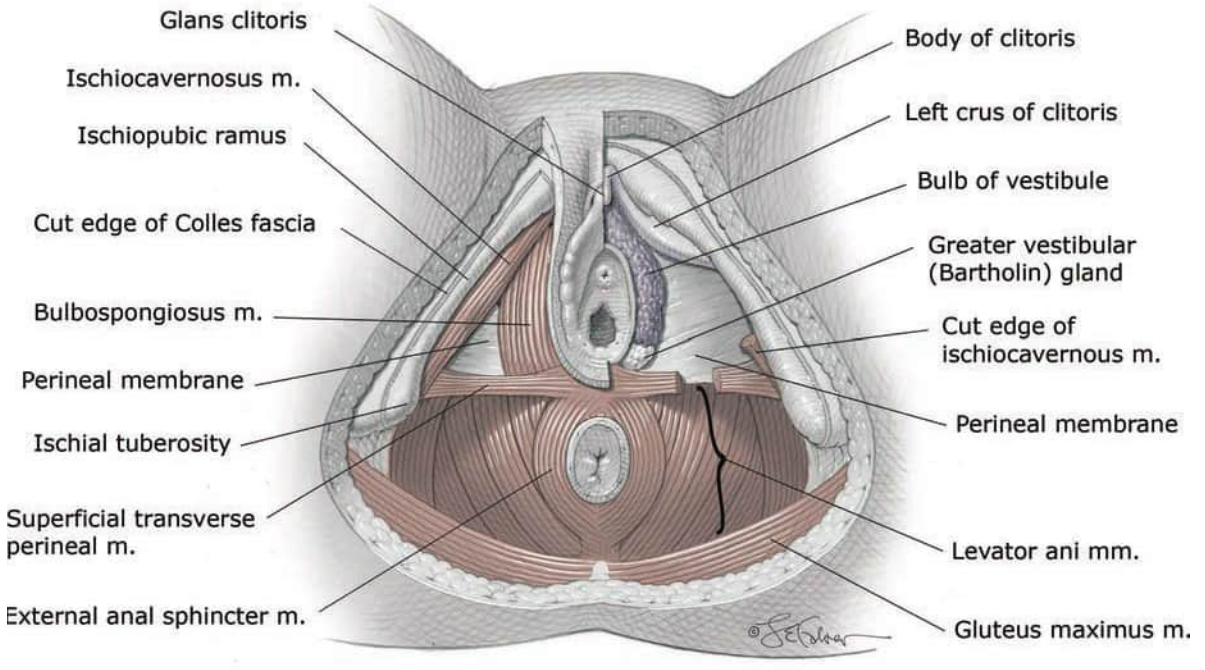


FIGURE 2-6 Superficial space of the urogenital triangle and anal triangle. Structures on the left side of the image can be seen after removal of Colles fascia. Those on the right side are noted after removal of the superficial muscles of the urogenital triangle. (Modified with permission from Corton MM: Anatomy. In Hoffman BL, Schorge JO, Halvorson LM, et al (eds): Williams Gynecology, 4th ed. New York, NY: McGraw Hill; 2020.)

transverse perineal muscles posteriorly (Fig. 2-6). It is divided into superficial and deep spaces by the perineal membrane. This membranous partition is a dense fibrous sheet that was previously known as the inferior fascia of the urogenital diaphragm. The perineal membrane attaches laterally to the ischiopubic rami, medially to the distal third of the urethra and vagina, posteriorly to the perineal body, and anteriorly to the arcuate ligament of the pubis (Stein, 2008). It lies at the depth of the hymeneal ring.

The superficial space has the perineal membrane as its deep wall and the Colles fascia as its superficial one. As noted earlier, the Colles fascia is the continuation of the Scarpa fascia onto the perineum. On the perineum, the Colles fascia securely attaches laterally to the pubic rami and fascia lata of the thigh, inferiorly to the superficial transverse perineal muscle and inferior border of the perineal membrane, and medially to the urethra, clitoris, and vagina. As such, the superficial space of the urogenital triangle is a relatively closed compartment.

This superficial space contains several important structures, which include the Bartholin glands, vestibular bulbs, clitoral body and crura, branches of the pudendal vessels and nerve, and the ischiocavernosus, bulbospongiosus, and superficial transverse perineal muscles. Of this muscular trio, the ischiocavernosus muscles each attach on their respective side to the medial aspect of the ischial tuberosity inferiorly and the ischiopubic ramus laterally. Anteriorly, each attaches to a clitoral crus and may help maintain clitoral erection by compressing the crus to obstruct venous drainage. Each bulbospongiosus muscle overlies a vestibular bulb and Bartholin gland. Anteriorly, they attach to the body of the clitoris and posteriorly, to the perineal body. Some more-recent anatomical studies instead describe that the bulbospongiosus muscles blend medially with the external anal sphincter (Baramee, 2020; Plochocki, 2016). The muscles constrict the vaginal lumen and aid release of Bartholin gland secretions. They also may contribute to clitoral erection by compressing the deep dorsal vein of the clitoris. The bulbospongiosus and ischiocavernosus muscles also pull the clitoris downward. Last, the superficial transverse perineal muscles are narrow strips that attach to the ischial tuberosities laterally and the perineal body medially.

Each vestibular bulb, also called bulb of vestibule, is an almond-shaped aggregation of veins that lie beneath the bulbospongiosus muscle on either side of the vestibule (Jeppson, 2018). They measure 5 cm long and 2 cm wide (Jackson, 2019). The bulbs terminate inferiorly at approximately the middle of the vaginal opening and extend upward toward the clitoris. Their anterior extensions merge in the midline, below the clitoral body. During childbirth, veins in the vestibular bulb may be lacerated or may rupture to create a hematoma enclosed within the superficial space of the urogenital triangle.

Deep Space

This space lies above or deep to the perineal membrane and below the inferior investing fascia of the levator ani muscle. It contains portions of urethra and vagina, certain portions of internal pudendal artery branches, and muscles of the striated urogenital sphincter complex (Fig. 2-7).

Urethra. The female urethra measures 3 to 4 cm and originates within the bladder trigone (p. 27) (Hamner, 2018; Rahn, 2007). The distal two thirds of the urethra are fused with the

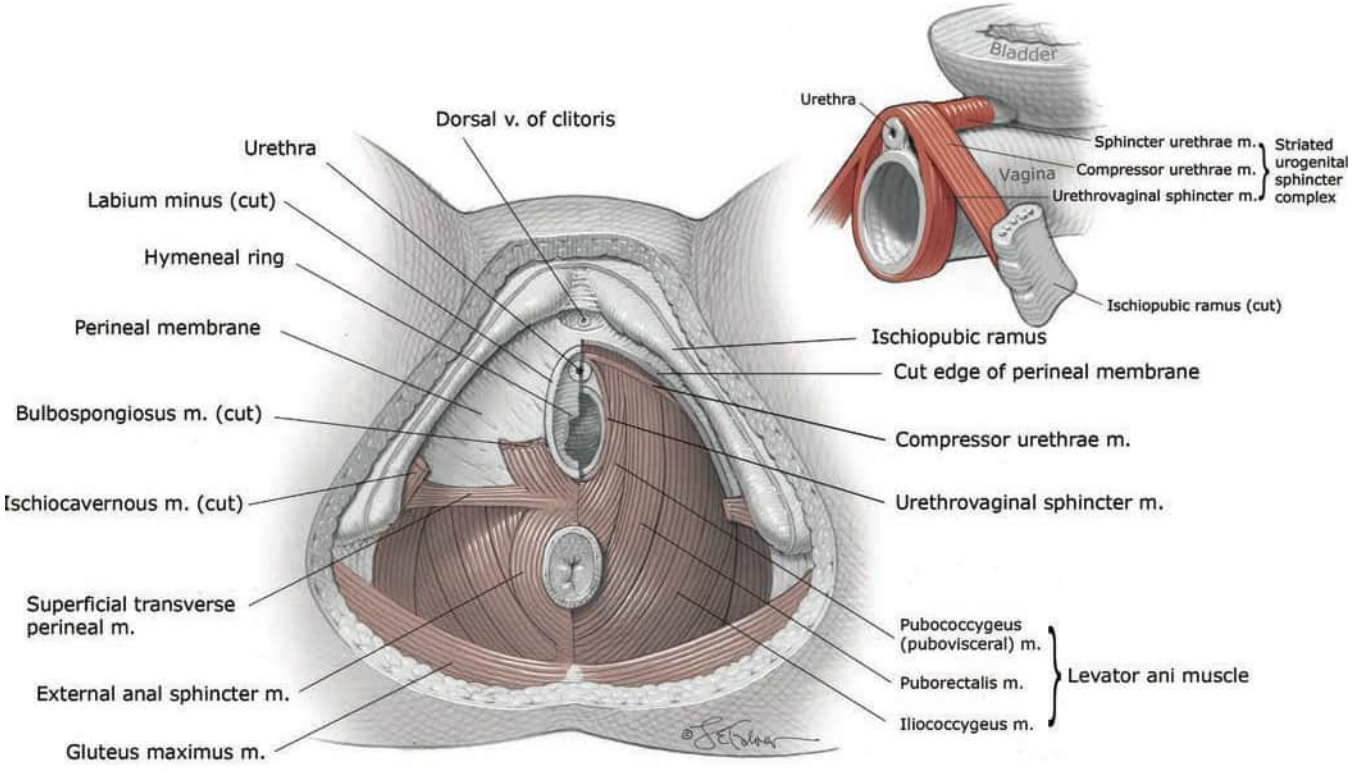


FIGURE 2-7 Deep space of urogenital triangle. Structures on the right side of the image can be seen after removal of the perineal membrane. Also shown are structures that attach to the perineal body: bulbospongiosus, superficial transverse perineal, external anal sphincter, and puboperinealis muscles as well as perineal membrane. (Modified with permission from Corton MM: Anatomy. In Hoffman BL, Schorge JO, Halvorson LM, et al (eds): Williams Gynecology, 4th ed. New York, NY: McGraw Hill; 2020.)

anterior vaginal wall. The epithelial lining of the urethra is transitional epithelium at the urethrovesical junction. It then changes to a pseudostratified columnar along its proximal length but is a nonkeratinized stratified squamous epithelium distally (Carlile, 1987).

The walls of the urethra consist of two layers of smooth muscle, an inner longitudinal and an outer circular. This is in turn surrounded by a circular layer of skeletal muscle referred to as the sphincter urethrae (see Fig. 2-7). Approximately at the junction of the middle and lower third of the urethra and within the deep perineal space, two straplike skeletal muscles called the sphincter urethrovaginalis and the compressor urethrae are found. Together with the sphincter urethrae, these constitute the external urethral sphincter (EUS), also called the striated urogenital sphincter complex (Mistry, 2020). The EUS supplies constant tonus and provides emergency reflex contraction to sustain continence.

Distal to the level of the perineal membrane, the walls of the urethra consist of fibrous tissue, serving to direct the urine stream. Here, the urethra has a prominent submucosal layer that is lined by hormonally sensitive stratified squamous epithelium. Within the submucosal layer on the dorsal (vaginal) surface of the urethra lie most paraurethral glands (p. 16).

The urethra receives its blood supply from branches of the inferior vesical, vaginal, or internal pudendal arteries. The pudendal nerve provides somatic innervation to the EUS. The urethra's smooth muscle receives sympathetic and parasympathetic innervation from the inferior hypogastric plexus (p. 26) (Colleselli, 1998).

■ Pelvic Diaphragm

The pelvic diaphragm spans the pelvic outlet and lies deep to the urogenital and anal triangles (p. 17). This broad muscular floor provides substantial support to the pelvic viscera and is composed of the coccygeus and levator ani muscles (see Fig. 2-7). The levator ani muscle, in turn, contains the pubococcygeus, puborectalis, and iliococcygeus muscles. The pubococcygeus muscle is also termed the pubovisceral muscle and is subdivided based on points of insertion and function. These include the pubovaginalis, puboperinealis, and puboanalis muscles, which insert into the vagina, perineal body, and anus, respectively (Kearney, 2004).

Vaginal birth can damage the levator ani muscle or its innervation (DeLancey, 2003; Weidner, 2006). Evidence suggests that levator ani trauma may predispose women to later pelvic organ prolapse (Berger, 2018; Dietz, 2008). Current research efforts aim to minimize these injuries.

■ Anal Triangle

This triangle contains the anal canal, anal sphincter complex, and ischioanal fossae. The sphincter complex consists of the internal anal sphincter, external anal sphincter, and puborectalis muscle. The anal triangle also contains branches of the pudendal nerve and internal pudendal vessels.

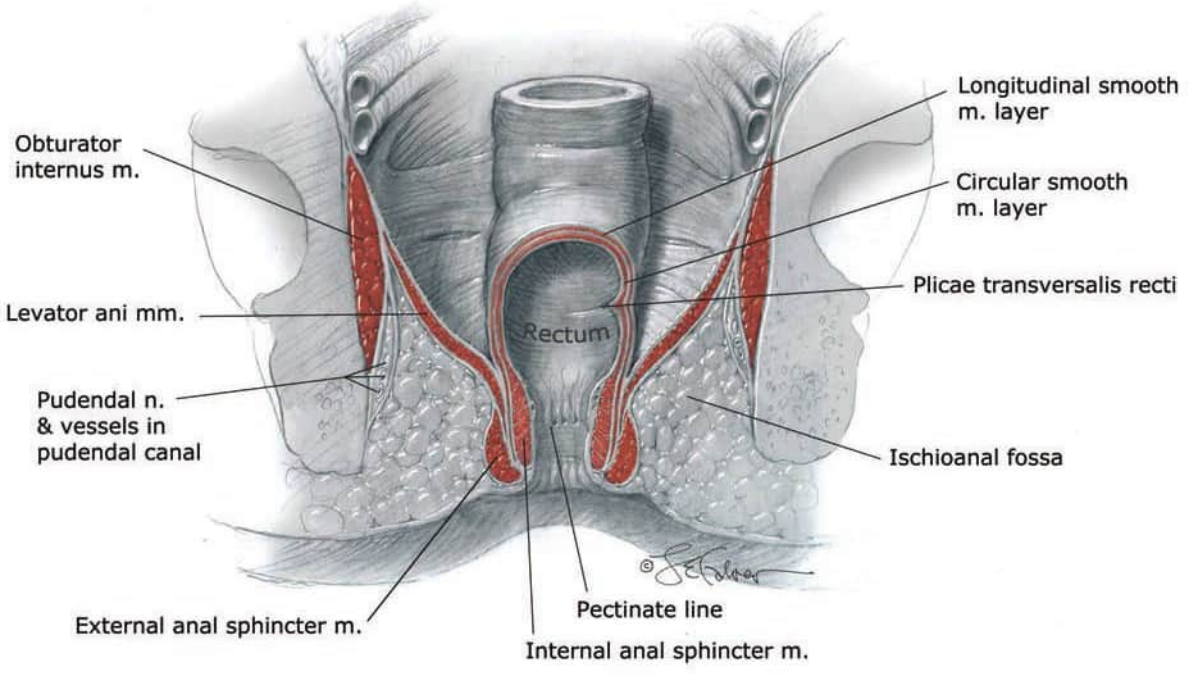


FIGURE 2-8 Anal canal and ischioanal fossa. (Modified with permission from Corton MM: Anatomy. In Hoffman BL, Schorge JO, Halvorson LM, et al (eds): Williams Gynecology, 4th ed. New York, NY: McGraw Hill; 2020.)

Anal Canal

This is the distal continuation of the rectum. Canal mucosa is a columnar epithelium proximally. However, at the pectinate line, also termed dentate line, simple stratified squamous epithelium begins and continues to the anal verge (Fig. 2-8). The anal verge is defined as the transition point at which a keratin layer and skin adnexa join the squamous epithelium. Two definitions describe anal canal boundaries. The *surgical* anal canal begins at the levator ani muscle, ends at the anal verge, and measures 4 cm. The *anatomical* anal canal lies between the pectineal line and anal verge and is 2 cm long (Nivatvongs, 1981).

The anal canal has several tissue layers. Inner layers include the anal mucosa, the internal anal sphincter, and an intersphincteric space that contains continuation of the rectum's longitudinal smooth muscle layer. An outer layer contains the external anal sphincter caudally and the puborectalis muscle cephalad.

Within the anal canal, three highly vascularized submucosal arteriovenous plexuses, termed anal cushions, aid complete closure of the canal and fecal continence when apposed. Increasing uterine size, excessive straining, and hard stool create raised pressure that ultimately leads to degeneration and subsequent laxity of the cushion's supportive connective tissue base. These cushions then protrude into and downward through the anal canal. This leads to venous engorgement within the cushions—now termed hemorrhoids. Venous stasis results in inflammation, erosion of the cushion's epithelium, and bleeding.

External hemorrhoids are those that arise distal to the pectinate line. They are covered by stratified squamous epithelium and receive sensory innervation from the inferior rectal nerve. Accordingly, pain and a palpable mass are typical complaints. Following resolution, a hemorrhoidal tag may remain and is composed of redundant anal skin and fibrotic tissue. In contrast, internal hemorrhoids are those that form above the pectinate line and are covered by insensitive anorectal mucosa. These may prolapse or bleed but rarely become painful unless they undergo thrombosis or necrosis.

Anal Sphincter Complex

Two sphincters surround the anal canal to provide fecal continence—the external and internal anal sphincters. Both lie near the vagina and may be torn during vaginal delivery. The internal anal sphincter (IAS) is a distal continuation of the rectal circular smooth muscle layer. It receives predominantly parasympathetic fibers, which pass through the pelvic splanchnic nerves. Along its length, this sphincter is supplied by the superior, middle, and inferior rectal arteries. The IAS contributes the bulk of anal canal resting pressure for fecal continence and relaxes prior to defecation. The IAS measures 3 to 4 cm in length, and at its distal margin, it overlaps the external sphincter for 1 to 2 cm (DeLancey, 1997). The distal site at which this overlap ends, called the intersphincteric groove, is palpable on digital examination. It is 2 to 3 mm thick (Rociu, 2000).

In contrast, the external anal sphincter (EAS) is a striated muscle ring that anteriorly attaches to the perineal body and posteriorly connects to the coccyx via the anococcygeal ligament. The EAS measures 1.5 to 2.5 cm deep and 6 to 15 mm thick (Fenner, 1998; Stewart, 2018). The EAS is considered to have one or more subdivisions, although the precise composition is disputed (Lee, 2018). Often, a surrounding fibrous capsule is described, but this most likely is perineal body rather than a true EAS sheath (Maldonado, 2020).

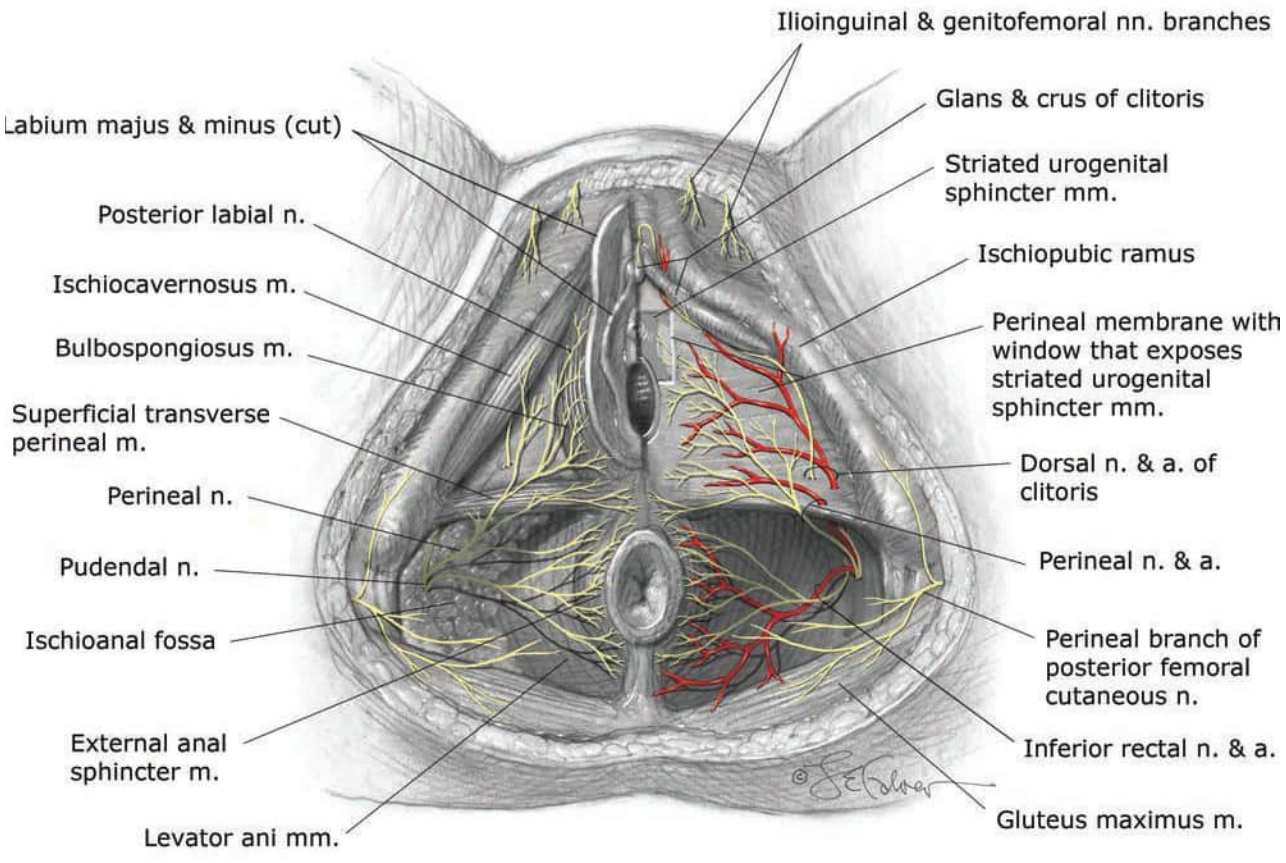


FIGURE 2-9 Branches of pudendal nerve and artery. (Modified with permission from Corton MM: Anatomy. In Hoffman BL, Schorge JO, Halvorson LM, et al (eds): Williams Gynecology, 4th ed. New York, NY: McGraw Hill; 2020.)

The EAS maintains a constant resting contraction to aid continence, provides additional squeeze pressure when continence is threatened, yet relaxes for defecation. The EAS receives blood supply from the inferior rectal artery, which is a branch of the internal pudendal artery. Somatic motor innervation derives from the inferior rectal branch of the pudendal nerve supply. Clinically, the IAS and EAS may be involved in third- and fourth-degree lacerations during vaginal delivery, and reunion of these rings is integral to defect repair (Chap. 27, p. 511).

Ischioanal Fossae

These two fat-filled wedge-shaped spaces are found on either side of the anal canal and constitute the bulk of the anal triangle (Figs. 2-8 and 2-9). Formerly known also as ischiorectal fossae, each fossa has skin as its superficial base, whereas its deep border is formed by the levator ani muscle. Other borders include: laterally, the obturator internus muscle and ischial tuberosity; medially, the anal sphincter complex and levator ani muscle; posteriorly, the gluteus maximus muscle and sacrotuberous ligament; and anteriorly, the inferior border of the urogenital triangle.

The fat found within each fossa provides support to surrounding organs yet allows rectal distention during defecation and vaginal stretching during delivery. Clinically, injury to vessels in the anal triangle can lead to hematoma formation in the ischioanal fossa. Moreover, the two fossae communicate posteriorly through the *deep postanal space*. This connection lies between the pelvic floor muscles and anococcygeal ligament (Llauger, 1998). As a result, episiotomy infection or hematoma may extend from one fossa into the other.

Pudendal Nerve

This is formed from the anterior rami of S_{2-4} spinal nerves. It courses between the piriformis and coccygeus muscles and exits through the greater sciatic foramen at a location posterior to the sacrospinous ligament and just medial to the ischial spine (Maldonado, 2015). Thus, when injecting local anesthetic for a pudendal nerve block, the ischial spine serves as an identifiable landmark (Chap. 25, p. 471). The pudendal nerve then runs beneath the sacrospinous ligament and above the sacrotuberous ligament as it reenters the lesser sciatic foramen to course across the obturator internus muscle. Atop this muscle, the nerve lies within the pudendal canal, also known as the Alcock canal. This space is formed by splitting of the obturator internus investing fascia (Shafik, 1999). In general, the pudendal nerve is relatively fixed as it courses behind the sacrospinous ligament and within the pudendal canal. Accordingly, it may be at risk of stretch injury during downward displacement of the pelvic floor during childbirth (Lien, 2005).

The pudendal nerve leaves this canal to enter the perineum and divides into three terminal branches (see Fig. 2-9). The first of these, the dorsal nerve of the clitoris, runs between the ischiocavernosus muscle and perineal membrane to supply the clitoral glans (Ginger, 2011b). Second, the perineal nerve runs superficial to the perineal membrane (Montoya, 2011). It divides into posterior labial branches and muscular branches, which serve the labial skin and the urogenital triangle muscles, respectively. Last, the inferior rectal branch runs through the ischioanal fossa to supply the external anal sphincter, the anal mucosa, and the perianal skin (Mahakkanukrauh, 2005).

The major blood supply to the perineum is from the internal pudendal artery, and its branches mirror the divisions of the pudendal nerve. Relevant to pudendal nerve blockade, the internal pudendal artery is the closest vascular structure, within 5 to 8 mm. It runs deep to the spine in most cases as it exits the greater sciatic foramen (Dueñas-Garcia, 2017; Roshanravan, 2007).

INTERNAL GENERATIVE ORGANS

Uterus

The nonpregnant uterus lies in the pelvic cavity between the bladder anteriorly and the rectum posteriorly. Anterior and posterior uterine walls are lined by serosa, that is, visceral peritoneum (Fig. 2-10). This peritoneum continues from the posterior wall to create the rectouterine space (see Fig. 2-5). It continues anteriorly to create the vesicouterine pouch. Clinically, during cesarean delivery, the peritoneum of the vesicouterine pouch is sharply incised, and the vesicocervical space is entered. This space is a well-defined loose connective tissue layer between the cervix and bladder (Balgobin, 2020). Dissection caudally within this space lifts the bladder safely off the cervix and lower uterine segment for hysterotomy and delivery (Chap. 30, p. 553).

The uterus is pear shaped and consists of two major but unequal parts. The upper, larger portion is the body or corpus, whereas the lower smaller cervix projects into the vagina. The isthmus is the union site of these two. It is of special obstetrical significance because it forms the lower uterine segment during pregnancy. At each superolateral margin of the body is a uterine cornu, from which a fallopian tube emerges. This area also contains the origins of the round and uteroovarian ligaments. Between the points of fallopian tube insertion is the convex upper uterine segment termed the fundus.

The bulk of the uterine body, but not the cervix, is muscle. The inner surfaces of the uterine walls lie almost in contact, and the intervening cavity forms a mere slit. The nulligravid uterus measures 6 to 8 cm in length compared with 9 to 10 cm in multiparas. The uterus averages 60 g and typically weighs more in parous women (Langlois, 1970; Sheikhazadi, 2010).

Pregnancy stimulates remarkable uterine growth due to muscle fiber hypertrophy. The uterine fundus, a previously flattened

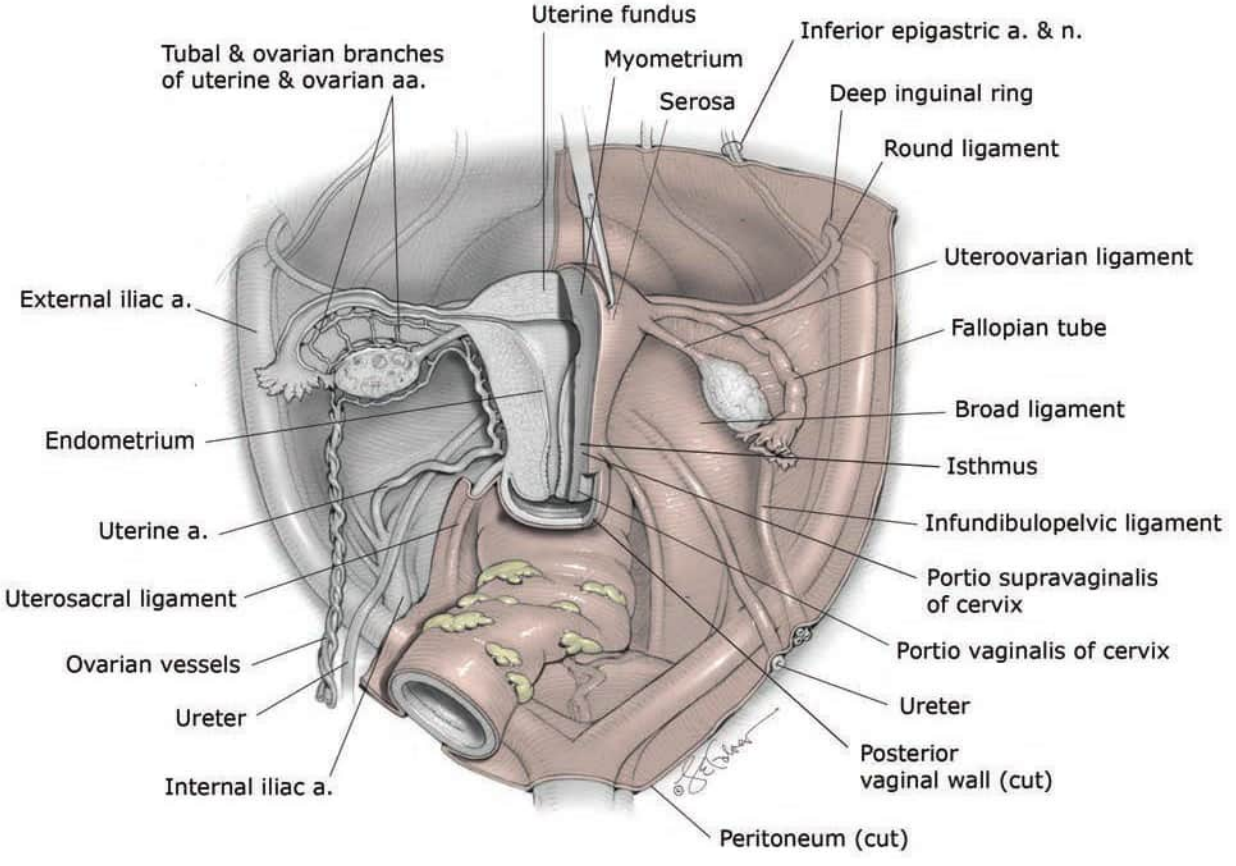


FIGURE 2-10 Uterus, adnexa, and associated anatomy. (Modified with permission from Corton MM: Anatomy. In Hoffman BL, Schorge JO, Halvorson LM, et al (eds): Williams Gynecology, 4th ed. New York, NY: McGraw Hill; 2020.)

convexity between tubal insertions, now becomes dome shaped. Moreover, the round ligaments appear to insert at the junction of the middle and upper thirds of the organ. The fallopian tubes elongate, but the ovaries grossly appear unchanged.

Cervix

This portion of the uterus is cylindrical and has small apertures at each end—the internal os and external os. The endocervical canal runs through the cervix and connects these ora. The cervix is divided into upper and lower portions by the vagina's attachment to its outer surface. The upper portion—the *portio supravaginalis*—begins at the internal os, which corresponds to the level of the vesicouterine peritoneum (see Figs. 2-5 and 2-10). The lower cervical portion protrudes into the vagina as the *portio vaginalis*.

Before childbirth, the external cervical os is a small, regular, oval opening. After labor, especially vaginal childbirth, the orifice is converted into a transverse slit that is divided such that there are the so-called anterior and posterior cervical lips. If torn deeply during labor or delivery, the cervix may heal in such a manner that it appears irregular, nodular, or stellate (Fig. 36-1, p. 635).

The cervical surface that radially surrounds the external os is called the ectocervix and is lined predominantly by nonkeratinized stratified squamous epithelium. In contrast, the endocervical canal is covered by a single layer of mucin-secreting columnar epithelium, which creates deep cleftlike infoldings or "glands." Commonly during pregnancy, the endocervical epithelium moves out and onto the ectocervix in a physiological process termed eversion (Chap. 4, p. 53).

The cervical stroma is composed mainly of collagen, elastin, and proteoglycans, but very little smooth muscle. As described in Chapter 21 (p. 406), changes in the amount, composition, and orientation of these components lead to cervical ripening prior to labor. In early pregnancy, increased vascularity within the cervix stroma beneath the epithelium creates an ectocervical blue tint that is characteristic of the Chadwick sign. Cervical edema leads to softening—the Goodell sign, whereas isthmic softening is the Hegar sign.

Myometrium and Endometrium

Most of the uterus is composed of myometrium, which contains smooth muscle bundles united by connective tissue with many elastic fibers. Interlacing myometrial fibers surround myometrial vessels and contract to compress these. This anatomy allows hemostasis at the placental site during third-stage labor.

The uterine cavity is lined with endometrium, which is composed of an overlying epithelium, invaginating glands, and a supportive, vascular stroma. Throughout the menstrual cycle, the endometrium varies greatly (Chap. 5, p. 83). It is divided into a functionalis layer, which is sloughed with menses, and a basalis layer, which serves to regenerate the functionalis layer following each menses. During pregnancy, the endometrium undergoes dramatic hormonally driven alterations and is termed decidua.

Ligaments

Several ligaments extend from the uterine surface toward the pelvic sidewalls and include the round, broad, cardinal, and uterosacral ligaments (see Fig. 2-10). Despite their appellation, the round and broad ligaments provide no substantial uterine support, which contrasts with the cardinal and uterosacral ligaments.

The round ligament originates somewhat below and anterior to the origin of the fallopian tubes. Clinically, this orientation can aid tube identification during puerperal sterilization (Chap. 39, p. 682). Each round ligament extends laterally and down into the inguinal canal, through which it passes, to terminate in the upper portion of the ipsilateral labium majus. The *artery to the round ligament*, formerly the Sampson artery, is a small branch of the uterine artery and runs within the ligament. In nonpregnant women, the round ligament varies from 3 to 5 mm in diameter and is composed of smooth muscle bundles separated by fibrous tissue septa (Mahran, 1965). During pregnancy, these ligaments hypertrophy and increase appreciably in both length and diameter. Rare, round ligament varicosities can mimic an inguinal hernia, and color Doppler interrogation of the mass aids diagnosis (Yonggang, 2017).

The broad ligaments are two winglike structures that extend from the lateral uterine margins to the pelvic sidewalls. Each broad ligament consists of a double-layer drape of peritoneum. The anterior and posterior layers of this drape are termed the anterior and posterior leaves, respectively. In forming the broad ligament, this peritoneum folds over structures extending from each cornu. Peritoneum that folds over the fallopian tube is termed the mesosalpinx, that around the round ligament is the mesoteres, and that over the ovarian ligament is the mesovarium. Peritoneum that extends beneath the fimbriated end of the uterine tube toward the pelvic wall forms infundibulopelvic ligament, which is also the *suspensory ligament of the ovary*. This contains nerves and the ovarian vessels, and during pregnancy, these vessels, especially the venous plexuses, are dramatically enlarged. Specifically, the diameter of the ovarian vascular pedicle increases from 0.9 cm to reach 2.6 cm at term (Hodgkinson, 1953).

The cardinal ligament—formerly the transverse cervical ligament or the Mackenrodt ligament—anchors medially to the uterus and upper vagina. The cardinal ligament is the thick base of the broad ligament. As such, during cesarean hysterectomy, sturdy clamps and suture are required for its transection and ligation.

Each uterosacral ligament originates with a posterolateral attachment to the supravaginal portion of the cervix and inserts into the fascia over the sacrum, with some variations (Ramanah, 2012; Umek, 2004). These ligaments are composed of connective tissue, small neurovascular bundles, and some smooth muscle. Covered by peritoneum, these ligaments form the lateral boundaries of the rectouterine space.

The term parametrium describes the connective tissues adjacent and lateral to the uterus within the broad ligament. Paracervical tissues are those adjacent to the cervix, whereas paracolpium is tissue lateral to the vaginal walls.

Pelvic Blood Supply

During pregnancy, uterine vasculature, which is supplied principally from the uterine and ovarian arteries, markedly hypertrophies (see Fig. 2-10). The uterine artery is a main branch of

the internal iliac artery (prior hypogastric artery) and enters the base of the broad ligament. From its origin, the uterine artery courses medially to the lateral side of the uterus. Approximately 2 cm lateral to the cervix, the uterine artery crosses over the ureter. This proximity is important surgically, as the ureter may be injured or ligated during hysterectomy when the uterine vessels are clamped and ligated.

Once the uterine artery reaches the cervix, it divides. The smaller cervicovaginal artery supplies blood to the lower cervix and upper vagina. Instead, the main uterine artery branch turns abruptly upward and travels cephalad along the lateral margin of the uterus. Along this path, the uterine artery gives rise to the arcuate arteries. Indicated by the name, each branch arches across either the anterior or posterior uterine wall and courses within the myometrium just beneath the serosal surface. Arcuate vessels from each side anastomose at the uterine midline. From the arcuate arteries, radial arteries originate at right angles and travel inward through the myometrium. Upon entering the endometrium/decidua, they branch to become either basal arteries or spiral arteries. The coiled spiral arteries supply the functionalis layer. The basal arteries, also called the straight arteries, extend only into the basalis layer.

As the uterine artery courses cephalad, it gives rise to the artery of the round ligament. At the each cornu, the uterine artery divides into three terminal branches. First, the tubal branch makes its way through the mesosalpinx and supplies part of the fallopian tube; whereas the fundal branch penetrates the uppermost uterus. Third, the ovarian branch of the uterine artery forms an anastomosis with the terminal branch of the ovarian artery.

The ovarian artery is a direct branch of the aorta and enters the broad ligament through the infundibulopelvic ligament. At the ovarian hilum, it divides into smaller branches that enter the ovary. As the ovarian artery runs along the hilum, it also sends several branches through the mesosalpinx to supply the fallopian tubes. Its main stem, however, traverses the entire length of the broad ligament toward the uterine cornu. Here, it forms an anastomosis with the ovarian branch of the uterine artery. This dual uterine blood supply creates a vascular reserve to prevent uterine ischemia if ligation of the uterine or internal iliac artery is performed to control postpartum hemorrhage.

Uterine veins accompany their respective arteries. As such, the arcuate veins unite to form the uterine vein, which empties into the internal iliac vein and then the common iliac vein. Some of the blood from the upper uterus, the ovary, and the upper part of the broad ligament is collected by several veins. These terminate in the ovarian vein. From here, the right ovarian vein empties into the vena cava. The left ovarian vein empties into the left renal vein.

Blood supply to the pelvis is predominantly provided by branches of the internal iliac artery (Fig. 2-11). These branches

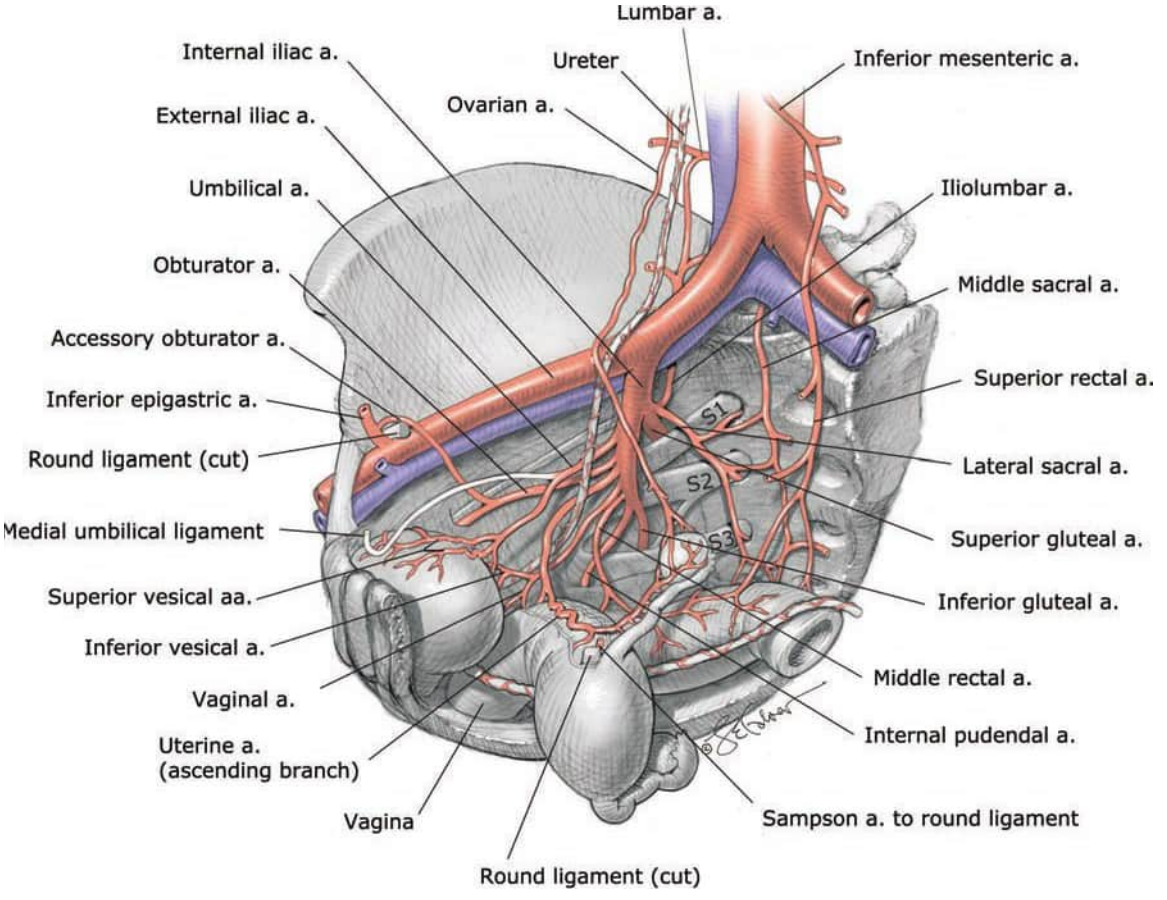


FIGURE 2-11 Pelvic arteries. (Modified with permission from Corton MM: Anatomy. In Hoffman BL, Schorge JO, Halvorson LM, et al (eds): Williams Gynecology, 4th ed. New York, NY: McGraw Hill; 2020.)

are organized into anterior and posterior divisions, and subsequent branches are highly variable between individuals. The anterior division provides blood supply to the pelvic organs and perineum and includes the inferior gluteal, internal pudendal, middle rectal, vaginal, uterine, and obturator arteries, as well as the umbilical artery and its continuation as the superior vesical artery. The posterior division branches extend to the buttock and thigh and include the superior gluteal, lateral sacral, and iliolumbar arteries. For this reason, during internal iliac artery ligation, many advocate ligation distal to the posterior division to avoid compromise to the areas supplied by this division (Bleich, 2007).

Pelvic Lymphatics

The lymphatic vessels from the uterine corpus generally empty into two nodal groups. Those from the cervix and lower uterine segment travel to the pelvic lymph nodes, which then drain into the paraaortic nodes. Vessels from the fundus, after joining lymphatics from the adnexa, directly terminate in the paraaortic lymph nodes. Vaginal lymphatic channels have extensive anastomoses. As a result, any node in the pelvis, groin, or anorectal area may drain any part of the vagina. Lymphatics of the vulva and distal vagina typically empty into the superficial inguinal nodal group. From here, lymph travels through the deep femoral lymphatics to the pelvic nodal groups.

Pelvic Innervation

As a brief review, the peripheral nervous system is divided into a somatic division, which innervates skeletal muscle, and an autonomic division, which innervates smooth muscle, cardiac muscle, and glands. Pelvic visceral innervation is predominantly autonomic, which is further divided into sympathetic and parasympathetic components.

Sympathetic innervation to pelvic viscera begins with the *superior hypogastric plexus*, also termed the presacral nerve (Fig. 2-12). This plexus is formed by sympathetic fibers arising from spinal levels T_{10} through L_2. At the level of the sacral promontory, the superior hypogastric plexus divides into a *right* and a *left hypogastric nerve*, which run downward along their respective pelvic sidewalls (Ripperda, 2017).

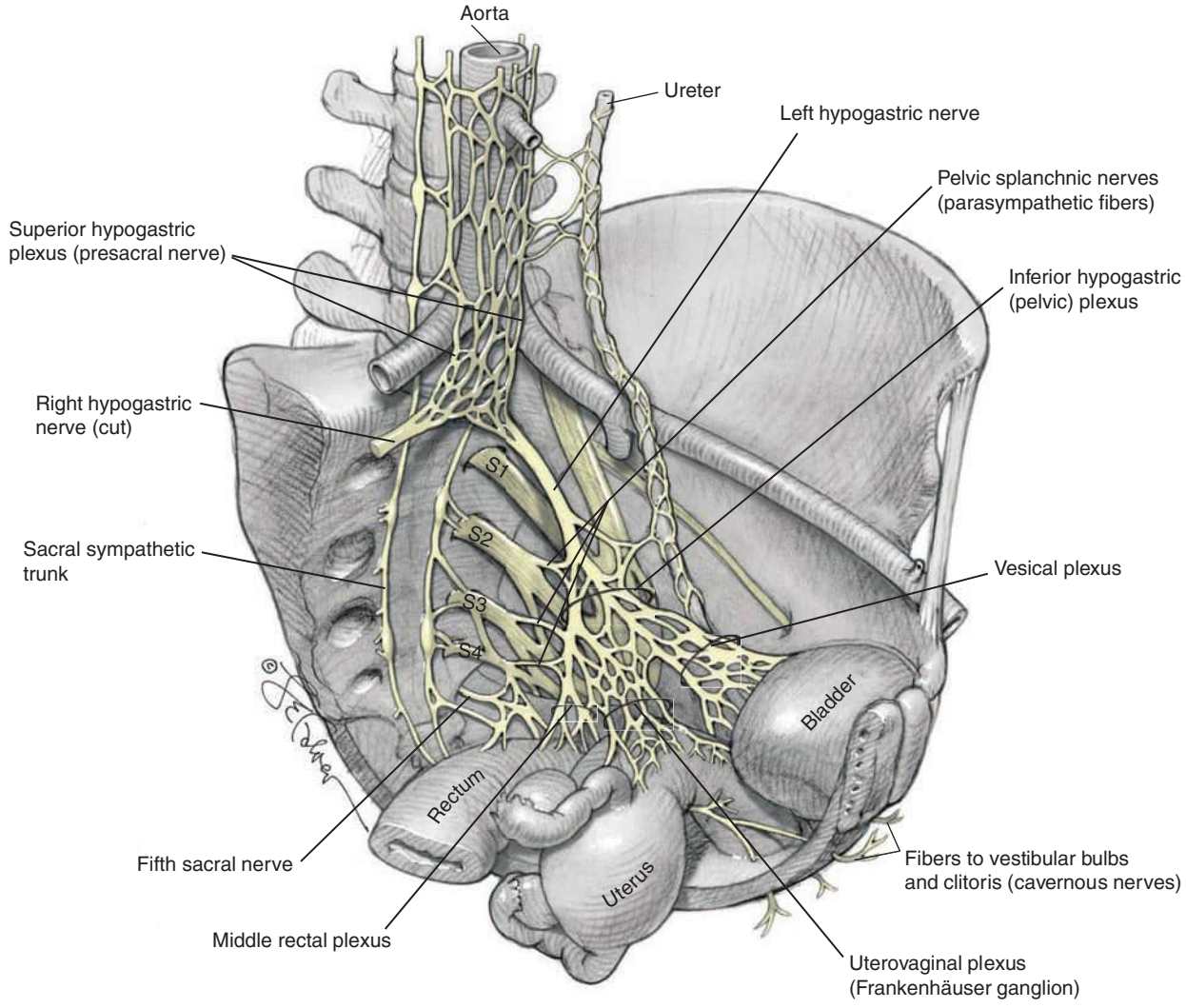


FIGURE 2-12 Pelvic innervation. (Modified with permission from Corton MM: Anatomy. In Hoffman BL, Schorge JO, Halvorson LM, et al (eds): Williams Gynecology, 4th ed. New York, NY: McGraw Hill; 2020.)

In contrast, parasympathetic innervation to the pelvic organs derives from spinal levels S_2 through S_4. Anterior rami of the spinal nerves for those levels combine on each side to form the *pelvic splanchnic nerves*, also termed nervi erigentes.

Blending of the two hypogastric nerves (sympathetic) and the two pelvic splanchnic nerves (parasympathetic) gives rise to the *inferior hypogastric plexus*, also termed the pelvic plexus. From here, fibers of this plexus extend to the bladder, uterus, upper vagina, and rectum (Ripperda, 2017; Spackman, 2007). Extensions of the inferior hypogastric plexus also reach the perineum to innervate the clitoris and vestibular bulbs (Montoya, 2011).

For the uterus, most of its afferent sensory fibers ascend through the inferior hypogastric plexus and enter the spinal cord via T_{10} through T_{12} and L_1 spinal nerves. These transmit the painful stimuli of contractions to the central nervous system. For the cervix and upper part of the birth canal, sensory nerves pass through the pelvic splanchnic nerves to the second, third, and fourth sacral nerves. Last, those from the lower portion of the birth canal pass primarily through the pudendal nerve. Anesthetic blocks used during delivery target these levels of innervation.

Ovaries

Along the pelvic sidewall, each ovary usually rests in the ovarian fossa, which is a slight depression between the external and internal iliac vessels. During childbearing years, ovaries variably measure 2.5 to 5 cm in length, 1.5 to 3 cm in width, and 0.6 to 1.5 cm in thickness.

The ovarian ligament, also called the uteroovarian ligament, originates from the posterolateral uterine cornu and extends to the uterine pole of the ovary (see Fig. 2-10). Measuring a few centimeters long and 3 to 4 mm in diameter, this ligament is made up of muscle and connective tissue and is covered by peritoneum—the mesovarium. Blood supply reaches the ovary through the mesovarium to enter the ovarian hilum.

The ovary consists of an outer cortex and inner medulla. In young women, the cortex is smooth, white, and lined by a single layer of cuboidal epithelium. This epithelium is supported by an inner connective tissue condensation, the tunica albuginea. Beneath this, the ovarian cortex contains oocytes and developing follicles. The medulla is composed of loose connective tissue, numerous arteries and veins, and a small amount of smooth muscle.

The ovaries are supplied with both sympathetic and parasympathetic nerves. The sympathetic nerves are derived primarily from the ovarian plexus that accompanies the ovarian vessels and originates in the renal plexus. Others derive from the plexus that surrounds the ovarian branch of the uterine artery. Parasympathetic input is from the vagus nerve. Sensory afferents follow the ovarian artery and enter at T_{10} spinal cord level.

Fallopian Tubes

Each of these serpentine tubes extend laterally 8 to 14 cm from their respective uterine cornu. Along their length, they contain an interstitial portion, isthmus, ampulla, and infundibulum (Fig. 2-13). Most proximal, the interstitial portion is embodied within the uterine muscular wall. Next, the narrow 2- to 3-mm wide isthmus widens gradually into the 5- to 8-mm wide ampulla. Last, the infundibulum is the funnel-shaped fimbriated distal extremity of the tube, which opens into the abdominal cavity. These latter three extrauterine portions are covered by the mesosalpinx, which is a superior extension of the broad ligament and described next.

In cross section, the uterine tube contains a mesosalpinx, myosalpinx, and endosalpinx. The outer of these, the mesosalpinx, is a single-cell mesothelial layer functioning as visceral peritoneum. In the myosalpinx, smooth muscle is arranged in an inner circular and an outer longitudinal layer. The tubal musculature undergoes rhythmic contractions constantly, the rate of which varies with cyclical ovarian hormonal changes.

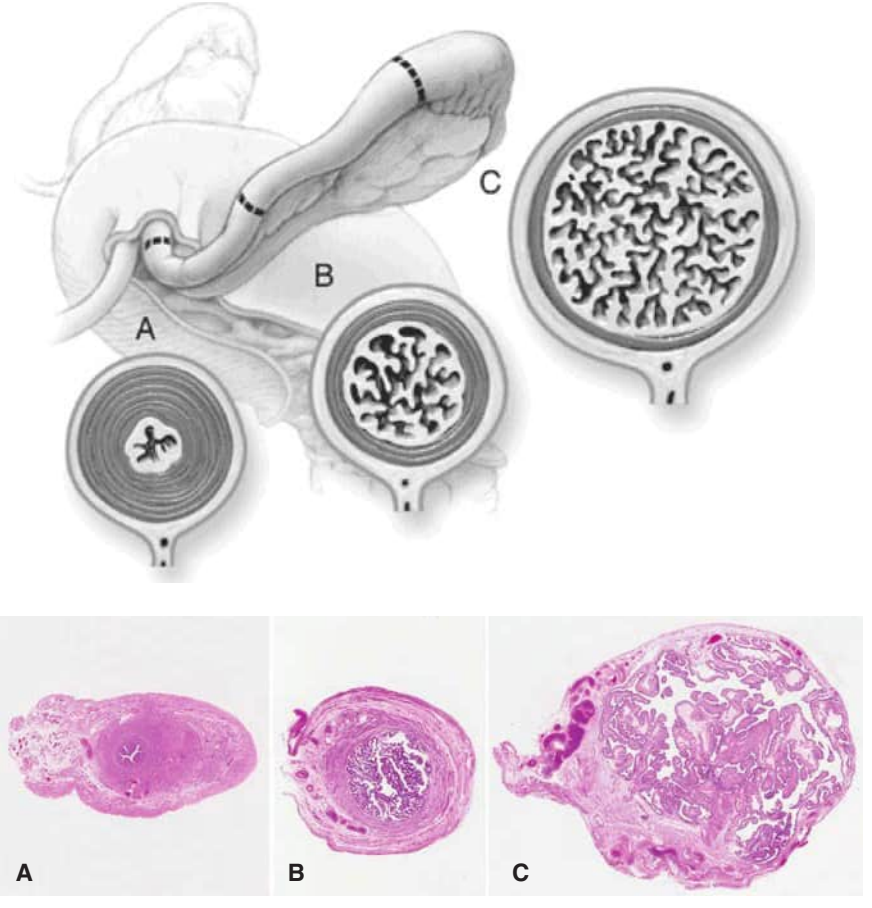


FIGURE 2-13 The fallopian tube of an adult woman with cross-sectioned illustrations of the gross structure in several portions: **(A)** isthmus, **(B)** ampulla, and **(C)** infundibulum. Below these are photographs of corresponding histological sections. (Reproduced with permission from Dr. Kelley S. Carrick.)

The *endosalpinx* (tubal mucosa) is a single layer of columnar epithelium made up of ciliated, secretory, and intercalary cells resting on a sparse lamina propria. Clinically, its close proximity to the underlying myosalpinx contributes to easy invasion by ectopic trophoblast. The tubal mucosa is arranged in longitudinal folds that become progressively more complex toward the fimbria. In the ampulla, the lumen is occupied almost completely by the arborescent mucosa. The current produced by the tubal cilia flows toward the uterine cavity. Tubal peristalsis created by cilia and muscular layer contraction aids ovum transport (Croxatto, 2002).

The tubes are supplied richly with elastic tissue, blood vessels, and lymphatics. Their sympathetic innervation is extensive, in contrast to their parasympathetic innervation. This nerve supply derives partly from the ovarian plexus and partly from the inferior hypogastric plexus. Sensory afferent fibers ascend to T_{10} spinal cord levels.

LOWER URINARY TRACT

Bladder

Anteriorly, the bladder rests against the inner surface of the pubic bones and then, as it fills, also against the anterior abdominal wall. Posteriorly, it rests against the vagina and cervix. The bladder is divided into a dome and a base approximately at the level of the ureteral orifices. The dome is thin walled and distensible, whereas the base is thicker and undergoes less distention during filling. The vesical trigone lies in the bladder base and contains both ureteral orifices and the internal urinary meatus. The urethral lumen begins at this meatus and then courses through the bladder base for less than 1 cm. This region where the urethral lumen traverses the bladder base is the bladder neck.

The bladder wall consists of coarse bundles of smooth muscle known as the detrusor muscle, which extends into the proximal part of the urethra. A submucosal layer intervenes between this detrusor muscle and the mucosa. The bladder mucosa consists of transitional epithelium and underlying lamina propria.

The blood supply to the bladder arises from the superior vesical arteries, which are branches of the patent portion of the umbilical artery and supply the dome (see Fig. 2-11). The inferior vesical arteries supply the base and variably arise from either the umbilical, uterine, or vaginal artery (de Treigny, 2017). The nerve supply to the bladder arises from the inferior hypogastric plexus (see Fig. 2-12).

Ureter

As the ureter enters the pelvis, it crosses over the bifurcation of the common iliac artery and passes just medial to the ovarian vessels (see Fig. 2-10). As the ureter descends into the pelvis, it lies medial to the internal iliac branches and anterolateral to the uterosacral ligaments. The ureter then traverses through the cardinal ligament approximately 1 to 2 cm lateral to the cervix. Near the level of the uterine isthmus, it courses below the uterine artery and travels anteromedially toward the bladder base. In this path, it runs close to the upper third of the anterior vaginal wall (Jackson, 2019; Rahn, 2007). Finally, the ureter enters the bladder and travels obliquely for approximately 1.5 cm before opening at the ureteral orifices.

The pelvic ureter receives blood supply from the vessels it passes: the common iliac, internal iliac, uterine, and superior vesical vessels. The ureter's course runs medial to these vessels, and thus its blood supply reaches the ureter from lateral sources. This is important during ureteral isolation. Vascular anastomoses on the connective tissue sheath enveloping the ureter form a longitudinal network of vessels.

PELVIC SKELETAL ANATOMY

Pelvic Bones and Joints

The pelvis is composed of four bones—the sacrum, coccyx, and two innominate bones. Each innominate bone is formed by the fusion of three bones—the ilium, ischium, and pubis (Fig. 2-14). Both innominate bones are joined to the sacrum at the sacroiliac joint. Anteriorly, they are joined at the symphysis pubis. This consists of fibrocartilage and the superior and inferior pubic ligaments. The latter ligament is frequently designated the *arcuate ligament of the pubis*.

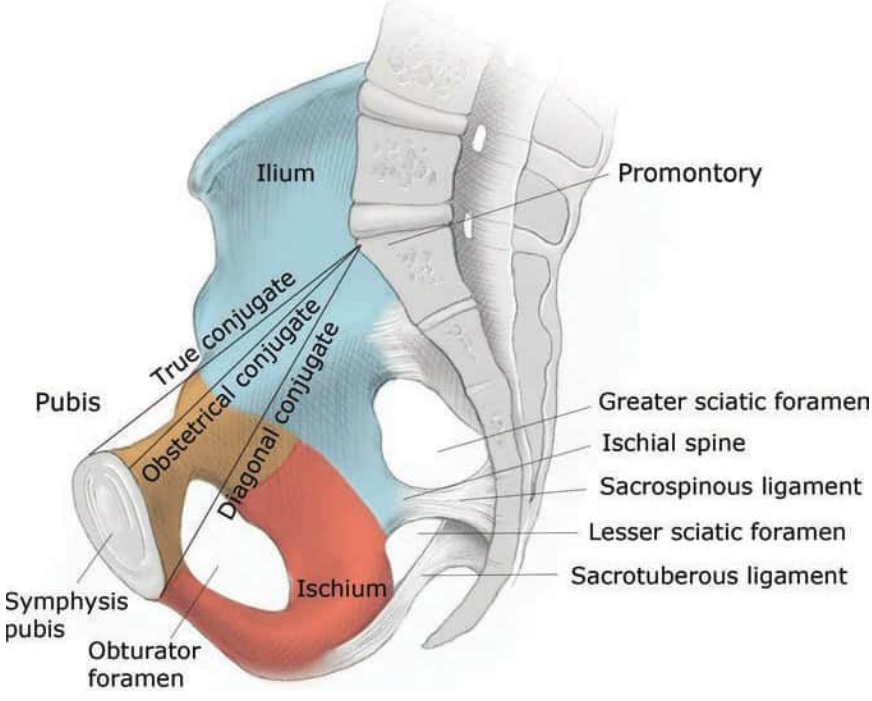


FIGURE 2-14 The innominate bone is composed of the pubis (*brown*), ischium (*red*), and ilium (*blue*). Of the three anteroposterior diameters of the pelvic inlet, only the diagonal conjugate can be measured clinically. The important obstetrical conjugate is derived by subtracting 1.5 cm from the diagonal conjugate.

These pelvic joints have a limited degree of mobility but can relax remarkably during pregnancy. For example, at term, the sacroiliac joint can glide upward. This is greatest in dorsal lithotomy position and may increase the diameter of the outlet by 1.5 to 2.0 cm for delivery (Borell, 1957). Sacroiliac joint mobility also likely aids the McRoberts maneuver to release an obstructed shoulder in cases of shoulder dystocia (Chap. 27, p. 502). These changes may also contribute to the success of the modified squatting position to hasten second-stage labor (Gardosi, 1989). Squatting may increase the interspinous diameter and the pelvic outlet diameter (Russell, 1969, 1982).

Planes and Diameters of the Pelvis

The pelvis is conceptually divided into false and true components. The false pelvis lies above the linea terminalis, and the true pelvis is below this boundary (Fig. 2-15). The false pelvis is bounded posteriorly by the lumbar vertebra and laterally by the iliac fossa. In front, the boundary is formed by the lower portion of the anterior abdominal wall.

The true pelvis is described by four imaginary planes:

1. The plane of the pelvic inlet—the superior strait.
2. The plane of the pelvic outlet—the inferior strait.
3. The plane of the midpelvis—the least pelvic dimensions.
4. The plane of greatest pelvic dimension—of no obstetrical significance.

Pelvic Inlet

The pelvic inlet is bounded posteriorly by the promontory, laterally by the linea terminalis, and anteriorly by the horizontal pubic rami and the symphysis pubis. During labor, fetal head engagement is defined by the fetal head's biparietal diameter passing through this plane.

Four diameters of the pelvic inlet are usually described: anteroposterior, transverse, and two oblique diameters. Of these, distinct anteroposterior diameters have been described using specific landmarks. Most cephalad, the anteroposterior diameter, termed the *true conjugate*, extends from the uppermost margin of the symphysis pubis to the sacral promontory (see Fig. 2-14). The clinically important *obstetrical conjugate* is the shortest, and thus the most limiting, distance between the sacral promontory and the symphysis pubis. Normally, this measures 10 cm or more, but unfortunately, it cannot be measured directly with examining fingers. Thus, the obstetrical conjugate is estimated indirectly by subtracting 1.5 to 2 cm from the *diagonal conjugate*. To measure the diagonal conjugate, a hand with the palm oriented laterally extends its index finger to the promontory. The distance from the fingertip to the point at which the lowest margin of the symphysis strikes the same finger's base is the diagonal conjugate.

The transverse diameter is constructed at right angles to the obstetrical conjugate and represents the greatest distance between the linea terminalis on either side (see Fig. 2-15). It usually intersects the obstetrical conjugate at a point approximately 5 cm in front of the promontory and measures approximately 13 cm.

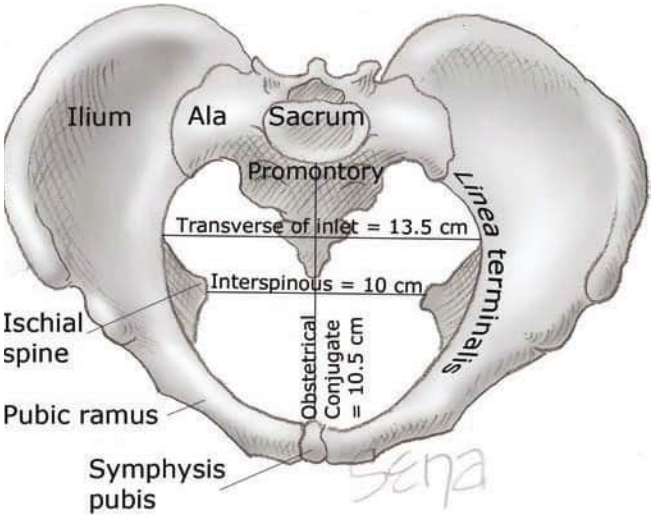


FIGURE 2-15 Axial view of a normal female pelvis. The clinically important obstetrical conjugate and transverse diameter of the pelvic inlet are illustrated. The interspinous diameter of the midpelvis also is marked.

Midpelvis and Pelvic Outlet

The midpelvis is measured at the level of the ischial spines, also called the midplane or plane of least pelvic dimensions (see Fig. 2-15). During labor, the degree of fetal head descent into the true pelvis may be described by station, and the midpelvis and ischial spines serve to mark zero station. The interspinous diameter is 10 cm or slightly greater and is usually the smallest overall pelvic diameter. The anteroposterior diameter through the level of the ischial spines normally measures at least 11.5 cm.

The pelvic outlet consists of two approximately triangular areas whose boundaries mirror those of the perineum described earlier (p. 14). They have a common base, which is a line drawn between the two ischial tuberosities. The apex of the posterior triangle is the tip of the sacrum, and the lateral boundaries are the sacrotuberous ligaments and the ischial tuberosities. The anterior triangle is formed by the descending inferior rami of the pubic bones. These rami unite at an angle of 90 to 100 degrees to form a rounded arch under which the fetal head must pass. Unless there is significant pelvic bony disease, the pelvic outlet seldom obstructs vaginal delivery.

Pelvic Shapes

The Caldwell–Moloy (1933, 1934) anatomical classification of the pelvis is based on shape, and its concepts aid an understanding of labor mechanisms. Specifically, the greatest transverse diameter of the inlet and its division into anterior and posterior segments are used to classify the pelvis as gynecoid, anthropoid, android, or platypelloid. The posterior segment determines the type of pelvis, whereas the anterior segment determines the tendency. These are both determined because many pelves are not pure but are mixed types. For example, a gynecoid pelvis with an android tendency means that the posterior pelvis is gynecoid and the anterior pelvis is android shaped.

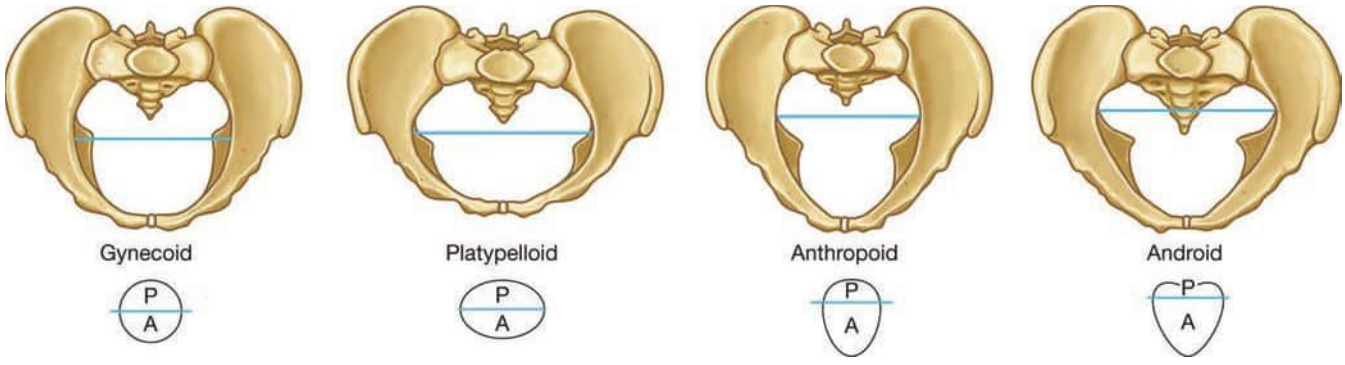


FIGURE 2-16 The four parent pelvic types of the Caldwell–Moloy classification are shown by anatomic and schematic drawings. In each, the blue line passes through the widest transverse diameter and divides the pelvic inlets into posterior (P) and anterior (A) segments. Mixed types are formed by combining anterior and posterior inlet segments from different parent types.

From viewing the four basic types in Figure 2-16, the configuration of the gynecoid pelvis would intuitively seem suited for delivery of most fetuses. Indeed, Caldwell (1939) reported that the gynecoid pelvis was found in almost half of women.

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CHAPTER 3

Congenital Genitourinary Abnormalities

In females, the external genitalia, gonads, and müllerian ducts each derive from different primordia and in close association with the urinary tract and hindgut. Abnormal embryogenesis can lead to reproductive organs that predispose to infertility, subfertility, miscarriage, or preterm delivery.

GENITOURINARY TRACT DEVELOPMENT

Urinary System

Between the 3rd and 5th gestational weeks, an elevation of intermediate mesoderm on each side of the fetus begins to develop into the urogenital tract. This *urogenital ridge* divides into the *genital ridge*, destined to become the gonads, and into the *nephrogenic ridge* (Fig. 3-1). Each nephrogenic ridge produces a mesonephros (mesonephric kidney). Recall that evolution of the renal system passes sequentially from the mesonephric stage to reach the permanent metanephric system (de Bakker, 2019; Upadhyay, 2014). Each nephrogenic ridge also gives rise to a mesonephric duct, also termed wolffian duct, and to a paramesonephric duct, also called müllerian duct.

The early urinary tract develops from the mesonephric ducts (Fig. 3-2A). Between the 4th and 5th weeks, each mesonephric duct gives rise to a ureteric bud, which grows cephalad (Fig. 3-2B). As each bud lengthens, it induces differentiation of the metanephros, which will become the final kidney (Fig. 3-2C) (Davidson, 2019). The metanephros ascends to its final position by the 9th week because of disproportionate growth of the embryo's caudal region (Jain, 2018). Each ureteric bud also gives rise to an elongation that becomes the metanephric duct or future ureter.

The cloaca begins as a common opening for the embryonic urinary, genital, and alimentary tracts (Gupta, 2014). By the 7th week, it is divided by the urorectal septum to create the hindgut and the urogenital sinus (Fig. 3-2D) (Valentini, 2016). The urogenital sinus is considered in three parts: (1) the cephalad or vesicle portion, which forms the urinary bladder; (2) the middle or pelvic portion, which creates the female urethra; and (3) the caudal or phallic part, which gives rise to the distal vagina and to the greater vestibular (Bartholin) and paraurethral glands.

Near the end of the first trimester, each mesonephros degenerates, and without testosterone, the mesonephric ducts regress as well. The ureterovesical junction forms from incorporation of the metanephric ducts into the bladder at the trigone. Abnormalities of this process lead to obstruction and vesicoureteral reflux (Liaw, 2018).

Genital Tract

The fallopian tubes, uterus, and upper vagina derive from the müllerian ducts (see Fig. 3-2B). Linear spatial development of these organs along the duct length is guided by several genes and notably by *Hox* genes (Du, 2004; Jacquinet, 2016). These ducts extend downward and then turn medially to meet and

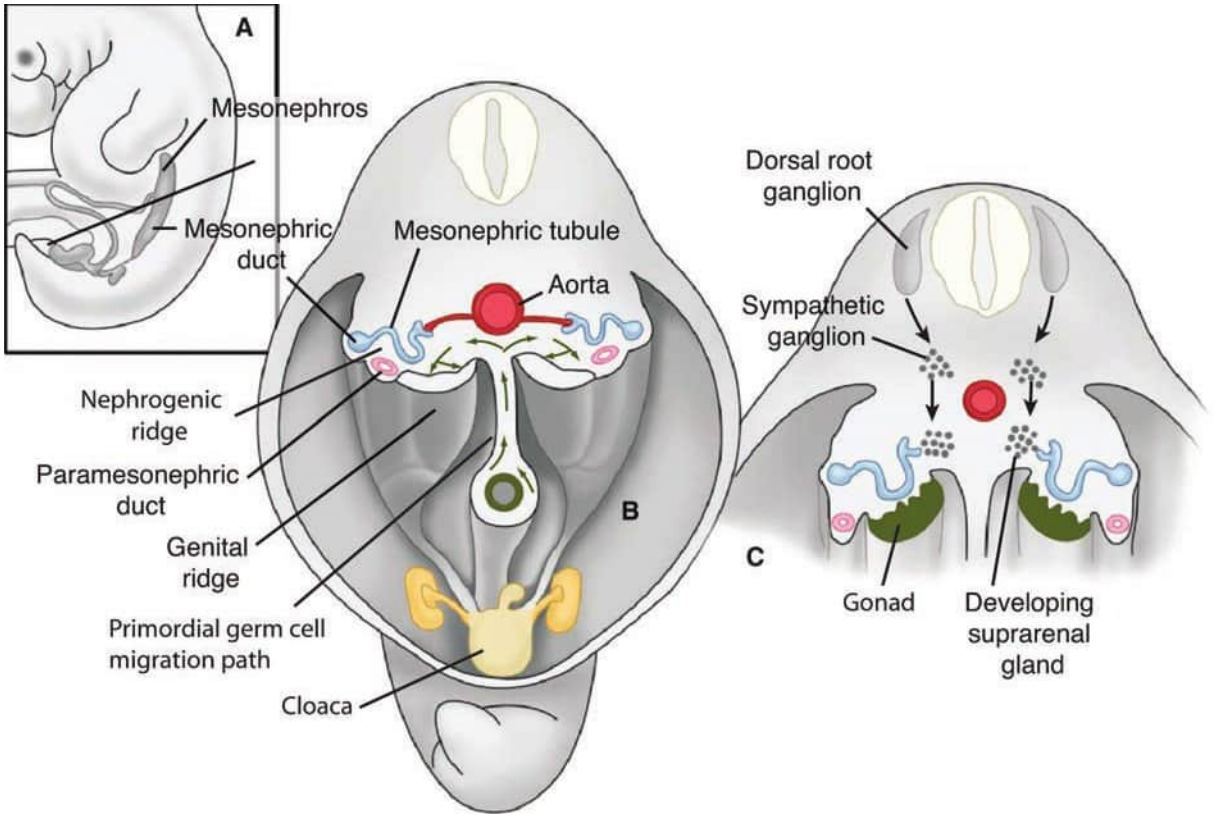

FIGURE 3-1 **A.** Cross-section of an embryo at 4 to 6 weeks. **B.** Primordial germ cells migrate (*arrows*) from the yolk sac to the area of germinal epithelium, within the genital ridge. **C.** Development of gonad. Also, migration of sympathetic cells from the spinal ganglia to a region above the developing kidney.

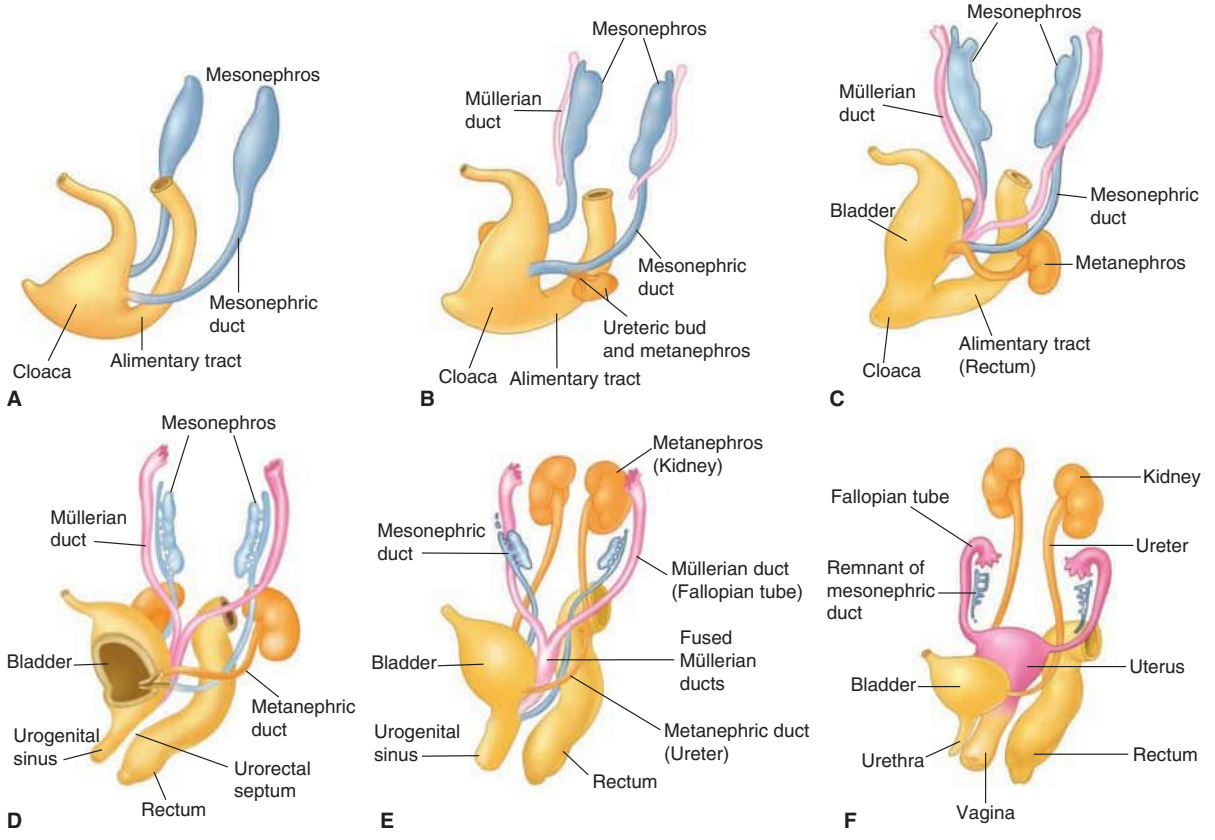

FIGURE 3-2 Embryonic development of the female genitourinary tract **(A–F)**. (Reproduced with permission from Shatzkes DR, Haller JO, Velcek FT: Imaging of uterovaginal anomalies in the pediatric patient, Urol Radiol 1991;13(1):58–66.)

fuse together in the midline. The uterus is formed by this union of the two müllerian ducts at approximately the 10th week (Fig. 3-2E) (Spencer, 2012). Fusion to create the uterus begins in the middle and then extends both caudally and cephalad. With cellular proliferation at the upper portion, a thick wedge of tissue creates the characteristic piriform uterine shape. At the same time, dissolution of cells at the lower pole forms the first uterine cavity (Fig. 3-2F). As the upper wedge-shaped septum is slowly reabsorbed, the final uterine cavity is usually formed by the 20th week (Toaff, 1984). If the two müllerian ducts fail to fuse, two separate uterine horns remain. In contrast, resorption failure of the common tissue between them results in various degrees of persistent uterine septum.

As the distal end of the fused müllerian ducts contacts the urogenital sinus, this induces endodermal outgrowths from the sinus, which are termed the sinovaginal bulbs. These bulbs proliferate and fuse to form the vaginal plate, which later resorbs to form the vaginal lumen. Vaginal canalization is generally completed by the 20th week (Crosby, 1962). However, the lumen remains separated from the urogenital sinus by the hymeneal membrane. This membrane further degenerates to leave only the hymeneal ring.

The close association of the mesonephric (wolffian) and paramesonephric (müllerian) ducts explains the potential to see simultaneous abnormalities in their end organs. Nearly half of females with uterovaginal malformations have associated urinary tract defects, and this association is explored later (p. 40) (Kenney, 1984; Semmens, 1962). With müllerian anomalies, ovaries are functionally normal but have a higher incidence of anatomical maldescent into the pelvis (Allen, 2012).

As discussed, the mesonephric ducts usually degenerate in the female. However, persistent remnants may become clinically apparent. Mesonephric, that is wolffian, vestiges can persist as Gartner duct cysts. These are typically located in the proximal anterolateral vaginal wall but may be found at other sites along the vaginal length. Most cysts are asymptomatic and benign and usually do not require surgical excision or drainage.

Intraabdominal wolffian remnants in the female include a few blind tubules in the mesovarium—the epoöphoron—and similar ones adjacent to the uterus—paroöphoron (see Fig. 3-2F) (Moore, 2020). The epoöphoron or paroöphoron may develop into clinically identifiable benign cysts in the adult.

Gonads

Because of separate gonadal and müllerian derivation, women with müllerian defects typically have functionally normal ovaries. At approximately 4 weeks, gonads form from the genital ridge, also known as the gonadal ridge. This ridge forms from the coelomic epithelium covering the medioventral surface of the mesonephros (Smith, 2014). Recall that coelomic epithelium arises from mesoderm and invests the body cavity's inner surface (Ariza, 2016). Next, strands of these epithelial cells extend into the underlying mesenchyme as the primary sex cords.

Another gonadal component is the primordial germ cell, the future oogonia. By the 6th week, primordial germ cells have migrated from the yolk sac along the dorsal mesentery to enter the genital ridge mesenchyme (see Fig. 3-1) (Fujimoto, 1977; Hen, 2019). The primordial germ cells are then incorporated into the primary sex cords.

In the 7th week, the sexes can be distinguished. Testes are recognized during microscopic sectioning by their well-defined radiating testis cords, which derived from the primary sex cords. These cords develop into the seminiferous tubules and rete testis. The rete testis connects with small tubes arising off the mesonephric duct. These small tubes become the efferent ducts that drain into the epididymis and then into the vas deferens, which are main mesonephric duct derivatives. After the 8th week, gonads begin to differ grossly as well (Shen, 2018).

In the female embryo, the primary sex cords give rise to the medullary cords, which persist only for a short time. The coelomic epithelium again proliferates into the underlying mesenchyme, and these strands are the cortical cords. By the 16th week, the cortical cords begin to form isolated cell clusters called primordial follicles. These follicles contain the oogonia, which derive from primordial germ cells, and a single surrounding layer of follicular cells, derived from the cortical cords. Follicular cells are supporting nutrient cells.

By 8 months, the ovary has become a long, narrow, lobulated structure that is attached to the body wall by the mesovarium. The coelomic epithelium has been separated by a band of connective tissue—the tunica albuginea—from the cortex. At this stage, the cortex contains follicles and is well defined from the inner medulla, which is composed of abundant blood vessels, lymphatic vessels, and nerve fibers.

External Genitalia

Early development of the external genitalia is similar in both sexes. By 6 weeks' gestation, three external protuberances have developed surrounding the cloacal membrane. These are the left and right cloacal folds, which meet ventrally to form the genital tubercle (Fig. 3-3A). With division of the cloacal membrane into anal and urogenital membranes in the early 7th week, the cloacal folds become the anal and urethral folds, respectively. Lateral to the urethral folds, genital swellings arise, and these become the labioscrotal folds. Between the urethral folds, the urogenital sinus extends onto the surface of the enlarging genital tubercle to form the urethral groove. Late in week 7, the urogenital membrane ruptures, exposing the cavity of the urogenital sinus to amnionic fluid.

The genital tubercle elongates to form the phallus in males and the clitoris in females. Still, it is not possible to visually differentiate between male and female external genitalia until week 12. In the male fetus, dihydrotestosterone (DHT) forms locally by the 5-α reduction of testosterone. DHT prompts the anogenital distance to lengthen, the phallus to enlarge, and the labioscrotal folds to fuse and form the scrotum (see Fig. 3-3B).

In the female fetus, without DHT, the anogenital distance does not lengthen, and the labioscrotal and urethral folds do not fuse (see Fig. 3-3C). The genital tubercle bends caudally to become the clitoris, and the urogenital sinus forms the

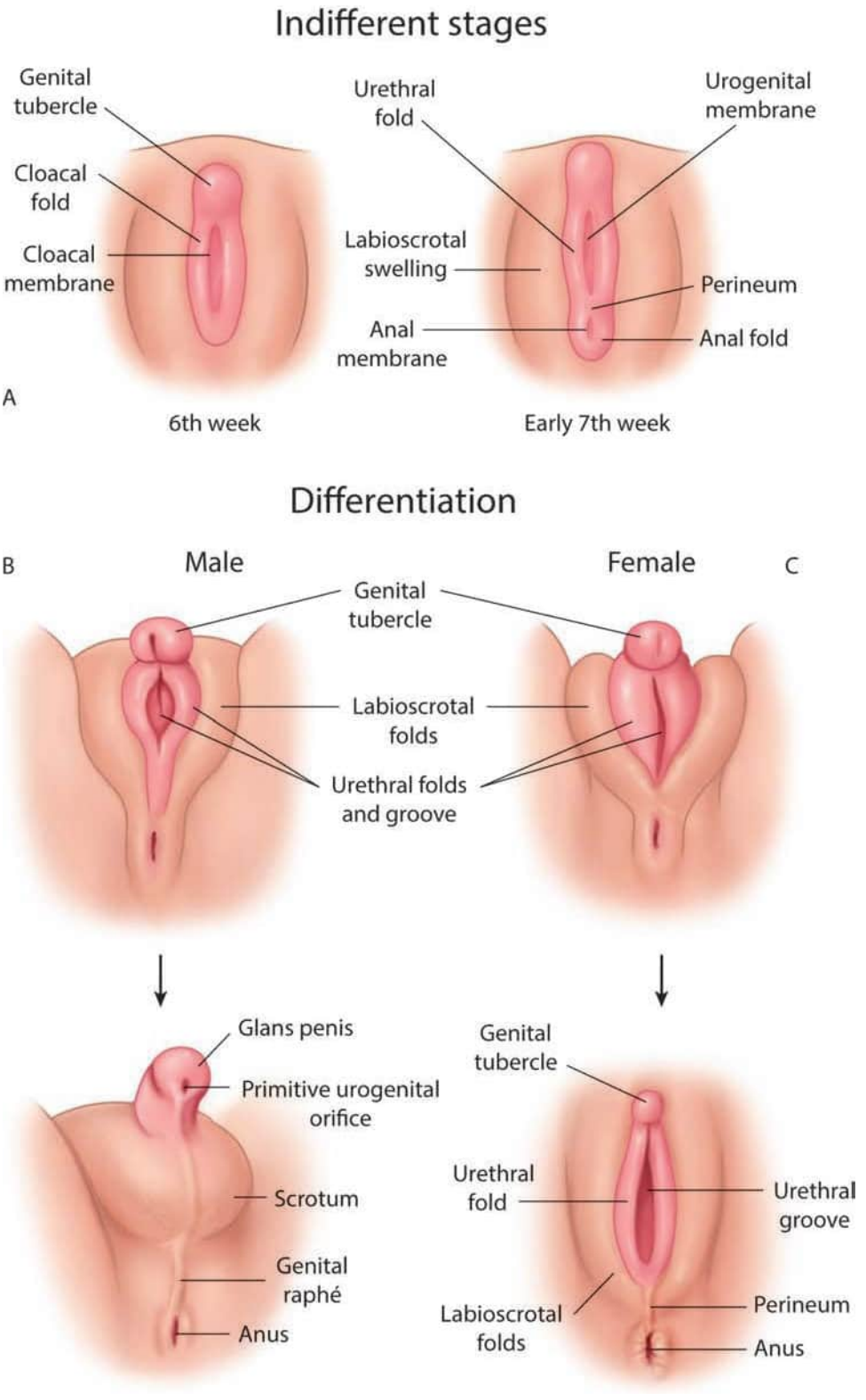

FIGURE 3-3 Development of the external genitalia. **A.** Indifferent stage. **B.** Virilization of external genitalia. **C.** Feminization.

vestibule of the vagina. The labioscrotal folds create the labia majora, whereas the urethral folds persist as the labia minora. Female external genitals are differentiated by 11 weeks, whereas male external genital differentiation is complete by 14 weeks.

To differentiate phenotypic gender early, first-trimester sonography relies on the angle of the genital tubercle off a horizontal line drawn parallel to the lumbosacral skin surface (Fig. 3-4) (Efrat, 2006). Specifically, male gender is assigned if the angle is >30°, and female gender if the angle is <10°.

SEXUAL DIFFERENTIATION

Defining gender incorporates genetic gender, gonadal gender, and phenotypic gender. *Genetic gender*—XX or XY—is established at fertilization. However, for the first 6 weeks, male and female embryos are morphologically indistinguishable.

Gonadal gender is heralded by the differentiation of the primordial gonad into a testis or an ovary. If a Y chromosome is present, the gonad begins developing into a testis. Testis development is directed by the *sex-determining region (SRY)* gene, located on the short arm of the Y chromosome (Sinclair, 1990). In addition, testis development requires other autosomal genes that include *SOX9*, *WT1*, *DAX1*, *WNT4*, and *NR5A1(SF1)* (Grinspon, 2019). Identified mutations in these and others are linked to disorders of sex development, described next.

The importance of the *SRY* gene is demonstrated in several paradoxical conditions. For example, 46,XX phenotypic males can result from translocation of the Y chromosome fragment containing *SRY* to the X chromosome during meiosis of male germ cells (Yue, 2019). Similarly, 46,XY individuals can appear phenotypically female if they carry a mutation in the *SRY* gene (Helszer, 2013).

Last, *phenotypic gender* begins at 8 weeks' gestation. Before this, urogenital tract development in both sexes is homologous. Thereafter, differentiation of the internal and external genitalia to the male phenotype is dependent on testicular function and response. In its absence, female differentiation ensues irrespective of genetic gender (Table 3-1) (She, 2017).

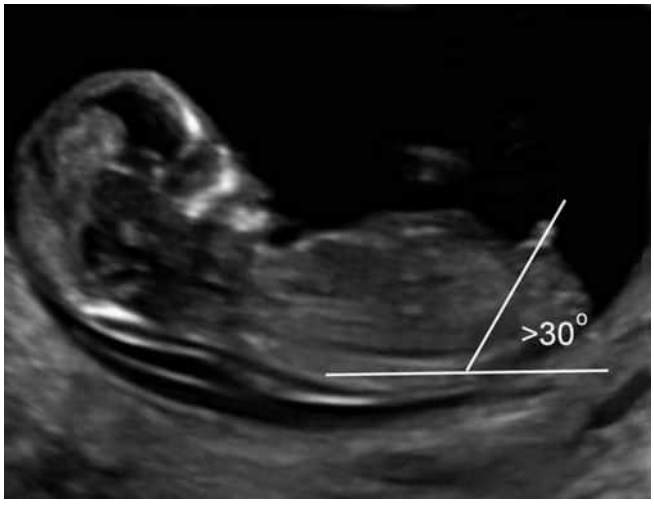

FIGURE 3-4 First-trimester transvaginal sonogram shows a male fetus, whose phallus lies at an angle that is ≥30 degrees above the horizontal. The horizontal line aligns with the fetal lumbosacral skin. (Reproduced with permission from Dr. Ashley Zink.)

In males, the Sertoli cells of the fetal testis secrete a protein called antimüllerian hormone (AMH), also named müllerian-inhibiting substance (MIS). It acts locally as a paracrine factor to cause müllerian duct regression (Grinspon, 2020; Mäkelä, 2019). Thus, it prevents development of the uterus, fallopian tube, and upper vagina. Sertoli cells secrete AMH before differentiation of Leydig cells, which synthesize testosterone. AMH is secreted as early as 7 weeks, and müllerian duct regression is completed by 9 to 10 weeks. Because AMH acts locally near its site of formation, if a testis were absent on one side, the müllerian duct on that side would persist, and the uterine horn and fallopian tube would develop on that side.

Through stimulation initially by human chorionic gonadotropin (hCG), and later by fetal pituitary luteinizing hormone (LH), Leydig cells secrete testosterone. This hormone acts directly on the wolffian duct to promote development of the vas deferens, epididymis, and seminal vesicles. Testosterone also enters fetal blood and acts on the external genitalia. In these tissues, testosterone is converted to 5α-DHT to cause virilization of the external genitalia. Leydig cells also produce insulin-like factor 3, which prompts embryonic testes to descend by acting on the gubernaculum (Ivell, 2009).

DISORDERS OF SEX DEVELOPMENT

Definitions

Abnormal sex development may involve the gonads, internal duct system, or external genitalia. Current classification of *disorders of sex development (DSDs)* include: (1) sex chromosome DSDs, (2) 46,XY DSDs, and (3) 46,XX DSDs (Table 3-2) (Hughes, 2006). Rates vary depending on included entities and approximate 1 case in every 5000 births (Lee, 2016).

Other terms describe abnormal phenotypic findings. First, some DSDs have abnormal, underdeveloped gonads, that is, *gonadal dysgenesis*. With this, a poorly formed testis is called a *dysgenetic testis*. A poorly formed ovary is a *streak gonad*. Underdeveloped gonads ultimately fail, which creates low sex steroid hormone levels but elevated follicle-stimulating hormone (FSH) and LH levels.

A second term, *ambiguous genitalia*, describes genitalia that do not appear clearly male or female. Abnormalities can include hypospadias, undescended testes, micropenis or enlarged clitoris, labial fusion, and labial mass.

Last, *ovotesticular* defines a rare state characterized by ovarian and testicular tissue in the same individual. It was formerly termed true hermaphroditism. In these cases, different gonad types can be paired. Pair combinations may include a normal testis, a normal ovary, a streak gonad, a dysgenetic testis, or an *ovotestis*. In the last, both ovarian and testicular elements are combined within the same gonad.

With ovotesticular cases, the internal ductal system structure depends on the type of ipsilateral gonad and its function. Specifically, the amount of AMH and testosterone determines the degree to which the internal ductal system is retained or

TABLE 3-1. Embryonic Urogenital Structures and Their Adult Homologues

Indifferent Structure	Female	Male
Genital ridge	Ovary	Testis
Primordial germ cells	Ova	Spermatozoa
Sex cords	Granulosa cells	Seminiferous tubules, Sertoli cells
Gubernaculum	Uteroovarian and round ligaments	Gubernaculum testis
Mesonephric tubules	Epoöphoron, paroöphoron	Efferent ductules, paradidymis
Mesonephric ducts	Gartner duct	Epididymis, vas deferens, ejaculatory duct
Paramesonephric ducts	Uterus, fallopian tubes, upper vagina	Prostatic utricle, appendix of testis
Urogenital sinus	Bladder, urethra	Bladder, urethra
	Vagina	Prostatic utricle
	Paraurethral glands	Prostate glands
	Greater (Bartholin) and lesser vestibular glands	Bulbourethral glands
Genital tubercle	Clitoris	Glans penis
Urogenital folds	Labia minora	Floor of penile urethra
Labioscrotal swellings	Labia majora	Scrotum

TABLE 3-2. Disorders of Sex Development (DSD) Classification

Sex Chromosome DSD
45,X Turner[a]
47,XXY Klinefelter[a]
45,X/46,XY Mixed gonadal dysgenesis
46,XX/46,XY Ovotesticular DSD
46,XY DSD
Testicular development abnormalities
Complete gonadal dysgenesis
Partial gonadal dysgenesis
Ovotesticular
Testicular regression syndrome
Androgen production or action defects
Androgen synthesis
Androgen receptor
LH/hCG receptor
AMH
Persistent müllerian duct syndrome
Other structure-affecting syndrome
Smith-Lemli-Opitz
46,XX DSD
Ovarian development abnormalities
Gonadal dysgenesis
Testicular
Ovotesticular
Androgen excess
Fetal
Maternal
Placental

[a]And syndrome variants.
AMH = antimüllerian hormone; hCG = human chorionic gonadotropin; LH = luteinizing hormone.

reabsorbed (p. 35). With inadequate AMH, müllerian duct derivatives persist. With inadequate testosterone, external genitalia are usually ambiguous and undermasculinized. Ovotesticular development may be found in all three of the DSD categories, and each of these sections describes examples (see Table 3-2).

Germ Cell Cancer

This cancer can develop in dysgenetic gonads of patients bearing all or part of the Y chromosome. On the Y chromosome, the gene for *testis-specific protein Y (TSPY)* is one putative cancer-predisposing gene. Other risks include disturbed gonadal development, delayed germ cell maturation, and presence of a gonadoblastoma (Cools, 2014). The last is a benign tumor that contains germ cells and immature granulosa cells (Roth, 2018).

Germ cell cancer (GCC) risk varies among DSD types, but for some, gonadectomy may be recommended by a multispecialty DSD team (Lee, 2016). Early surgery benefits those with higher GCC risk and those in whom gonadal hormones may run counter to preferred pubertal development for the individual's chosen gender identity. Later surgery may benefit those with low GCC risk and in whom gonadal hormones would advance desired pubertal development (van der Zwan, 2015).

In addition to dysgenetic gonads, undescended testes also have higher GCC rates (Kolon, 2014). Instead of gonadectomy, orchiopexy, which translocates and fixes a testis into the scrotum, may be protective (Radmayr, 2016; Walsh, 2007).

Sex Chromosome DSD

Cases in this first DSD category typically arise from an abnormal number of sex chromosomes, that is, *sex chromosome aneuploidy (SCA)*. The population rate approximates 1 case per 2500 births (Howard-Bath, 2018).

Discussed fully in Chapter 17 (p. 333), prenatal screening methods allow detection of aneuploidies, including SCAs (Norton, 2016). Sonographically, a thick nuchal translucency or the presence of cystic hygromas is associated with an increased SCA risk (American College of Obstetricians and Gynecologists, 2020; Reiss, 2017). Cell-free DNA present in the maternal blood is another common aneuploidy screening tool (Fig. 16-14, p. 328) (Huang, 2018; Vogel, 2019). Its selection solely for gender identification and without a medical indication is not recommended by the American College of Medical Genetics and Genomics (Gregg, 2016). Still, with cell-free DNA use for other indications, antenatal detection of SCAs will likely rise. Interpretation and management of findings is discussed in Chapter 17 (p. 335). Advantageously, early recognition of sex chromosome DSD offers an opportunity for patient education. Decisions to end or continue pregnancies are best guided by clinical geneticists. For continued pregnancies, prenatal diagnosis allows early postnatal interventions (Gravholt, 2017).

Turner Syndrome

This develops from de novo loss or severe structural abnormality of one X chromosome in a phenotypic female. Most affected fetuses are spontaneously aborted. However, 1 in 2000 female live births are affected (Lin, 2019). In survivors with Turner syndrome, phenotype varies but nearly all affected patients have short stature. Associated problems can include hypertension; cardiac abnormalities, especially aortic coarctation, bicuspid aortic valve, and QT-interval prolongation; and renal, skeletal, and otolaryngological anomalies. A webbed posterior neck results from cystic hygromas. Metabolic concerns are diabetes mellitus (DM), autoimmune thyroiditis, celiac disease, and elevated liver enzymes (Gravholt, 2019). Two streak ovaries are typically found, and this syndrome is the most common form of gonadal dysgenesis that leads to primary ovarian insufficiency (POI). POI is the depletion or dysfunction of ovarian follicles that leads to failing sex hormone production. The uterus and vagina are normal and respond to prescribed hormones (Matthews, 2017).

Despite eventual POI, women with Turner syndrome may conceive with assisted reproductive technologies (ART) and rarely spontaneously (Hovatta, 1999; Oktay, 2016). In gravidas with Turner syndrome, cardiac morbidity stems from aortic dissection, aortic valve stenosis, and hypertension. For

this reason, maternal–fetal medicine preconceptional counseling and cardiologist evaluation is essential. For aortic dissection, risk rises as the aortic diameter increases. The ascending *aortic size index (ASI)*, which is the aortic diameter divided by body surface area, better reflects risk because it accounts for short stature. Conception should be avoided with an ASI >2.5 cm/m^2 or with an ASI of 2.0 to 2.5 cm/m^2 plus comorbid aortic dissection risk factors. These include bicuspid aortic valve, transverse aortic arch elongation, aortic coarctation, and hypertension (Gravholt, 2017; Silberbach, 2018). The American Society for Reproductive Medicine (2012) recommends against pregnancy with an ASI >2 cm. Even without identified risk, aortic dissection can develop in pregnancy (Carlson, 2007).

If conception is planned, preconceptional evaluation includes echocardiography, combined computed tomography plus cardiac magnetic resonance (CMR) imaging of the heart/aorta, 24-hour ambulatory blood pressure monitoring, exercise testing to reveal exercise-induced hypertension, and electrocardiogram (Gravholt, 2017). Cardiac disorders may require surveillance with serial echocardiograms.

This syndrome carries higher fetal rates of miscarriage, preterm birth, and small-for-gestational age. Preeclampsia, gestational diabetes, and cholestasis of pregnancy are other maternal risks (Dotters-Katz, 2016a; Grewal, 2021). Thus, baseline serum tests ideally assess renal, liver, and thyroid function and screen for DM (Bouet, 2016). These complications and cephalopelvic disproportion account for cesarean delivery rates of 40 to 80 percent in gravidas with Turner syndrome (Cadoret, 2018; Campens, 2021; Dotters-Katz, 2016a).

Klinefelter Syndrome

This syndrome has an estimated prevalence of 1 case per 650 newborn males fetuses (Bojesen, 2003; Radicioni, 2010). With chromosome complement of 47,XXY, these individuals tend to be tall, undervirilized males with gynecomastia and two small, firm testes. They have greatly reduced fertility from hypogonadism due to gradual testicular failure. These men are at increased risk for mediastinal germ cell tumors, osteoporosis, hypothyroidism, DM, breast cancer, cardiovascular abnormalities, and neurobehavioral disorders (Groth, 2013).

Affected fetuses may show a thick NT during first-trimester sonography (Gruchy, 2011). Antepartum risks include preterm birth, cesarean delivery, small-for-gestational-age fetus, and neonatal death (Dotters-Katz, 2016b).

47,XXX and 47,XYY Karyotypes

These rare karyotypes are found in 1 in 10,000 newborn females and 2 in 10,000 newborn males, respectively (Berglund, 2019). Sonographically, fetuses with either karyotype may show a thick NT and fetal-growth restriction (Gruchy, 2016). Phenotypic range is wide, but both may be taller, show subtle facial and skeletal dysmorphisms, and display neurobehavioral problems such as autism spectrum and attention-deficit/hyperactivity disorders (Bardsley, 2013; Urbanus, 2020; Widby 2016). Hormone levels and fertility are unaffected in most, although POI and semen abnormalities may be seen, respectively.

Sex Chromosomal Ovotesticular DSD

In the sex chromosome DSD group, ovotesticular DSD may arise from a 46,XX/46,XY karyotype. Here, an ovary, testis, or ovotestis may be paired. For others, ovotesticular DSD arises from a chromosomal mosaic such as 45,X/46,XY. With this karyotype, *mixed gonadal dysgenesis* shows a streak gonad on one side and either a dysgenetic testis or normal testis on the other. For this reason, phenotypic gender varies widely.

46,XY DSD

Insufficient androgen exposure of a fetus destined to be a male leads to 46,XY DSD—formerly called male pseudohermaphroditism. Testes are often present, and the uterus is generally absent due to the normal action of AMH. These individuals are usually sterile from abnormal spermatogenesis and a small phallus that is inadequate for coitus. Described next, the etiology of 46,XY DSD may stem from abnormal testis development or from abnormal androgen production or action (see Table 3-2). Rarely, 46,XY DSD may be part of another metabolic syndrome that alters structural development, such as Smith-Lemli-Opitz syndrome (Neri, 1999).

46,XY Gonadal Dysgenesis

This spectrum of abnormal gonad underdevelopment includes complete, partial, or mixed 46,XY gonadal dysgenesis. These are defined by karyotype and by the amount of abnormal testicular tissue. Because of the potential for GCC, gonadectomy is often recommended (p. 36).

Of these, *complete gonadal dysgenesis* results from a mutation in the *SRY* gene or in other genes with testis-determining effects (Hutson, 2014). Swyer syndrome reflects *SRY* defects, whereas Frasier and Denys-Drash syndromes have *WT1* mutations. With both mutations, underdeveloped dysgenetic gonads fail to produce androgens or AMH, which results a normal prepubertal female phenotype and a normal müllerian system.

Partial gonadal dysgenesis defines those with gonad development intermediate between normal and dysgenetic testes. Depending on percentages, wolffian and müllerian structures and genital ambiguity are variably expressed.

Mixed gonadal dysgenesis is one type of ovotesticular DSD. As discussed in the last section, one gonad is streak, and the other is a normal testis or a dysgenetic testis. The phenotype is wide ranging.

Last, *testicular regression* can follow initial testis development (McElreavey, 2020). The phenotypic spectrum is broad and depends on the timing of testis failure.

Abnormal Androgen Production or Action

Some cases of 46,XY DSD stem from abnormalities in: (1) testosterone biosynthesis, (2) LH-receptor function, (3) AMH function, or (4) androgen-receptor action. First, the sex-steroid biosynthesis pathway can suffer enzymatic defects that block testosterone production. Depending on blockade timing and degree, undervirilized males or phenotypic females may result. In contrast to these central enzymatic defects, peripheral defects can be causative. Namely, abnormal action of 5α-reductase

type 2 enzyme impairs conversion of testosterone to DHT and blunts virilization.

Second, hCG/LH receptor abnormalities within the testes can lead to Leydig cell hypoplasia and decreased testosterone production. In contrast, disorders of AMH and AMH receptors result in persistent müllerian duct syndrome (PMDS). These patients appear as males but have a persistent uterus and fallopian tubes due to failed AMH action.

Last, the androgen receptor may be defective and result in androgen-insensitivity syndrome (AIS). Resistance to androgens may be incomplete and result in varying degrees of virilization and genital ambiguity. Milder forms may lead to poorly virilized men with severe male-factor infertility.

Those with complete androgen-insensitivity syndrome (CAIS) are phenotypically normal females. Girls often present at puberty with primary amenorrhea. External genitalia appear normal; pubic and axillary hair are scant or absent; the vagina is markedly shortened; and the uterus and fallopian tubes are absent. However, these individuals develop breasts during puberty due to conversion of androgen to estrogen. Testes may be palpable in the labia or groin or may lie intraabdominally. Traditionally, testes are removed. However, women with AIS have a low risk of GCC, and retention until after puberty allows hormone-mediated breast and bone mass development. Despite hormone replacement after ultimate gonadectomy, many individuals describe hormone-related mood imbalance. New cancer-surveillance protocols may allow gonad retention (Cools, 2017; Weidler, 2019).

46,XX DSD

This DSD group may stem from abnormal ovarian development or from excess androgen exposure.

Abnormal Ovarian Development

Disorders of ovarian development in those with a 46,XX complement include: (1) gonadal dysgenesis, (2) testicular DSD, and (3) ovotesticular DSD.

With *46,XX gonadal dysgenesis*, similar to Turner syndrome, streak gonads develop. These lead to hypogonadism, prepubertal normal female genitalia, and normal müllerian structures. However, other Turner stigmata are absent.

With *46,XX testicular DSD*, several genetic mutations lead to testis-like formation. Most commonly, defects stem from *SRY* translocation onto one paternal X chromosome. Less often, other genes with testis-determining effects are activated. Regardless, AMH prompts müllerian system regression, and androgens promote wolffian system development and external genitalia masculinization. Spermatogenesis, however, is absent because needed genes on the long arm of the Y chromosome are lacking. These persons are not usually diagnosed until puberty or during infertility evaluation.

With *46,XX ovotesticular DSD*, individuals possess a unilateral ovotestis with a contralateral ovary or testis, or bilateral ovotestes. An overexpression of *SOX* genes, which are testis promoting, or deficient ovarian promoting genes are implicated (Grinspon, 2019). Phenotypic findings depend on the degree of androgen exposure.

Androgen Excess

Discordance between female gonadal sex and phenotypically masculine external genitalia may also result from excessive fetal androgen exposure. The prior term was female pseudohermaphroditism. In affected individuals, the ovaries and female internal ductal structures such as the uterus, cervix, and upper vagina develop. Thus, patients are potentially fertile. The external genitalia, however, are variably virilized depending on the amount and timing of androgen exposure. The embryonic clitoris, labioscrotal folds, and urogenital sinus are commonly affected by elevated androgen levels. Virilization may range from modest clitoromegaly to posterior labial fusion and a phallus with a penile urethra. Degrees of virilization can be described by the *Prader score*, which ranges from 0 for a normal-appearing female to 5 for a normal, virilized male. The *external genitalia score* is another and similarly ranges from 0 to 12, respectively (Ahmed, 2000; van der Straaten, 2020).

Fetal, placental, or maternal sources can provide the excessive androgen levels. Maternally derived androgen excess may come from virilizing ovarian tumors such as luteoma and Sertoli-Leydig cell tumor or from virilizing adrenal tumors. Fortunately, these neoplasms infrequently cause fetal effects because of the placental syncytiotrophoblast's tremendous ability to convert C_{19} steroids—androstenedione and testosterone—into estradiol via the enzyme aromatase (Chap. 5, p. 101). As another source, drugs such as testosterone, danazol, and other androgen derivatives may virilize.

Of fetal sources, exposure can arise from fetal congenital adrenal hyperplasia (CAH). This stems from a fetal enzyme deficiency in the steroidogenic pathway and leads to androgen accumulation. Most cases have a 21-hydroxylase deficiency. Rarely, others involve deficient 3β-hydroxysteroid dehydrogenase, 17α-hydroxylase, cholesterol side-chain cleavage enzyme, P450 oxidoreductase, or 11β-hydroxylase (El-Maouche, 2017; Narasimhan, 2019). CAH is a frequent cause of virilization, and its approximate incidence in the United States is 1 case in 18,000 live births (Chan, 2013; Pearce, 2016).

With CAH, phenotypes depend on the enzyme defect's location in the steroidogenic pathway and its severity (Miller, 2011). Classically, deficient enzymes block corticosteroid production, which feeds back to raise adrenocorticotropic hormone (ACTH) levels. This prompts increased levels of precursors, which detour into pathways that generate androgens. With severe deficiency, affected newborns also have blocked aldosterone production that leads to life-threatening salt wasting. This is typified by hyponatremia, hyperkalemia, metabolic acidosis, and hypovolemia (Bizzarri, 2016). Other mutations may prompt fetal virilization alone (Auchus, 2015).

The mildest abnormalities present later and are described as "nonclassic," "late-onset," or "adult-onset" CAH. In these patients, adrenal axis activation at puberty increases steroidogenesis and unmasks mild enzymatic deficiency. Excess androgen provides negative feedback to gonadotropin-releasing hormone (GnRH) receptors in the hypothalamus. These patients often have hirsutism, acne, and anovulation. Thus, late-onset CAH may mimic polycystic ovarian syndrome (McCann-Crosby, 2014).

In some instances, CAH can be diagnosed antenatally. Early maternal dexamethasone therapy can dampen androgen excess to minimize virilization (Chap. 19, p. 369). Cell-free DNA can identify fetal gonadal gender. If Y-chromosome cell-free DNA is identified, androgens will not harm the male fetus and maternal dexamethasone treatment can be stopped (Tardy-Guidollet, 2014).

Of rare placental sources, placental aromatase deficiency from a fetal *CYP19* gene mutation causes accumulation of placental androgen and underproduction of placental estrogens (Chap. 5, p. 102) (Jones, 2007). Consequently, both the mother and the 46,XX fetus are virilized.

Gender Assignment

Delivery of a newborn with a DSD is a potential medical emergency and can also create possible long-lasting psychosexual and social ramifications for the individual and family. Ideally, once the affected neonate is stable, parents are encouraged to hold the child. The newborn is referred to as "your baby," and suggested terms include "phallus," "gonads," "folds," and "urogenital sinus" to reference underdeveloped structures. An obstetrician explains that the genitalia are incompletely formed and emphasizes the situation's seriousness and need for rapid consultation and laboratory testing.

Because similar or identical phenotypes may have several etiologies, identification of a specific DSD may require several diagnostic tools (McCann-Crosby, 2015). Relevant historical questions seek prior obstetrical outcomes, medication inventory, consanguinity, germane antenatal testing and sonography results, and family history of genetic or structural anomalies. Signs of maternal hyperandrogenism are sought. Neonatal physical examination evaluates: (1) ability to palpate gonads in the labioscrotal or inguinal regions, (2) ability to palpate uterus during rectal examination, (3) phallus size, (4) other syndromic features, and (5) genitalia pigmentation, which derives from increased melanocyte-stimulating hormone levels that can accompany ACTH secretion. The newborn metabolic condition is assessed, and hyperkalemia, hyponatremia, and hypoglycemia may indicate CAH. Other neonatal tests include genetic studies, hormone measurements, imaging, and in some cases endoscopic, laparoscopic, and gonadal biopsy. Sonography or magnetic resonance (MR) imaging can help identify müllerian/wolffian structures, gonad location, and associated malformations such as renal anomalies.

BLADDER AND PERINEAL ABNORMALITIES

During embryo formation, a bilaminar cloacal membrane lies at the caudal end of the germinal disc and forms the infraumbilical abdominal wall. Normally, an ingrowth of mesoderm between the ectodermal and endodermal layers leads to formation of the lower abdominal musculature and pelvic bones. Without this reinforcement, the cloacal membrane may prematurely rupture. Depending on the infraumbilical defect's extent, cloacal exstrophy, bladder exstrophy, or epispadias may result, and all are rare.

Cloacal exstrophy, also known as the omphalocele, bladder exstrophy, imperforate anus, spina bifida (OEIS) complex, affects approximately 1 in 300,000 live births (Keppler-Noreuil, 2007; Woo, 2010). With *bladder exstrophy*, the bladder lies outside the abdomen, is open, drains directly into amnionic fluid, and thus does not fill. Sonography in the first trimester may show a thin-walled, lower-abdominal cystic structure and a thick NT (Mallmann, 2014; Tonni, 2011). During second-trimester scans, findings are a midline, infraumbilical, anterior-abdominal-wall defect, failure to see the bladder, and associated OEIS defects (Ben-Neriah, 2007). Prenatal karyotyping is recommended. Delivery route is usually dictated by the associated spina bifida defect. Postnatal repair is complex, and individuals may struggle with urinary and fecal incontinence and the challenges of neonatal gender assignment (Woo, 2010).

With *bladder exstrophy*, associated findings often include abnormal external genitalia and a widened symphysis pubis. At the same time, however, the uterus, fallopian tubes, and ovaries are typically normal except for occasional müllerian duct fusion defects. Although often not identified in affected fetuses, sonographic indicators are inability to see the bladder, solid mass between the umbilical arteries, low umbilical insertion into the abdomen, divergent pubic rami, normal amnionic fluid volume, and in males, a small penis with anteriorly displaced scrotum (Mallmann, 2019). The differential diagnosis includes bladder exstrophy or agenesis, bilateral ectopic ureters, patent urachus, cloacal exstrophy, and simple nonvisualization of the bladder. MR imaging may be a helpful adjunct (Goldman, 2013). Fetal karyotyping is considered if genitalia are ambiguous. For an affected fetus, the prenatal course is typically routine, and cesarean delivery is reserved for obstetrical indications.

For a gravida with bladder exstrophy herself, pregnancy is associated with greater risk for antepartum pyelonephritis, urinary retention, ureteral obstruction, pelvic organ prolapse, miscarriage, preterm birth, and breech presentation. The American Urological Association has published management guidelines for pregnancy (Eswara, 2016). Due to the extensive adhesions from prior repair and altered anatomy typically encountered, some recommend planned early cesarean delivery at a tertiary center (Deans, 2012; Greenwell, 2003). Dy and coworkers (2015) described using paramedian abdominal wall and vertical uterine incisions.

Epispadias without bladder exstrophy is rare and develops in association with other anomalies such as a widened, patulous urethra; absent or bifid clitoris; nonfused labial folds; and flattened mons pubis. Vertebral abnormalities and pubic symphysis diathesis are also common.

Clitoral anomalies are rare. One is clitoral duplication or bifid clitoris, which usually develops in association with bladder exstrophy or epispadias. With *female phallic urethra*, the urethra opens at the clitoral tip. Last, *clitoromegaly* noted at birth suggests fetal exposure to excessive androgens (p. 38). Without a DSD, idiopathic congenital clitoromegaly in females born extremely premature is rare but well-recognized, and observation is recommended (Williams, 2013).

As noted, the hymen marks the embryological boundary between structures derived from the müllerian and urogenital sinus. *Hymeneal anomalies* include imperforate, microperforate,

cribriform (sievelike), navicular (boat-shaped), and septate hymens. They result from failure of the inferior end of the vaginal plate—the hymeneal membrane—to canalize. Rarely, with an imperforate hymen, secretions may markedly accumulate in the fetal uterus and vagina, that is, hydrometrocolpos (HMC). Most cases of HMC are asymptomatic and resolve postnatally as mucus is reabsorbed and estrogen levels decline. Rarely, perinatal urinary tract obstruction results from mass effect and is relieved with cruciate incision of the hymen (Grimstad, 2019).

Fetal HMC sonographically appears as a cystic mass behind the bladder. The differential diagnosis includes reproductive tract outlet obstruction of the hymen, vagina, or cervix; ureterocele; megacystis; ovarian, urachal, or mesenteric cyst; anterior meningocele; bowel or bladder duplications; and urogenital sinus or cloacal dysgenesis. Rare associated syndromes are McKusick-Kaufman, Ellis-van Creveld, or Bardet-Biedl syndromes (Garcia Rodriguez, 2018).

MÜLLERIAN ABNORMALITIES

Four principal abnormalities arise from defective müllerian duct embryological steps: (1) agenesis of both ducts, either focally or along the entire duct length; (2) unilateral maturation of one müllerian duct with incomplete or absent development of the opposite side; (3) absent or faulty midline fusion of the ducts; or (4) defective canalization. Various classifications have been proposed, and Table 3-3 shows the one from the American Fertility Society (1988). This classification system is the most widely used, although several others have been created (Grimbizis, 2013, 2016; Ludwin, 2018b).

TABLE 3-3. Classification of Müllerian Anomalies

- **I. Segmental müllerian hypoplasia or agenesis**
  - a. Vaginal
  - b. Cervical
  - c. Uterine fundal
  - d. Tubal
  - e. Combined anomalies
- **II. Unicornuate uterus**
  - a. Communicating rudimentary horn
  - b. Noncommunicating horn
  - c. No endometrial cavity
  - d. No rudimentary horn
- **III. Uterine didelphys**
- **IV. Bicornuate uterus**
  - a. Complete—division to internal os
  - b. Partial
- **V. Septate uterus**
  - a. Complete—septum to internal os
  - b. Partial
- **VI. Arcuate**
- **VII. Diethylstilbestrol related**

Data from American Fertility Society: The American Fertility Society classifications of adnexal adhesions, distal tubal occlusion, tubal occlusion secondary to tubal ligation, tubal pregnancies, Müllerian anomalies and intrauterine adhesions, Fertil Steril 1988 Jun;49(6):944–955.

A müllerian anomaly is suspected if a vaginal septum, blind-ending vagina, or duplicated cervix is found. Amenorrhea may be an initial complaint for those with agenesis of a müllerian component. In those with outlet obstruction but functioning endometrium, pelvic pain may arise from occult blood that accumulates and distends the vagina, uterus, or fallopian tubes (Kapczuk, 2018; Patel, 2016). Endometriosis and its associated dysmenorrhea, dyspareunia, and chronic pain are also frequent with outlet obstruction (Matalliotakis, 2017).

Comorbid Renal Anomalies

Renal anomalies most frequently accompany unicornuate uterus, uterine didelphys, and anomalies with an ipsilateral obstructive vaginal septum. Less often, partial bicornuate, and partial septate uteri are associated (Heinonen, 2018). When müllerian anomalies are identified, the urinary system can be evaluated with sonography, MR imaging, or intravenous pyelography (Hall-Craggs, 2013). The last two are advantageous because ureteral anatomy can be affected too. An absent unilateral kidney is the most common finding. On the other hand, if renal agenesis is found first, reproductive-tract imaging in early puberty may help identify müllerian anomalies early (Friedman, 2018).

Müllerian Agenesis (Class I)

Class I segmental defects are caused by müllerian hypoplasia or agenesis as shown in Figure 3-5 (American Fertility Society, 1988). These developmental defects can affect the vagina, cervix, uterus, or fallopian tubes and may be isolated or may coexist with other müllerian anomalies.

Vaginal Abnormalities

Of these, vaginal agenesis is the most profound and may be isolated or associated with other müllerian anomalies. One example is the Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome, in which upper vaginal agenesis is typically associated with uterine hypoplasia or agenesis. Less often, this syndrome also displays additional abnormalities and is known by the acronym MURCS (müllerian duct aplasia, renal aplasia, and cervicothoracic somite dysplasia) (Rall, 2015).

The obstetrical significance of vaginal anomalies depends greatly on the degree of obstruction. Complete vaginal agenesis, unless corrected surgically, precludes pregnancy by vaginal intercourse. With MRKH syndrome, a functional vagina can be created, but uterine agenesis proscribes childbearing. In these women, however, ova can be retrieved for in vitro fertilization (IVF) and carriage by a surrogate mother (Reichman, 2010). Uterine transplantation is experimental but holds promise for these women (Johannesson, 2021; Jones, 2019).

Of other vaginal anomalies, congenital septa may form longitudinally or transversely, and each can arise from a fusion or resorption defect. A *longitudinal septum* divides the vagina into right and left portions. It may be complete and extend the

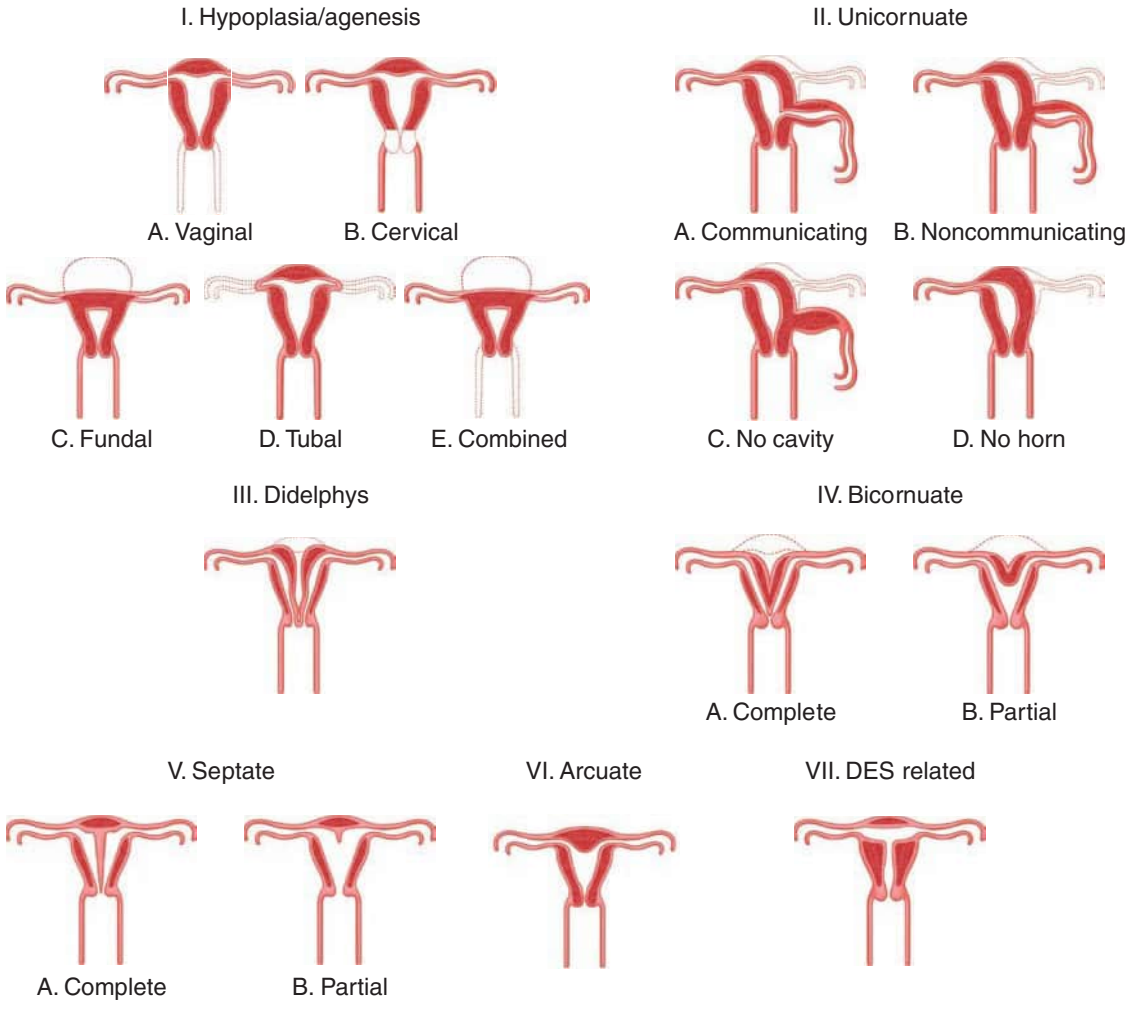

FIGURE 3-5 Classification of müllerian anomalies. DES = diethylstilbestrol.

entire vaginal length. A partial septum usually forms high in the vagina but may develop at lower levels. These septa are often associated with other müllerian anomalies (Haddad, 1997).

During examination, the provider can usually guide a speculum up along one side of the septum. Similarly, in labor, a complete longitudinal vaginal septum usually does not cause dystocia because the fetus can descend through one vaginal side, which dilates sufficiently. An incomplete distal longitudinal septum, however, may interfere with descent, and antepartum resection is preferred (Hoffman, 2020). Rarely, a woman with an incomplete distal longitudinal septum instead presents in labor. During second-stage labor, this septum usually becomes attenuated by pressure from the fetal head. After ensuring adequate analgesia, the attachment of the septum to the posterior vaginal wall is isolated between two clamps, transected, and ligated. Following placenta delivery, the superior attachment is similarly isolated between clamps and transected, while carefully avoiding urethral injury.

A *transverse septum* poses an obstruction of variable thickness. It may develop at any depth within the vagina, but most lie in the lower third (Williams, 2014). Septa may or may not be perforate, and thus obstruction or infertility is possible.

In labor, perforate strictures may be mistaken for the upper limit of the vaginal vault, and the septal opening is misidentified as an undilated cervix (Kumar, 2014). If encountered during labor, and after the cervix has dilated completely, the head impinges on the septum and causes it to bulge downward. If the septum does not spontaneously yield, slightly stretching its opening usually leads to further dilation. Occasionally cruciate incisions that avoid the urethra and rectum are required to permit delivery (Blanton, 2003; Levin, 1963). For a thick transverse septum, cesarean delivery may be necessary.

■ Cervical Abnormalities

Developmental abnormalities of the cervix include partial or complete agenesis, duplication, or a longitudinal dividing septum. Complete agenesis is incompatible with pregnancy. IVF with gestational surrogacy or with transmyometrial embryo transfer are options (Al-Jaroudi, 2011; Xu, 2009). Instead, surgical correction by uterovaginal anastomosis successfully relieves outlet obstruction, but subsequent pregnancy and live birth rates are low (Mikos, 2020). Significant complications including deaths have accompanied such corrective surgery. Some experts recommend hysterectomy for complete cervical agenesis and reserve reconstruction attempts for carefully selected patients with cervical dysgenesis (Roberts, 2011; Rock, 2010).

Uterine Abnormalities

From a large variety, a few of the more common congenital uterine malformations are shown in Table 3-3. Assessing an accurate population prevalence is difficult because the best diagnostic techniques are invasive. The prevalence found with imaging ranges from 0.4 to 10 percent, and rates in women with recurrent miscarriage are significantly higher (Byrne, 2000; Dreisler, 2014; Saravelos, 2008). In a general population, the most frequent finding is arcuate uterus, followed in descending order by septate, bicornuate, didelphic, and unicornuate classes (Chan, 2011b).

As a group, these anomalies pose greater risk for miscarriage, malpresentation, preterm birth, and poor fetal growth (Chan, 2011a; Hua, 2011; Reichman, 2009). Vaginal delivery is the preferred delivery route when feasible. The cervix of the pregnancy-containing uterus or horn will typically dilate sufficiently. Similarly, any proximal longitudinal septum will stretch to permit fetal descent.

Müllerian uterine anomalies may be discovered first during pelvic examination, cesarean delivery, tubal sterilization, or infertility evaluation. Depending on clinical presentation, sonography, hysterosalpingography (HSG), MR imaging, laparoscopy, and hysteroscopy may also be diagnostic. Each has limitations and thus may be combined to completely define anatomy.

If a müllerian anomaly is suspected, two-dimensional transvaginal sonography (2-D TVS) is initially performed in most clinical settings. For this indication, the pooled accuracy for 2-D TVS is 90 to 92 percent (Pellerito, 1992). Three-dimensional (3-D) TVS is more accurate than 2-D TVS because it provides uterine images from virtually any angle. The diagnostic accuracy of 3-D TVS approaches 97 percent (Vaz, 2017). Thus, coronal images can be constructed, and these are essential in evaluating both internal and external uterine contours. Both 2-D and 3-D TVS are suitable for use in pregnancy (Fig. 3-6).

Several studies reported good concordance between 3-D TVS and MR imaging of müllerian uterine anomalies (Deutch, 2008; Graupera, 2015). MR imaging is often preferred for complex anatomy, especially cases for which corrective surgery is planned. MR imaging provides clear delineation of both the internal and external uterine anatomy and has a reported accuracy of up to 100 percent for müllerian anomaly evaluation (Bermejo, 2010; Pellerito, 1992). Moreover, secondary diagnoses such as renal or skeletal anomalies can be concurrently evaluated. MR imaging without contrast is safe in pregnancy.

Saline infusion sonography (SIS) is a technique that instills fluid into the uterine cavity to distend and define cavity shape. It improves delineation of internal uterine morphology. However, SIS is contraindicated in pregnancy. It requires a patent endometrial cavity.

In women undergoing fertility evaluation, HSG is usually selected for uterine cavity and tubal patency assessment. It is contraindicated during pregnancy. HSG poorly defines the external uterine contour and can delineate only patent cavities. Described next, remember that some unicornuate rudimentary horns lack a cavity. Also, outlet obstructions will preclude dye filling. For infertility, hysteroscopy and/or laparoscopy plus chromotubation may help confirm or treat uterine cavity or tubal pathologies. These also screen for endometriosis, which often coexists with both infertility and müllerian anomalies (American Society for Reproductive Medicine, 2015). In pregnancy, laparoscopy is rarely used to diagnose müllerian defects, and hysteroscopy is contraindicated.

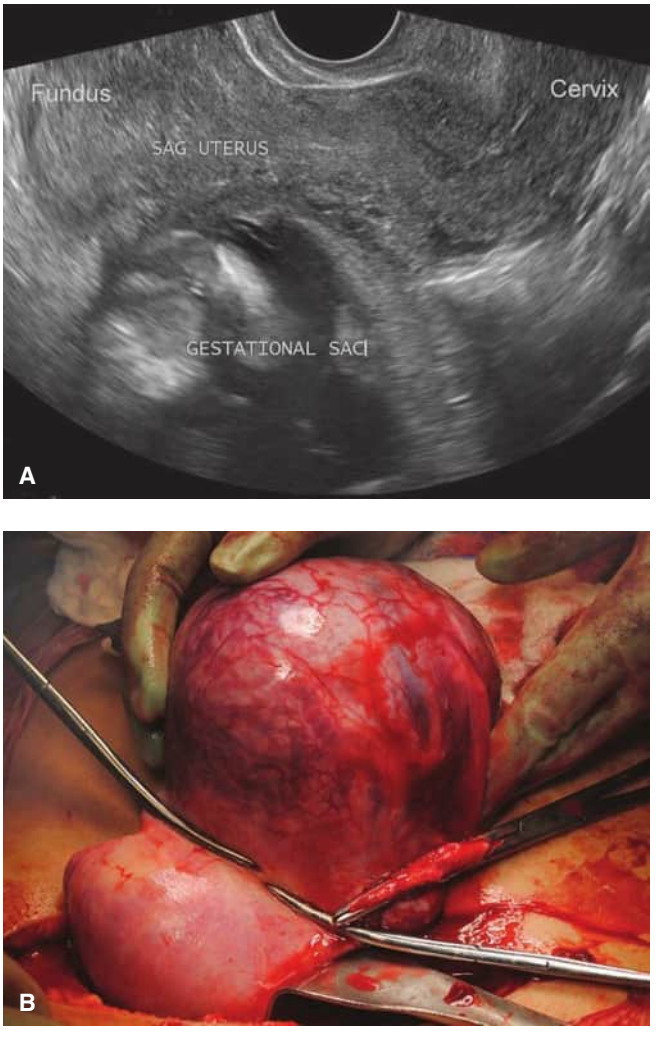

FIGURE 3-6 A. Sagittal transvaginal sonogram shows a gestational sac surrounded by myometrium. The gestational sac is not contiguous with the endocervical canal or with the main horn's endometrium. **B.** Here, two Pean clamps are placed across the vascular tissue bridge that separates the rudimentary horn (*above*) from the main uterine horn (*below*). (Reproduced with permission from Dr. Elaine L. Duryea.)

Unicornuate Uterus (Class II)

General population estimates cite an incidence of 1 case in 4000 women (Reichman, 2009). In class II-D forms, only one uterine horn is present (see Fig. 3-5). Instead, an underdeveloped rudimentary horn may be present. The rudiment may or may not communicate with the dominant horn and may or may not contain an endometrium-lined cavity. With noncommunicating types, the rudiment may lie near the uterus or may lie anywhere along the embryological migration path of the paramesonephros. This starts at the back and sweeps forward along the broad ligament.

This anomaly may be detected during fertility evaluation by HSG, but false-negative examinations stem from noncavitary or noncommunicating horns failing to fill with dye. If this anomaly is suspected, 3-D TVS raises diagnostic accuracy, but again MR imaging may be preferred to define endometrium (Fukunaga, 2017). Importantly, 40 percent of affected women will have renal anomalies (Fedele, 1996).

Main Horn. Pregnancies developing in the main horn carry significant obstetrical risks. These include first- and second-trimester miscarriage, malpresentation, fetal-growth restriction, fetal demise, prematurely ruptured membranes, and preterm delivery (Chan, 2011a; Hua, 2011; Reichman, 2009). These risks theoretically stem from abnormal uterine blood flow, cervical insufficiency, and diminished cavity size and muscle mass (Donderwinkel, 1992). The main unicornuate horn is indeed smaller than normal uterine lengths of 7- to 8-cm (Hawkins, 2013). One small study of 140 nulligravidas found a median uterine length of 5 cm (Li, 2019). Those with lengths from the internal os to fundus <4.5 cm prior to pregnancy had higher preterm labor rates during subsequent pregnancy compared with longer hemiuteri. Thus, a heightened awareness of potential complications is prudent. However, specific surveillance for poor fetal growth or preterm labor is mainly guided by prior pregnancy outcomes.

Rudimentary Horn. Ectopic pregnancy, correctly termed a *cornual pregnancy*, can develop within a remnant (Arleo, 2014). This risk includes noncommunicating cavitary rudiments, for which transperitoneal sperm migration permits ovum fertilization and pregnancy (Nahum, 2004). Although less common than other unicornuate pregnancy complications, rupture can create life-threatening hemorrhage. Convergence of uterine and ovarian branches near the pregnancy and the commonly associated placenta accreta spectrum (PAS) explain this risk.

In a report of 70 such pregnancies, Rolen and associates (1966) found that most rudimentary uterine horn pregnancies ruptured prior to 20 weeks' gestation. Nahum (2002) reviewed the literature from 1900 to 1999 and identified 588 rudimentary horn pregnancies. Half had uterine rupture, and 80 percent did so before the third trimester. Of the total 588, the neonatal survival rate was only 6 percent.

First-trimester sonography allows an earlier diagnosis and rudiment excision before rupture. The main horn shows an empty endometrium continuous with the cervical canal, and the interstitial portion of a fallopian tube is seen only on one side. The rudimentary horn pregnancy displays: (1) no continuity between the cervical canal and gestational sac, (2) myometrium surrounding the gestation, (3) PAS-associated hypervascularity surrounding the gestational sac, and (4) a vascular pedicle connecting the main horn and the sac's surrounding myometrium (Mavrelos, 2007; Tsafrir, 2005). If necessary, 3-D TVS is an appropriate adjunct (Tolani, 2018). As seen in Figure 3-6, the connecting pedicle can be broad and vascular.

Treatment is surgical and removes the rudimentary horn and in situ pregnancy. The ipsilateral fallopian tube is also excised to avert future ectopic pregnancies (Dove, 2017; Worley, 2008). Steps include sequential division of the uteroovarian ligament, mesosalpinx, round ligament, and pedicle to the main horn. Ideally, the ovary is spared, but large pregnancies with a short uteroovarian ligament may prompt adnexectomy. Surgical route is dictated by pregnancy size and laparoscopic capabilities.

In nonpregnant women, most unicornuate uteri are asymptomatic. Those with a noncommunicating cavitary rudiment may present with outlet obstruction symptoms at puberty. In this instance, comorbid endometriosis can club fimbria and obstruct tubal egress of blood. In all cases, prophylactic excision of a cavitary rudiment is recommended to avoid pregnancy in an inadequately sized horn (Fedele, 2005; Rackow, 2007; Schneiderman, 2018). Data regarding subsequent pregnancy after excision are scarce. In one series of eight women, all had a preterm cesarean delivery (Pados, 2014).

Uterine Didelphys (Class III)

This anomaly arises from incomplete fusion that results in two entirely separate hemiuteri, two cervices, and usually two vaginas or a longitudinal vaginal septum (see Fig. 3-5). Uterine didelphys may be isolated or part of a rare triad with an obstructed hemivagina and ipsilateral renal agenesis (OHVIRA), also known as Herlyn-Werner-Wunderlich syndrome (Tong, 2014). Rarely diagnosed antenatally, it is considered in a fetus with renal agenesis and a cystic pelvic mass, which reflects hydrometrocolpos (p. 40) (Tuna, 2019). Fetal MR imaging aids diagnosis.

Uterine didelphys is suspected on pelvic examination by identification of a longitudinal vaginal septum and two cervices. During HSG for fertility evaluation, contrast shows two separate endocervical canals. These open into separate noncommunicating fusiform endometrial cavities that each ends with a solitary fallopian tube. In women without fertility issues, 2- or 3-D TVS is a logical initial imaging tool, and separate divergent uterine horns with a large intervening fundal cleft are seen. Endometrial cavities and two cervices are uniformly separate. MR imaging can clarify cases lacking classic findings.

Adverse obstetrical outcomes associated with uterine didelphys are similar to but less frequent than those seen with unicornuate uterus. Increased risks include miscarriage, preterm birth, and malpresentation (Chan, 2011a; Hua, 2011).

Metroplasty for either uterine didelphys or bicornuate uterus involves resection of intervening myometrium and fundal recombination (Alborzi, 2015). These rarely performed surgeries are chosen for highly selected patients with otherwise unexplained recurrent miscarriage at later gestational ages. After metroplasty, scheduled delivery prior to labor is prudent to avoid uterine rupture (Ayhan, 1992).

Bicornuate Uterus (Class IV)

This fusion anomaly results in two hemiuteri. As shown in Figure 3-5, the central myometrium runs either partially or completely to the cervix. A complete bicornuate uterus may extend to the internal cervical os and have a single cervix (bicornuate unicollis) or reach the external os (bicornuate bicollis). As with uterine didelphys, a coexistent longitudinal vaginal septum is common.

Radiological discrimination of a bicornuate uterus from a septate uterus can be challenging, and defining criteria vary. This distinction, however, is important because septate uterus can be treated with hysteroscopic septal resection. HSG or 2-D TVS may initially suggest an anomaly, but further distinction is provided by 3-D TVS or MR imaging. With these, the intercornual angle, fundal contour, and a straight line drawn between the imaged tubal ostia serve as defining thresholds (Fig. 3-7).

Bicornuate uterus carries increased risks for miscarriage, preterm birth, and malpresentation (Chan, 2011a; Mastrolia, 2017). As discussed in the prior section, rare surgical correction by metroplasty is reserved for highly selected cases.

Septate Uterus (Class V)

With this anomaly, a resorption defect leads to a persistent complete or partial longitudinal uterine septum (see Fig. 3-5).

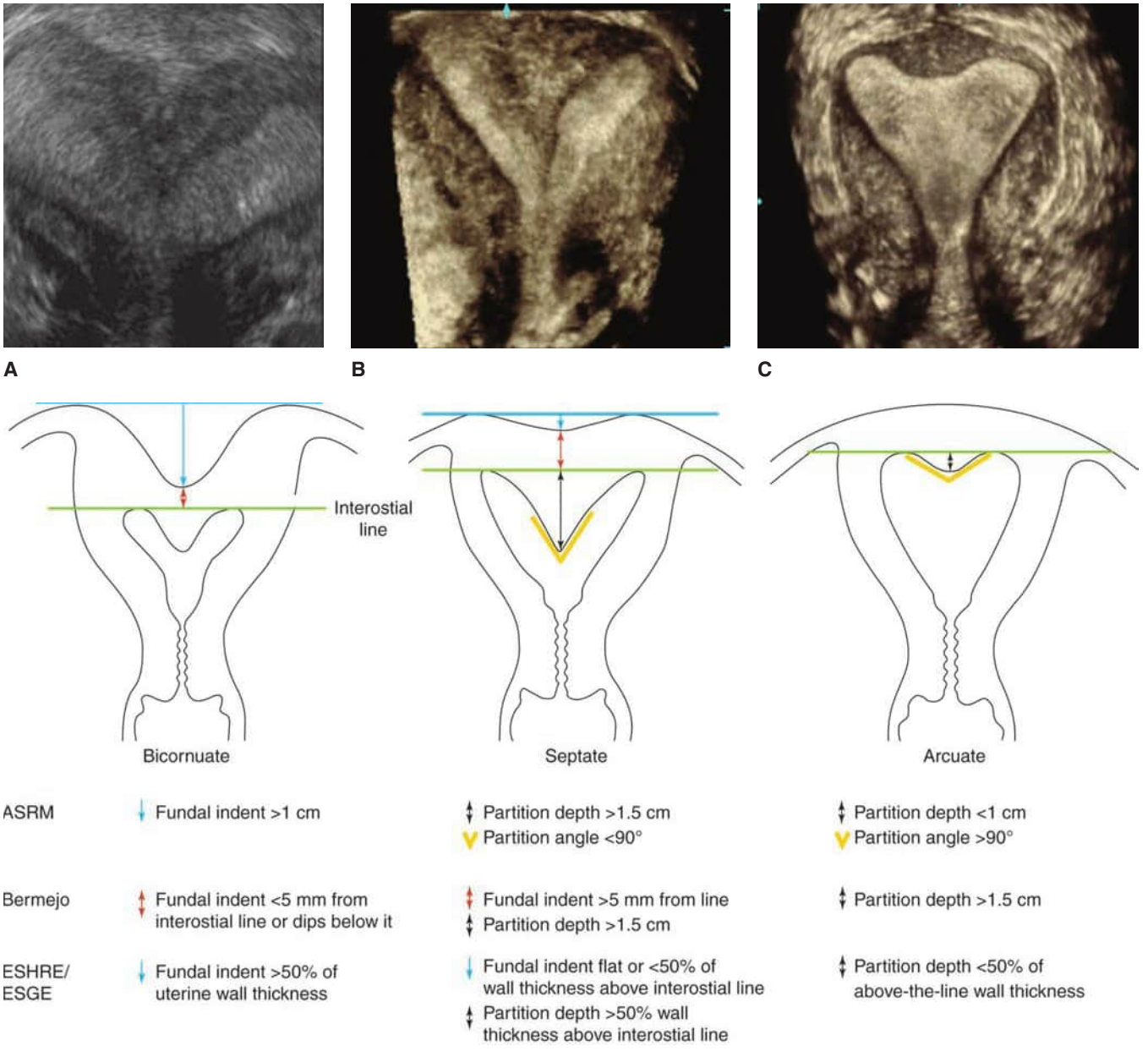

FIGURE 3-7 Three-dimensional transvaginal sonography (3-D TVS) images of müllerian uterine anomalies in the coronal plane. Below each are corresponding diagrammatic uteri and differing organizational definitions. **A.** Bicornuate uterus. This 3-D TVS rendered image demonstrates a concave external fundal contour that dips to a point near or below the interostial line (*green line*). (Reproduced with permission from Dr. Elysia Moschos.) **B.** Septate uterus. This sonogram depicts the narrow angle between the two small endometrial cavities, which is characteristic of a septate) uterus. The external contour here is flat but may show minor fundal indentation. **C.** Arcuate uterus. This image illustrates the normal external uterine contour and obtuse angle of the endometrial cleft that is characteristic of an arcuate uterus. Organizations vary among their use of the terms intercornual, interostial, or interstitial line. ASRM = American Society for Reproductive Medicine; ESHRE/ESGE = European Society of Human Reproduction and Embryology/European Society for Gynaecological Endoscopy. (Data from American Society for Reproductive Medicine, 2016, Bermejo, 2010, Grimbizis, 2013, 2016.)

In the rare Robert uterus, an asymmetric longitudinal septum creates a sequestered noncommunicating hemicavity that acts similar to a rudimentary horn (Ludwin, 2018a).

Many septate uteri are identified during evaluation of infertility or recurrent pregnancy loss. Although an abnormality may be identified with HSG or 2-D TVS, typically 3-D TVS or MR imaging is required to differentiate septate and bicornuate uteri. Experts still debate diagnostic criteria (see Fig. 3-7).

Septate anomalies can be associated with increased risks for adverse pregnancy outcomes that include miscarriage, preterm delivery, and malpresentation (Chan, 2011a; Ghi, 2012). In those with recurrent pregnancy loss, hysteroscopic septal resection may improve birth rates (American Society for Reproductive Medicine, 2016; Corroenne, 2018; Valle, 2013). During a subsequent labor, those with prior septal resection, especially if complicated by uterine perforation, carry a small risk for uterine rupture (Homer, 2000; Sentilhes, 2005).

Arcuate Uterus (Class VI)

This malformation is a mild deviation from the normally developed uterus (see Fig. 3-7). Most consider this anomaly benign, but some have found excessive second-trimester losses, preterm labor, and malpresentation (Chan, 2011a; Mucowski, 2010; Prior, 2018; Woelfer, 2001).

Cesarean Delivery

As noted in the above sections, cesarean delivery rates are increased with müllerian uterine anomalies. Data regarding subsequent trial of labor after cesarean (TOLAC) are few and show evidence both for and against its success and safety (Erez, 2007; Ravasia, 1999). Failed TOLAC attempts or the risk of rupture may stem from smaller than normal cavity size, abnormal propagation of myometrial action potentials, and a weaker cesarean scar due to congenitally altered vascular anatomy (Altwerger, 2015). Other factors that support or disfavor TOLAC are similar to those for women with normal-shaped uteri and are outlined in Chapter 31.

In those without prior cesarean delivery, external cephalic version (ECV) is reasonable to avoid primary cesarean delivery for malpresentation. A smaller uterine cavity or an obstructing midline partition may limit fetal turning. These are added to the traditional list of factors that should be reviewed when assessing a potential ECV candidate (Chap. 28, p. 528).

At times, a müllerian anomaly may not be diagnosed until cesarean delivery, and additional information should be methodically sought. Prior to hysterotomy closure, the cavity is manually explored to define the length of any cavity partition. If a rudimentary horn is found, the main cavity is also digitally explored for a communication. However, this may be missed due to its narrow caliber.

After closure, the fundus is examined. The external contour is delineated to differentiate bicornuate from didelphys types. If only one adnexum is found, a unicornuate uterus is suspected. In this case, if an obvious rudiment is not attached to the main horn, the surgeon should trace the embryological migratory path of the paramesonephric duct starting at the patient's back and sweeping forward. If found, the rudiment may be removed or at minimum its accompanying fallopian tube should be ligated to prevent later ectopic pregnancy.

With any müllerian anomaly, both renal fossae are examined intraoperatively to confirm kidneys. Postoperative radiologic assessment of the urinary collecting anatomy is reasonable.

Treatment with Cerclage

Uterine anomalies are one risk for cervical insufficiency (Althuisius, 2001; Berghella, 1999; Mastrolia, 2018). Some women with uterine anomalies and repetitive pregnancy loss after the first trimester may benefit from cervical cerclage (Golan, 1992; Yassaee, 2011). Others with partial cervical atresia or hypoplasia also may benefit (Ludmir, 1991; Song, 2015). For women with a uterine anomaly, candidacy for cervical length sonographic screening or for cerclage placement is determined by the same criteria used for women without a uterine defect (American College of Obstetricians and Gynecologists, 2021; Society for Maternal–Fetal Medicine, 2016). These topics are discussed in Chapters 45 (p. 794) and 11 (p. 205), respectively.

■ Diethylstilbestrol-related Abnormalities (Class VII)

In the 1960s, a synthetic nonsteroidal estrogen—diethylstilbestrol (DES)—was used to treat threatened abortion, preterm labor, preeclampsia, and diabetes. It was remarkably ineffective. Moreover, women exposed as fetuses carry increased risks for vaginal clear cell adenocarcinoma, cervical intraepithelial neoplasia, and vaginal adenosis (Hatch, 2001; Herbst, 1971; Robboy, 1984). Women exposed in utero can also show a cervix or vagina with a transverse septum, circumferential ridge, or cervical collar. Uteri are potentially smaller or have a T-shaped cavity (see Fig. 3-5) (Kaufman, 1984). Women exposed as fetuses are now postreproductive, but they did suffer risks for infertility and adverse pregnancy outcome (Kaufman, 2000; Palmer, 2001).

■ Fallopian Tube Abnormalities

The fallopian tubes develop from the unpaired distal ends of the müllerian ducts. Congenital anomalies include accessory ostia, complete or segmental tubal agenesis, and several embryonic cystic remnants. The most common is a small, benign cyst attached by a pedicle to the distal end of the fallopian tube—the hydatid of Morgagni. In other cases, benign paratubal cysts may be of mesonephric or mesothelial origin. Last, in utero exposure to DES is associated with various tubal abnormalities (DeCherney, 1981).

UTERINE FLEXION

Moderate flexion of the pregnant uterus is typically inconsequential, but exaggerated flexion may pose unique complications. *Anteflexion* describes forward angling of the uterine fundus in the sagittal plane relative to the cervix. In extreme cases, the fundus later in pregnancy falls forward to lie below the lower margin of the symphysis. Abdominal wall laxity is contributory. This uterine position can prevent proper transmission of labor contractions but is usually corrected by repositioning and application of an abdominal binder.

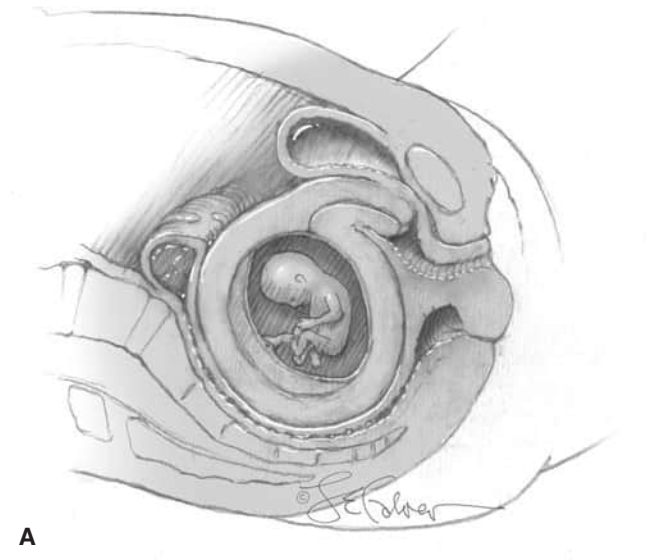

FIGURE 3-8 A. With uterine incarceration, the uterus is wedged between the sacral promontory and symphysis pubis. Resulting pressure against the urethra and rectum can cause urinary retention and constipation, respectively (Reproduced with permission from Corton MM: Anatomy. In Yeomans ER, Hoffman BL, Gilstrap LC III, et al (eds): Cunningham and Gilstrap's Operative Obstetrics, 3rd ed. New York, NY: McGraw Hill; 2017.) **B.** Sagittal transvaginal sonogram shows a first-trimester fetus and incarcerated uterine fundus. The marked retroflexion brings the fundus to lie beneath the cervix. (Reproduced with permission from Dr. Angela Seasley.)

Retroflexion describes uterine fundal angling posteriorly in the sagittal plane. A growing retroflexed uterus fundus will occasionally become trapped in the hollow of the sacrum (Fig. 3-8). Symptoms include pelvic pressure or pain plus voiding dysfunction or retention. During bimanual pelvic examination, the cervix will be anterior and behind the symphysis pubis, whereas the uterus is wedged in the deep pelvis. Sonography or MR imaging can aid diagnosis (Gardner, 2013; Grossenburg, 2011).

With continued uterine growth, the incarcerated uterus can spontaneously resolve over 1 to 2 weeks. A knee-chest position assumed by the patient several times daily may assist resolution (Hooker, 2009). An indwelling urinary catheter or intermittent self-catheterization resolves retention. Persistent cases require manual repositioning. For this, after bladder catheterization, the uterus can usually be pushed out of the pelvis when the woman is placed in a knee-chest position. Often, this is best accomplished by digital pressure applied through the rectum or vagina. Intravenous sedation or spinal analgesia aids comfort and allows sufficient dislodging forces (Hire, 2019). Afterward, insertion of a soft, space-filling pessary for a few weeks usually prevents recurrence (Gibbons, 1969).

For rare resistant cases, advancing a colonoscope or colonoscopic insufflation can dislodge the fundus (Newell, 2014; Seubert, 1999). Upward round ligament traction during laparoscopy also has been described (Lettieri, 1994).

Rarely, *sacculation* may form as an extensive lower uterine segment dilation due to persistent uterine entrapment. Clinically, the elongated vagina extends above the level of the deeply descended fetal head. The Foley catheter is frequently palpated above the level of the umbilicus! In these extreme cases, sonography and MR imaging help define anatomy (Gottschalk, 2008; Lee, 2008). To avoid uterine rupture, cesarean delivery is necessary when sacculation is marked. Spearing (1978) recommended extending the abdominal incision above the umbilicus and delivering the entire uterus from the abdomen before hysterotomy. Correct anatomical relationships are ideally restored to help prevent inadvertent incisions into and through the vagina and bladder (Fig. 3-9). (Singh, 2007; Uma, 2002).

Uterine torsion is another rare acquired anomaly. During pregnancy, the uterus commonly rotates gently to the maternal right. Rotation exceeding 180 degrees creates torsion, and most cases stem from uterine leiomyomas, müllerian anomalies, fetal malpresentation, pelvic adhesions, or laxity of the abdominal wall or uterine ligaments. In one review of 212 cases, associated symptoms were obstructed labor, intestinal or urinary complaints,

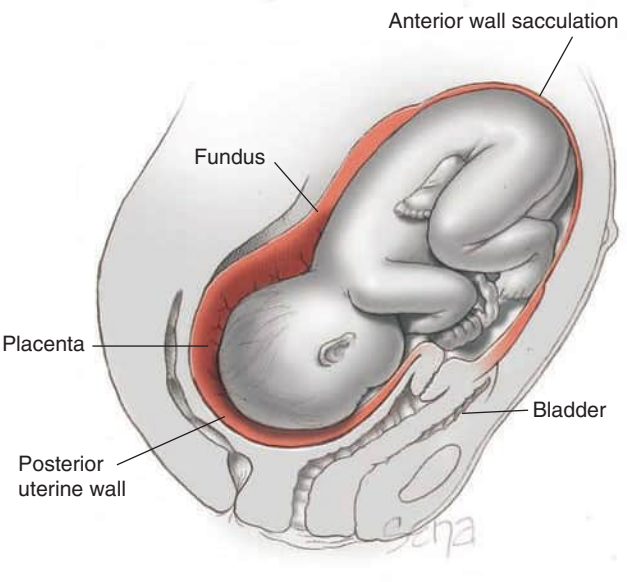

FIGURE 3-9 With anterior sacculation, note the markedly attenuated anterior uterine wall and atypical location of the true uterine fundus.

abdominal pain, uterine hypertonus, vaginal bleeding, or hypotension (Jensen, 1992).

In some women, torsion can be confirmed preoperatively with MR imaging, which shows a twisted vagina that appears X-shaped rather than its normal H-shape (Nicholson, 1995). Flipped placenta location and abnormal umbilical Doppler findings have been described sonographically (Rood, 2014). However, uterine torsion is usually found at the time of cesarean delivery, and the severely rotated uterus should be repositioned anatomically before hysterotomy. In some cases, an inability to reposition or a failure to recognize the torsion may lead to a posterior hysterotomy incision (Albayrak, 2011; Karavani, 2017). Rotation of 90 degrees risks uterine vessel laceration (Berger, 2020).

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CHAPTER 4

Maternal Physiology

The anatomical, physiological, and biochemical adaptations of pregnancy are profound. Many gestational changes begin soon after fertilization and continue throughout pregnancy. Equally astounding is the almost complete return to the prepregnancy state after delivery and lactation. Most pregnancy-related changes are prompted by stimuli provided by the fetus and placenta. Virtually every organ system undergoes alterations, and these can appreciably modify criteria for disease diagnosis and treatment. Thus, an understanding of pregnancy adaptations is essential to avoid misinterpretation. Moreover, some normal physiological changes can unmask or worsen preexisting disease.

REPRODUCTIVE TRACT

Uterus

In the nonpregnant woman, the uterus weighs approximately 70 g and is almost solid, except for a cavity of 10 mL or less. During pregnancy, the uterus is transformed into a thin-walled muscular organ of sufficient capacity to accommodate the fetus, placenta, and amnionic fluid. The total volume of the contents at term averages 5 L but may be 20 L or more! Thus, by the end of pregnancy, the uterus has achieved a capacity that is 500 to 1000 times greater than the nonpregnant state. The corresponding increase in uterine weight is such that, by term, the organ weighs nearly 1100 g.

Uterine hypertrophy early in pregnancy is probably stimulated by the action of estrogen and perhaps progesterone. Thus, similar uterine changes can be observed with ectopic pregnancy. But after approximately 12 weeks' gestation, uterine growth is related predominantly to pressure exerted by the expanding products of conception.

Within the uterus, enlargement is most marked in the fundus. The extent of uterine hypertrophy is also influenced by the position of the placenta. Namely, the myometrium surrounding the placental site grows more rapidly than does the rest.

During pregnancy, uterine enlargement involves stretching and marked hypertrophy of muscle cells, whereas the production of new myocytes is limited. Fibrous tissue also accumulates, particularly in the external muscle layer, together with a considerable rise in elastic tissue content. The walls of the corpus considerably thicken and strengthen during the first few months of pregnancy but then gradually thin. By term, the myometrium is only 1 to 2 cm thick, and the fetus usually can be palpated through the soft, readily indentable uterine walls.

The uterine musculature during pregnancy is arranged in three strata. The first is an outer hoodlike layer, which arches over the fundus and extends into the various ligaments. The middle layer is a dense network of muscle fibers perforated in all directions by blood vessels. Last is an internal layer, with sphincter-like fibers around the fallopian tube orifices and internal cervical os. Most of the uterine wall is formed by the middle layer. Here, each myocyte has a double curve so that the interlacing of any two cells forms a figure eight. This crucial arrangement permits myocytes to contract after delivery and constrict penetrating blood vessels to halt bleeding.

Uterine Shape and Position

For the first few weeks, the uterus maintains its original piriform or pear shape. But, as pregnancy advances, the corpus and fundus become globular and almost spherical by 12 weeks' gestation. Subsequently, the organ grows more rapidly in length than in width and becomes ovoid. By the end of 12 weeks, the enlarged uterus extends out of the pelvis. With growth, it contacts the anterior abdominal wall, displaces the intestines laterally and superiorly, and ultimately reaches almost to the liver. As it ascends, the uterus usually rotates to the right, and this dextrorotation likely is caused by the rectosigmoid on the left side of the pelvis. As the uterus rises, tension is exerted on the broad and round ligaments.

With the pregnant woman standing, the longitudinal axis of the uterus corresponds to an extension of the pelvic inlet axis. The abdominal wall supports the uterus and maintains this axis, unless the wall is lax. When the pregnant woman lies supine, the uterus falls back to rest on the vertebral column and the adjacent great vessels.

Uterine Contractility

Beginning in early pregnancy, the uterus contracts irregularly, and these may be perceived as mild cramps. During the second trimester, these contractions can be detected by bimanual examination. In 1872, J. Braxton Hicks first brought attention to these contractions, which now bear his name. These appear unpredictably and sporadically. Their intensity varies between 5 and 25 mm Hg (Alvarez, 1950). Until near term, these *Braxton Hicks contractions* are infrequent, but their number rises during the last week or two. At this time, the uterus may contract as often as every 10 to 20 minutes and with some degree of rhythmicity. Correspondingly, uterine electrical activity is low and uncoordinated early in gestation but becomes progressively more intense and synchronized by term (Rabotti, 2015). This synchrony develops twice as fast in multiparas compared with nulliparas (Govindan, 2015). Late in pregnancy, these contractions may cause some discomfort and account for so-called false labor (Chap 21, p. 401).

Uteroplacental Blood Flow

The delivery of most substances essential for fetal and placental growth, metabolism, and waste removal requires the placental intervillous space to be adequately perfused (Chap. 5, p. 86). Placental perfusion depends on total uterine blood flow, but simultaneous measurement of uterine, ovarian, and collateral vessels is not yet possible, even using magnetic resonance (MR) angiography (Pates, 2010). For this measurement, early results using four-dimensional flow MR imaging in the primate are promising (MacDonald, 2019).

Doppler ultrasound interrogation of the uterine arteries shows a progressive increase in uteroplacental blood flow during pregnancy. Flow rates rise from approximately 450 mL/min in the midtrimester to nearly 500 to 750 mL/min at 36 weeks' gestation (Flo, 2014; Wilson, 2007). These measures are similar to flow estimates ascertained indirectly using clearance rates of androstenedione and xenon-133 (Edman, 1981; Kauppila, 1980). These values also mirror older ones—500 to 750 mL/min—obtained with invasive methods (Assali, 1953; Metcalfe, 1955). Logically, such massively increased uteroplacental blood flow requires adaptation of the uterine veins as well. The resulting increased venous caliber and distensibility can result in uterine vein varices that rarely may rupture (Lim, 2014).

As noted first from animal studies, uterine contractions, either spontaneous or induced, lower uterine blood flow proportionally to contraction intensity (Assali, 1968). A tetanic contraction yields a precipitous fall in uterine blood flow. In humans, three-dimensional power Doppler angiography has also demonstrated reduced uterine blood flow during contractions (Jones, 2009). Using a similar technique, resistance to blood flow in both maternal and fetal vessels was found to be greater during the second stage of labor compared with the first (Baron, 2015). Given that baseline uterine blood flow is diminished in pregnancies complicated by fetal-growth restriction, these fetuses often tolerate spontaneous labor less effectively (Simeone, 2017).

Uteroplacental Blood Flow Regulation

The vessels that supply the uterine corpus widen and elongate yet preserve their contractile function (Mandala, 2012). As an exception, the spiral arteries, which directly supply the placenta, vasodilate but completely lose contractility. This presumably stems from endovascular trophoblast invasion, which destroys the intramural muscular elements (Chap. 5, p. 92). This vasodilation allows maternal–placental blood flow to progressively rise during gestation. Given that blood flow increases proportionally to the fourth power of the radius of the vessel, small widening of a vessel diameter results in tremendous augmentation of flow. In one study, the uterine artery diameter grew from only 3.3 mm to 3.7 mm between 22 and 29 weeks' gestation, but mean blood flow velocity increased 50 percent, from 29 to 43 cm/sec (Flo, 2010).

The downstream fall in vascular resistance is another key factor that accelerates flow and shear stress in upstream vessels. In turn, shear stress leads to circumferential vessel growth. Nitric oxide—a potent vasodilator—appears to play a central role in regulating this process and is discussed later (p. 65). Endothelial nitric oxide synthase (eNOS) and nitric oxide production are augmented by endothelial shear stress and several hormones and growth factors (Osol, 2019; Zhang, 2017). Factors include estrogen, progesterone, activin, placental growth factor (PlGF), and vascular endothelial growth factor (VEGF), which is a promoter of angiogenesis. As an important aside, VEGF and PlGF signaling is attenuated in response to excess placental secretion of their soluble receptor—*soluble FMS-like tyrosine kinase 1*

(sFlt-1). An elevated maternal sFlt-1 level inactivates and lowers circulating PlGF and VEGF concentrations and is important in preeclampsia pathogenesis (Chap. 40, p. 694).

Normal pregnancy is also characterized by vascular refractoriness to the pressor effects of infused angiotensin II, and this raises uteroplacental blood flow (Rosenfeld, 2012). Other factors that augment uteroplacental blood flow include relaxin and certain adipocytokines (Vodstrcil, 2012). *Chemerin* is an adipocytokine secreted by several tissues, including the placenta (Kasher-Meron, 2014). Its concentration rises as gestation advances and serves to increase human umbilical eNOS activity (Wang, 2015). Another adipocytokine—*visfatin*—raises VEGF secretion and VEGF receptor 2 expression in epithelial cells derived from the placental amnion (Astern, 2013). Other adipocytokines include *leptin*, *resistin,* and *adiponectin,* which all enhance umbilical vein endothelial cell proliferation (Połeć, 2014).

Last, certain microRNA species mediate vascular remodeling and uterine blood flow early in placentation (Santa, 2015). In particular, members of the miR-17–92 cluster and miR-34 are important in spiral artery remodeling and invasion. MicroRNA dysfunction has been reported in preeclampsia, fetal-growth restriction, and gestational diabetes.

Cervix

As early as 1 month after conception, the cervix begins to soften and gain bluish tones. These changes result from increased vascularity and edema of the entire cervix, from alterations in the collagen network, and from hypertrophy and hyperplasia of the cervical glands (Peralta, 2015). Although the cervix contains a small amount of smooth muscle, its major component is connective tissue. Rearrangement of this collagen-rich tissue aids the cervix in retention of the pregnancy until term, in dilation to aid delivery, and in postpartum repair and reconstitution to permit a subsequent successful pregnancy (Myers, 2015). As detailed in Chapter 21 (p. 405), cervical ripening involves connective tissue remodeling that lowers collagen and proteoglycan concentrations and raises water content compared with the nonpregnant cervix.

Cervical glands undergo marked proliferation, and by the end of pregnancy, they occupy up to one half of the entire cervical mass. This normal pregnancy-induced change prompts an extension, or *eversion*, of the proliferating columnar endocervical glands onto the ectocervical portio (Fig. 4-1). This tissue appears red and velvety and bleeds even with minor trauma, such as with Pap smear testing.

The endocervical mucosal cells produce copious amounts of tenacious mucus that obstructs the cervical canal soon after conception (Bastholm, 2017). This mucus is rich in immunoglobulins and cytokines and may act as an immunological barrier to protect the uterine contents against infection (Hansen, 2014). At labor onset, if not before, this *mucus plug* is expelled, resulting in a *bloody show.* Moreover, the cervical mucus consistency changes during pregnancy. Specifically, in most pregnant women, as a result of progesterone, when cervical mucus is spread and dried on a glass slide, it shows poor crystallization, termed *beading*. In some gravidas, as a result of amnionic fluid leakage, an arborization of ice-like crystals, called *fern*ing, is seen microscopically.

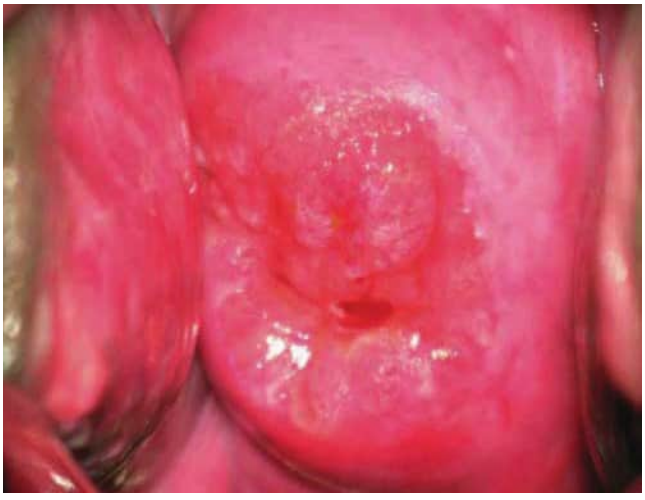

FIGURE 4-1 Cervical eversion of pregnancy as viewed through a colposcope. The eversion represents columnar epithelium on the portio of the cervix. (Reproduced with permission from Dr. Claudia Werner.)

Histologically, basal cells near the squamocolumnar junction can be prominent in size, shape, and staining quality in pregnancy. These changes are considered to be estrogen induced. In addition, pregnancy is associated with both endocervical gland hyperplasia and hypersecretory appearance—the *Arias-Stella reaction*. This cytologic change can make differentiating these from truly atypical glandular cells during Pap test evaluation particularly difficult (Rosai, 2015).

Ovaries

Ovulation ceases during pregnancy, and maturation of new follicles is suspended. The single corpus luteum functions maximally during the first 6 to 7 weeks of pregnancy—4 to 5 weeks postovulation. Thereafter, it contributes relatively little to progesterone production. As discussed in Chapter 66 (p. 1170), surgical removal of the corpus luteum before 7 weeks' gestation prompts a rapid fall in maternal serum progesterone levels and spontaneous abortion (Csapo, 1973). In these cases, exogenous progesterone is necessary for pregnancy maintenance until placental function is sufficient. After 7 weeks, however, corpus luteum excision ordinarily does not cause abortion.

An extrauterine *decidual reaction* on and just beneath the ovarian surface is common in pregnancy and is usually observed at cesarean delivery. These appear as slightly elevated clear or red blisters or patches that bleed easily and may, on first glance, resemble freshly torn adhesions. Similar decidual reactions are seen on the uterine serosa and other pelvic, or even extrapelvic, abdominal organs (Bloom, 2010). These areas arise from subcoelomic mesenchyme or endometriotic lesions that have been stimulated by progesterone. They histologically appear similar to progestin-stimulated intrauterine endometrial stroma (Kim, 2015).

The enormous caliber of the ovarian veins viewed at cesarean delivery is startling. Hodgkinson (1953) found that the diameter of the ovarian vascular pedicle increased during pregnancy from 0.9 cm to approximately 2.6 cm at term. Again, recall

that flow in a tubular structure increases exponentially as the diameter enlarges.

Relaxin

This protein hormone is secreted by the corpus luteum, the decidua, and the placenta in a pattern similar to that of human chorionic gonadotropin (hCG) (Chap. 5, p. 97). Relaxin is also expressed in brain, heart, and kidney. It is mentioned here because its secretion by the corpus luteum appears to aid many maternal physiological adaptations, such as remodeling of reproductive-tract connective tissue to accommodate labor (Vrachnis, 2015). Relaxin also appears important in initiating augmented renal hemodynamics, lowering serum osmolality, and increasing arterial compliance, which are all associated with normal pregnancy (Conrad, 2015). Despite its name, serum relaxin levels do not contribute to greater peripheral joint laxity or pelvic girdle pain during pregnancy (Aldabe, 2012; Marnach, 2003).

Theca-Lutein Cysts

These benign ovarian lesions reflect exaggerated physiological follicle stimulation, which is termed *hyperreactio luteinalis.* The resulting bilateral cystic ovaries are variably enlarged. The reaction is usually linked to markedly elevated serum hCG levels. Logically, theca-lutein cysts are found frequently with gestational trophoblastic disease (Fig. 13-3, p. 238). They may also develop with the placentomegaly that can accompany diabetes, anti-D alloimmunization, and multifetal gestation. Hyperreactio luteinalis is associated with preeclampsia and hyperthyroidism, which may contribute to elevated risks for fetal-growth restriction and preterm birth (Lynn, 2013; Malinowski, 2015). These cysts are also encountered in women with otherwise uncomplicated pregnancies. In these cases, an exaggerated response of the ovaries to normal levels of circulating hCG is suspected (Sarmento Gonçalves, 2015).

Although usually asymptomatic, hemorrhage into the cysts can cause acute abdominal pain (Amoah, 2011). Maternal virilization may be seen in up to 30 percent of women, however, virilization of the fetus has only rarely been reported. Maternal findings that include temporal balding, hirsutism, and clitoromegaly are associated with massively elevated levels of androstenedione and testosterone. The diagnosis typically is based on sonographic findings of bilateral enlarged ovaries containing multiple cysts in the appropriate clinical settings. The condition is self-limited and resolves following delivery. Its management was reviewed by Malinowski (2015) and discussed further in Chapter 66 (p. 1171).

Fallopian Tubes

The fallopian tube musculature, that is, the *myosalpinx*, undergoes little hypertrophy during pregnancy. The epithelium of the *endosalpinx* somewhat flattens. Decidual cells may develop in the stroma of the endosalpinx, but a continuous decidual membrane is not formed. Rarely, a fallopian tube may twist during uterine enlargement, but this torsion is more common with comorbid paratubal or ovarian cysts (Lee, 2015; Macedo, 2017).

Vagina and Perineum

During pregnancy, greater vascularity and hyperemia develop in the skin and muscles of the perineum and vulva, and the underlying abundant connective tissue softens. This augmented vascularity prominently affects the vagina and cervix and results in the violet color characteristic of the *Chadwick sign.*

Within the vagina, the considerably elevated volume of cervical secretions during pregnancy forms a somewhat thick, white discharge. The pH is acidic and varies from 3.5 to 6. This pH results from increased production of lactic acid by *Lactobacillus acidophilus* during metabolism of glycogen energy stores in the vaginal epithelium. Pregnancy is associated with an elevated risk of vulvovaginal candidiasis, particularly during the second and third trimesters. Higher infection rates may stem from immunological and hormonal changes and from greater vaginal glycogen stores (Aguin, 2015).

The vaginal walls undergo striking changes in preparation for the distention that accompanies labor and delivery. These include considerable epithelial thickening, connective tissue loosening, and hypertrophy of smooth muscle cells.

Pelvic Organ Prolapse

Pelvic Organ Prolapse Quantification (POP-Q) scores and sonographic studies show that vaginal support changes across pregnancy. In particular, vaginal lengthening, posterior vaginal wall and hiatal relaxation, increased levator hiatal area, and greater first-trimester vaginal elastase activity are all associated with uncomplicated spontaneous vaginal delivery (Oliphant, 2014). The larger hiatal area persists in women who deliver vaginally compared with women delivering by prelabor or early-labor cesarean delivery. However, all women show greater hiatal distensibility after delivery, which is potentially a factor in later pelvic floor dysfunction (Blomqvist, 2018; Friedman, 2019).

In women with existing apical vaginal prolapse, the cervix, and occasionally a portion of the uterine body, can protrude variably from the vulva during early pregnancy. With further growth, the uterus usually rises above the pelvis and can draw the cervix up with it. If the uterus persists in its prolapsed position, symptoms of incarceration may develop at 10 to 14 weeks' gestation (Chap. 3, p. 46). As a preventive measure, the uterus can be replaced early in pregnancy and held in position with a space-filling pessary.

Attenuation of anterior vaginal wall support can lead to prolapse of the bladder, that is, cystocele. Associated urinary stasis can predispose to infection. Pregnancy may also worsen coexistent *stress urinary incontinence (SUI)*, likely because urethral closing pressures do not rise sufficiently to compensate for altered bladder neck support. Urinary incontinence affects nearly 20 percent of women during the first trimester and nearly 40 percent during the third trimester. Most cases stem from SUI rather than urgency urinary incontinence (Abdullah, 2016; Franco, 2014). In primigravidas, maternal age greater than 30 years, obesity, smoking, constipation, and gestational diabetes mellitus are all risk factors associated with incontinence during pregnancy (Sangsawang, 2014).

Attenuation of posterior vaginal wall support can lead to rectocele, and a large defect may fill with feces. Splinting, in

which a finger is inserted into the vagina, can bolster posterior wall support to aid evacuation. Occasionally, digital rectal disimpaction is needed. Uncommonly during labor, fetal descent is blocked by a cystocele or rectocele. Emptying by catheterization or enema and compressing the bulge with vaginal fingers will resolve the impasse. Rarely, a large enterocele may bulge into the vagina to block descent. Similarly, the hernia sac and its abdominal contents are gently reduced.

BREASTS

In early pregnancy, women often experience breast tenderness and paresthesias. After the second month, the breasts grow in size, and delicate veins are visible just beneath the skin. The nipples become considerably larger, more deeply pigmented, and more erectile. After the first few months, a thick, yellowish fluid—*colostrum*—can often be expressed from the nipples by gentle massage. During the same months, the areolae become broader and more deeply pigmented. Scattered through each areola are several small elevations, the *glands of Montgomery*, which are hypertrophic sebaceous glands. If breasts gain extensive size, skin striae similar to those observed in the abdomen may develop. Rarely, breasts can become pathologically enlarged—referred to as *gigantomastia*—which may require consideration of postpartum bromocriptine and later surgical reduction (Rezai, 2015; Türkan, 2016).

For most, prepregnancy breast size and ultimate volume of breast milk do not correlate. Multiple factors influence milk production and are discussed in Chapter 36 (p. 640).

SKIN

Skin changes are common, and Fernandes and Amaral (2015) described dermatological changes in more than 900 pregnant women. They found at least one physiological cutaneous change in 89 percent of the women examined. Dermatological pathologies during pregnancy are found in Chapter 65.

Abdominal Wall

Beginning after midpregnancy, reddish, slightly depressed streaks commonly develop in the skin. These are called *striae gravidarum* or *stretch marks.* In multiparas, glistening, silvery lines that represent the cicatrices of previous striae frequently coexist. In one study of 800 primiparas, 70 percent developed striae gravidarum on their abdomen; 33 percent on their breasts; and 41 percent on their hips and thighs (Picard, 2015). The strongest associated risk factors included younger maternal age, family history, and prepregnancy weight and weight gain during pregnancy. The etiology of striae gravidarum is unknown, but aloe vera gel and almond oil decrease itching and may help to prevent progression (Hajhashemi, 2018).

Occasionally, the muscles of the abdominal walls do not withstand the tension of the expanding pregnancy. As a result, rectus muscles separate in the midline, creating *diastasis recti* of varying extent. If severe, a considerable portion of the anterior uterine wall is covered by only a layer of skin, attenuated fascia, and peritoneum to form a ventral hernia.

Hyperpigmentation

This develops in up to 90 percent of women and is usually more accentuated in those with darker complexion (Bieber, 2017). Of specific sites, the pigmented skin line in the midline of the anterior abdominal wall—the *linea alba*—takes on dark brown-black pigmentation to form the *linea nigra.* Occasionally, irregular brownish patches of varying size appear on the face and neck, giving rise to *chloasma* or *melasma gravidarum*—the *mask of pregnancy*. Pigmentation of the areolae and genital skin also may be accentuated. After delivery, these pigmentary changes usually disappear or at least regress considerably. Oral contraceptives may cause similar alterations (Handel, 2014).

The etiology of these pigmentary changes is incompletely understood, however, hormonal and genetic factors are implicated. Levels of melanocyte-stimulating hormone, a polypeptide similar to corticotropin, are elevated remarkably throughout pregnancy, and estrogen and progesterone also are reported to have melanocyte-stimulating effects.

Vascular Changes

Angiomas, called *vascular spiders*, are particularly common on the face, neck, upper chest, and arms. These are minute, red skin papules with radicles branching out from a central lesion. The condition is often designated as nevus, angioma, or telangiectasis. *Palmar erythema* is encountered during pregnancy. Both conditions lack clinical significance and disappear in most gravidas shortly after pregnancy. They are likely the consequence of hyperestrogenemia. In addition to these discrete lesions, increased cutaneous blood flow in pregnancy serves to dissipate excess heat generated by augmented metabolism.

Hair Changes

Throughout life, the human hair follicle undergoes a pattern of cyclic activity that includes periods of hair growth (anagen phase), apoptosis-driven involution (catagen phase), and a resting period (telogen phase). Based on a study of 116 healthy pregnant women, the anagen phase lengthens during pregnancy and the telogen rate increases postpartum (Gizlenti, 2014). Neither is exaggerated in most gravidas, but excessive hair loss in the puerperium is termed *telogen effluvium* (Stoehr, 2019).

METABOLIC CHANGES

In response to the greater demands of the rapidly growing fetus and placenta, the pregnant woman undergoes numerous metabolic changes. By the third trimester, maternal basal metabolic rate rises by 20 percent compared with that of the nonpregnant state (Berggren, 2015). This rate grows by an additional 10 percent in women with a twin gestation (Shinagawa, 2005). This is stratified as 85, 285, and 475 kcal/d during the first, second, and third trimesters, respectively (Table 4-1) (World Health Organization, 2004). Of note, Abeysekera and coworkers (2016) reported that women accrue fat mass during pregnancy despite the increased total energy expenditure and without significant change in energy intake. This suggests more efficient energy storage.

TABLE 4-1. Additional Energy Demands During Normal Pregnancy[a]

	Rates of Tissue Deposition			
	1st Trimester g/d	2nd Trimester g/d	3rd Trimester g/d	Total Deposition g/280 d
Weight gain	17	60	54	12,000
Protein deposition	0	1.3	5.1	597
Fat deposition	5.2	18.9	16.9	3741

Energy Cost of Pregnancy Estimated from Basal Metabolic Rate and Energy Deposition					
	1st Trimester kJ/d	2nd Trimester kJ/d	3rd Trimester kJ/d	Total Energy Cost	
				MJ	Kcal
Protein deposition	0	30	121	14.1	3370
Fat deposition	202	732	654	144.8	34,600
Efficiency of energy utilization[b]	20	76	77	15.9	3800
Basal metabolic rate	199	397	993	147.8	35,130
Total energy cost of pregnancy	**421**	**1235**	**1845**	**322.6**	**77,100**

[a]Assumes an average gestational weight gain of 12 kg.
[b]Efficiency of food energy utilization for protein and fat deposition estimated as 0.90.

Most of the normal weight gain in pregnancy is attributable to the uterus and its contents, the breasts, and expanded blood and extravascular extracellular fluid volumes. A smaller fraction results from metabolic alterations that promote accumulation of cellular water, fat, and protein, which are so-called maternal reserves. The average weight gain during pregnancy approximates 12.5 kg or 27.5 lb, and this value has remained consistent across studies and over time (Hytten, 1991; Jebeile, 2016). Weight gain is detailed in Table 4-2 and in Chapter 10 (p. 183) (Hytten, 1991).

Water Metabolism

In pregnancy, greater water retention is normal and mediated in part by a drop in plasma osmolality of 10 mOsm/kg. As shown in Figure 4-2, this decline develops in early pregnancy and is induced by a reset of osmotic thresholds for thirst and vasopressin secretion (Lindheimer, 2001). Relaxin and other hormones are thought to play a role (Conrad, 2013).

TABLE 4-2. Weight Gain Based on Pregnancy-Related Components

	Cumulative Increase in Weight (g)			
Tissues and Fluids	10 Weeks	20 Weeks	30 Weeks	40 Weeks
Fetus	5	300	1500	3400
Placenta	20	170	430	650
Amnionic fluid	30	350	750	800
Uterus	140	320	600	970
Breasts	45	180	360	405
Blood	100	600	1300	1450
Extravascular fluid	0	30	80	1480
Maternal stores (fat)	310	2050	3480	3345
Total	**650**	**4000**	**8500**	**12,500**

Maternal serum osmolality is significantly lower than umbilical arterial osmolality to favor water transport to the fetus (Moen, 2018). At term, the water content of the fetus, placenta, and amnionic fluid approximates 3.5 L. Another 3.0 L accumulates from expanded maternal blood volume and from uterus and breast growth. Thus, the minimum amount of extra water that the average woman accrues during normal pregnancy approximates 6.5 L. This corresponds to almost 15 lb.

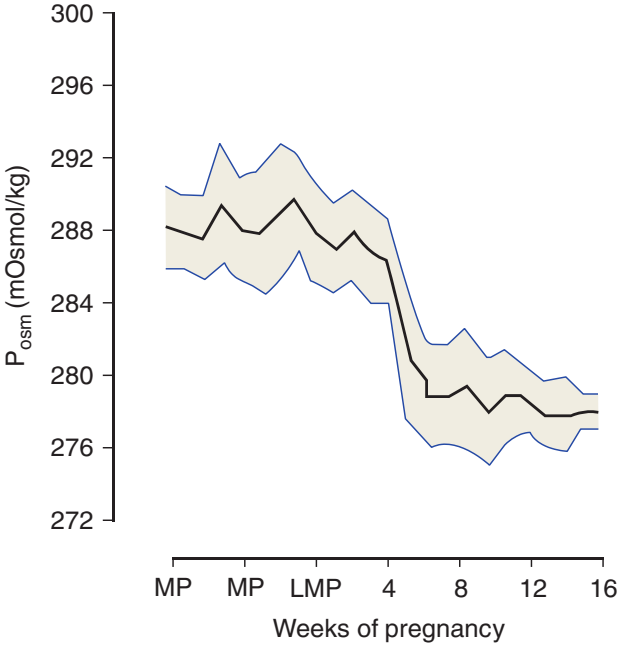

FIGURE 4-2 Mean values (*black line*) ± standard deviations (*blue lines*) for plasma osmolality (P_{osm}) measured at weekly intervals in nine women from preconception to 16 weeks. LMP = last menstrual period; MP = menstrual period. (Redrawn from Davison JM, Dunlop W. Renal hemodynamics and tubular function normal human pregnancy, Kidney Int 1980 Aug;18(2):152–161.)

Demonstrable pitting edema of the ankles and legs is seen in most gravidas, especially at the day's end. This fluid accumulation may amount to a liter or so. It results from greater venous pressure below the level of the uterus as a consequence of partial vena cava occlusion. A decline in interstitial colloid osmotic pressure induced by normal pregnancy also favors edema late in pregnancy (Øian, 1985).

Longitudinal studies of body composition show a progressive accumulation of total body water and fat mass during pregnancy. These two components as well as initial maternal weight and weight gained during pregnancy are highly associated with neonatal birthweight (Lederman, 1999). As discussed in Chapter 51 (p. 905), "overnourished" women are more likely to deliver oversized neonates, even when glucose tolerant.

Protein Metabolism

The products of conception, the uterus, and maternal blood are relatively rich in protein rather than fat or carbohydrate. At term, the normally grown fetus and placenta together weigh about 4 kg and contain approximately 500 g of protein, or about half of the total pregnancy increase. The remaining 500 g is added to the uterus as contractile protein, to the breasts primarily in the glands, and to maternal blood as hemoglobin and plasma proteins.

Amino acid concentrations are higher in the fetal than in the maternal compartment and generally result from facilitated transport across the placenta (Panitchob, 2015). This greater concentration is largely regulated by the placenta through an incompletely understood process (Chap. 7, p. 136). In particular, placental transport is variable for individuals and for different amino acids. For example, tyrosine is a conditionally essential amino acid in the preterm neonate but not in the fetus (Van den Akker, 2011). The placenta concentrates amino acids into the fetal circulation and is also involved in protein synthesis, oxidation, and transamination of some nonessential amino acids (Galan, 2009).

Maternal protein intake does not appear to be a critical determinant for birthweight among well-nourished women (Chong, 2015). Still, recent data suggest that current recommendations for protein intake may be too low. These guidelines are extrapolated from nonpregnant adults and may underestimate actual needs. Stephens and colleagues (2015) prospectively analyzed maternal protein intake and metabolism. They estimated average requirements of 1.22 g/kg/d of protein for early pregnancy and 1.52 g/kg/d for late pregnancy. These levels are higher than the current recommendation of 0.88 g/kg/d. Dietary protein intake is discussed in Chapter 10 (p. 185).

Carbohydrate Metabolism

Normal pregnancy is characterized by mild fasting hypoglycemia, postprandial hyperglycemia, and hyperinsulinemia (Fig. 4-3) (Phelps, 1981). This elevated basal level of plasma insulin in normal pregnancy is associated with several unique responses to glucose ingestion. Specifically, after an oral

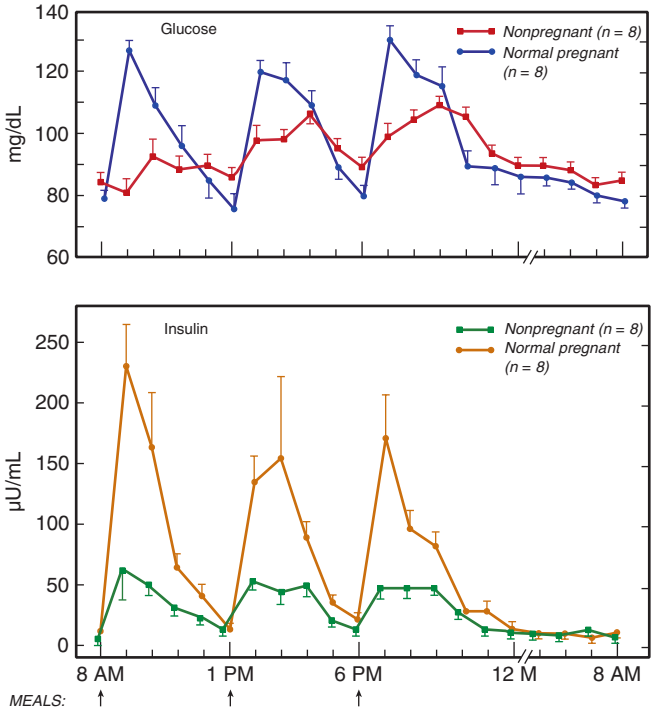

FIGURE 4-3 Diurnal changes in plasma glucose and insulin in normal late pregnancy.

glucose meal, gravidas demonstrate prolonged hyperglycemia and hyperinsulinemia and a greater suppression of glucagon. This cannot be explained by an increased metabolism of insulin because its half-life during pregnancy is not changed appreciably (Lind, 1977). Instead, this response reflects a pregnancy-induced state of peripheral insulin resistance, which ensures a sustained postprandial supply of glucose to the fetus. Indeed, insulin sensitivity in late normal pregnancy is 30 to 70 percent lower than that of nonpregnant women (Lowe, 2014).

The mechanisms responsible for this reduced insulin sensitivity include numerous endocrine and inflammatory factors (Angueira, 2015). In particular, pregnancy-related hormones such as progesterone, placentally derived growth hormone, prolactin, and cortisol; cytokines such as tumor necrosis factor; and hormones derived from central adiposity, particularly leptin and its interplay with prolactin, all have a role in the insulin resistance of pregnancy. Even so, insulin resistance is not the only factor to elevate postprandial glucose values. Hepatic gluconeogenesis is augmented during both diabetic and nondiabetic pregnancies, particularly in the third trimester (Angueira, 2015).

When fasting overnight, the pregnant woman changes from a postprandial state characterized by elevated and sustained glucose levels to a fasting state characterized by lower levels of plasma glucose and some amino acids. Instead, plasma concentrations of free fatty acids, triglycerides, and cholesterol are higher in the fasting state. This pregnancy-induced switch in fuels from glucose to lipids has been called *accelerated starvation.* Certainly, when fasting is prolonged in the pregnant woman, these alterations are exaggerated and ketonemia rapidly appears.

Fat Metabolism

The concentrations of lipids, lipoproteins, and apolipoproteins in plasma rise appreciably during pregnancy (Appendix, p. 1231). Increased insulin resistance and estrogen stimulation during pregnancy are responsible for maternal hyperlipidemia. Augmented lipid synthesis and food intake contribute to maternal fat accumulation during the first two trimesters. Overweight women who have excessive gestational weight gain accrue fat mass (Berggren, 2016). In the third trimester, however, fat storage declines or ceases. This is a consequence of enhanced lipolytic activity, and decreased lipoprotein lipase activity reduces circulating triglyceride uptake into adipose tissue. This transition to a catabolic state favors maternal use of lipids as an energy source and spares glucose and amino acids for the fetus.

Maternal hyperlipidemia is one of the most consistent and striking changes of lipid metabolism during late pregnancy. Triacylglycerol and cholesterol levels in very-low-density lipoproteins (VLDLs), low-density lipoproteins (LDLs), and high-density lipoproteins (HDLs) are increased during the third trimester compared with those in nonpregnant women (Table 4-3). After delivery, the concentrations of these lipids, lipoproteins, and apolipoproteins decline. Breastfeeding drops maternal triglyceride levels but increases those of HDL cholesterol (HDL-C). The effects on total cholesterol and LDL cholesterol levels are unclear (Gunderson, 2014).

Hyperlipidemia is theoretically a concern because it is associated with endothelial dysfunction. That said, endothelium-dependent vasodilation responses actually improve across pregnancy (Saarelainen, 2006). This is partly because increased HDL-C concentrations likely inhibit LDL oxidation and thus protect the endothelium. These findings suggest that the increased cardiovascular disease risk in multiparas may be related to factors other than maternal hypercholesterolemia.

Leptin

This peptide hormone is primarily secreted by adipose tissue in nonpregnant humans. It plays a key role in body fat and energy expenditure regulation and in reproduction. For example, leptin is important for implantation, cell proliferation, and angiogenesis (Vazquez, 2015). Leptin deficiency is associated with anovulation and infertility, whereas certain leptin mutations cause extreme obesity (Tsai, 2015).

Among normal-weight gravidas, serum leptin levels rise and peak during the second trimester and plateau until term in concentrations two to four times higher than those in nonpregnant women. Among obese women, leptin levels correlate with adiposity (Tsai, 2015). In all cases, leptin levels fall after delivery, reflecting the significant amounts produced by the placenta (Vazquez, 2015).

Leptin participates in regulating energy metabolism during pregnancy. Despite the rise in leptin concentrations during pregnancy, reduced leptin sensitivity to food intake during pregnancy has been described (Chehab, 2014). This "leptin resistance" may serve to promote energy storage during pregnancy and for later lactation.

Higher leptin levels during pregnancy may be disadvantageous under certain situations, such as maternal obesity. Leptin functions as a proinflammatory cytokine in white adipose tissue, which may dysregulate the inflammatory cascade and lead to placental dysfunction in obese women (Vazquez, 2015). In addition, abnormally elevated leptin levels have been associated with preeclampsia, gestational diabetes, and fetal distress (Rabiepoor, 2019; Taylor, 2015).

Fetal leptin is important for the development of several organs that include the pancreas, kidney, heart, and brain. Fetal levels correlate with maternal body mass index and birthweight (Özdemir, 2020). Lower levels are linked to fetal-growth restriction (Briffa, 2015).

TABLE 4-3. Plasma Concentrations of Lipids

Lipid	Nonpregnant	Third Trimester[a,b]
Total cholesterol	<200 mg/dL	267 ± 30 mg/dL
LDL	<100 mg/dL	136 ± 33 mg/dL
HDL	40–60 mg/dL	81 ± 17 mg/dL
Triglycerides	<150 mg/dL	245 ± 73 mg/dL

[a]Values from the Appendix (p. 1231).
[b]Values expressed as mean ± standard deviation.
HDL = high-density lipoprotein; LDL = low-density lipoprotein.

Other Adipocytokines

Dozens of hormones with metabolic and/or inflammatory functions are produced by adipose tissue. *Adiponectin* is a peptide produced primarily in maternal fat but not in the placenta (Haghiac, 2014). It may play a role in early pregnancy to assure a source of glycogen for fetal energy (Duval, 2018). Adiponectin levels inversely correlate with adiposity, and it acts as a potent insulin sensitizer. Despite reduced adiponectin levels in women with gestational diabetes, directed assays are not useful for predicting diabetes development (Hauguel-de Mouzon, 2013).

Ghrelin is a peptide secreted mainly by the stomach in response to hunger. It cooperates with other neuroendocrine factors, such as leptin, in energy homeostasis. Ghrelin is also expressed in the placenta and likely has a role in fetal growth and cell proliferation (González-Domínguez, 2016).

Visfatin is a peptide that was first identified as a growth factor for B lymphocytes but is mainly produced within adipose tissue. Mumtaz and associates (2015) propose that elevated levels of visfatin and leptin impair uterine contractility. Such findings may provide a physiological basis for the observation that maternal obesity raises the risk for dysfunctional labor.

Electrolyte and Mineral Metabolism

During normal pregnancy, nearly 1000 mEq of *sodium* and 300 mEq of *potassium* are retained (Lindheimer, 1987). The glomerular filtration rate of sodium and potassium is increased, but the excretion of these electrolytes is unchanged during pregnancy as a result of enhanced tubular resorption (Brown, 1988). Although total accumulations of sodium and potassium are elevated, their serum concentrations are diminished slightly (Appendix, p. 1229). Several mechanisms may explain these

lower levels (Odutayo, 2012). In the case of potassium, it possibly involves the expanded plasma volume of pregnancy. With respect to sodium, osmoregulation is altered, and the threshold for arginine vasopressin release is lowered. This promotes free water retention and diminished sodium levels.

Total serum *calcium* levels, which include both ionized and nonionized calcium, decrease during pregnancy. This reduction follows lowered plasma albumin concentrations and in turn a consequent decline in the amount of circulating protein-bound nonionized calcium. Serum ionized calcium levels, however, remain unchanged (Olausson, 2012).

The developing fetus imposes a significant demand on maternal calcium homeostasis. For example, the fetal skeleton accrues approximately 30 g of calcium by term, 80 percent of which is deposited during the third trimester. This demand is largely met by a doubling of maternal intestinal calcium absorption mediated partly by 1,25-dihydroxyvitamin D_3, the serum levels of which also are doubled. These higher levels of vitamin D are possibly stimulated by a twofold rise in parathyroid hormone (PTH)-related peptide levels produced by several tissues including the placenta (Olausson, 2012). To help compensate, dietary intake of sufficient calcium is necessary to prevent excess depletion from the mother. A list of all recommended daily allowances is found in Table 10-5 (p. 184). This is especially important for pregnant adolescents, in whom bones are still developing (Cullers, 2019). Unfortunately, a lack of robust data prevents drawing firm conclusions regarding the utility of calcium and vitamin D supplements during pregnancy (Bi, 2018; Hofmeyr, 2018).

Serum *magnesium* levels also decline during pregnancy. Compared with nonpregnant women, both total and ionized magnesium concentrations are significantly lower during normal pregnancy (Rylander, 2014).

Serum *phosphate* levels lie within the nonpregnant range (Larsson, 2008). Although calcitonin is an important regulator of serum calcium and phosphate, the importance of calcitonin as it relates to pregnancy is poorly understood (Olausson, 2012).

Iodine requirements increase during normal pregnancy for several reasons (Moleti, 2014). First, maternal thyroxine (T4) production rises to maintain maternal euthyroidism and to transfer thyroid hormone to the fetus prior to fetal thyroid functioning. Second, fetal thyroid hormone production increases during the second half of pregnancy. This contributes to greater maternal iodine requirements because iodine readily crosses the placenta. Third, the primary route of iodine excretion is the kidney. Beginning in early pregnancy, the iodine glomerular filtration rate increases by 30 to 50 percent. In sum, because of greater thyroid hormone production, fetal iodine requirements, and augmented renal clearance, dietary iodine needs are higher during normal gestation (Velasco, 2018).

Although the placenta has the ability to store iodine, whether this organ functions to protect the fetus from inadequate maternal dietary iodine is currently unknown. Iodine deficiency is discussed later in this chapter (p. 72) and in Chapter 61 (p. 1097). Extremely low or high maternal iodine intake may affect childhood neurodevelopment (Zhou, 2019). At the extreme, maternal supplements containing excessive iodine have been associated with congenital hypothyroidism. This stems from autoregulation in the thyroid gland—known as the *Wolff-Chaikoff effect*—to curb T4 production in response to iodine overconsumption.

The serum levels of many of these minerals are listed in the Appendix (p. 1229). With respect to most other minerals, pregnancy induces little change in their metabolism other than their retention in amounts equivalent to those needed for growth. An important exception is the considerably greater requirement for *iron*, which is discussed subsequently (Georgieff, 2021).

HEMATOLOGICAL CHANGES

Blood Volume

The well-known hypervolemia associated with normal pregnancy averages 40 to 45 percent above the nonpregnant blood volume after 32 to 34 weeks' gestation (Pritchard, 1965; Zeeman, 2009). In some, accumulated volume rises only modestly, whereas in others blood volume nearly doubles. A fetus is not essential, as augmented blood volume develops in some with hydatidiform mole. The stimulus is not known, but it likely is related to renin and prorenin with its effects on sodium and water retention (Fu, 2018). Simultaneously, vascular plasticity accommodates the larger blood volume (Osol, 2019).

Pregnancy-induced hypervolemia serves several functions. First, it meets the metabolic demands of the enlarged uterus and its greatly hypertrophied vascular system. It also provides abundant nutrients and elements to support the rapidly growing placenta and fetus. The expanded intravascular volume protects the mother, and in turn the fetus, against the deleterious effects of impaired venous return in the supine and erect positions. Last, it safeguards the mother against the adverse effects of parturition-associated blood loss.

Maternal blood volume begins to accrue during the first trimester. By 12 menstrual weeks, plasma volume expands by approximately 15 percent compared with that prior to pregnancy (Bernstein, 2001). Maternal blood volume grows most rapidly during the midtrimester, rises at a much slower rate during the third trimester, and reaches a plateau during the last several weeks of pregnancy (Fig. 4-4) (Thomsen, 1994). Blood volume accrues even more dramatically in twin gestations.

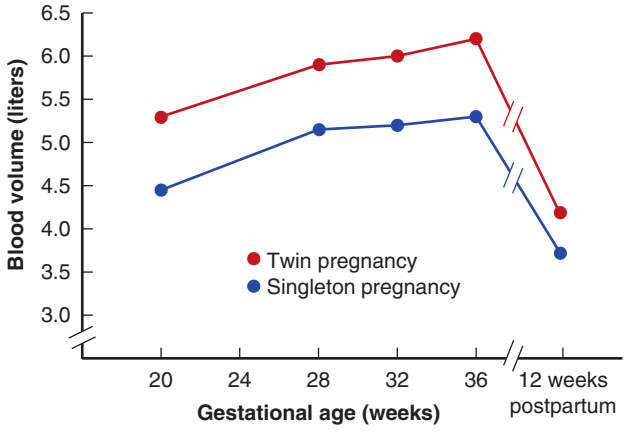

FIGURE 4-4 Blood volume expansion during pregnancy in twins (n = 10) and singletons (n = 40). Data shown as medians.

During blood volume expansion, plasma volume and erythrocyte mass increase. Although more plasma than erythrocytes is usually added to the maternal circulation, the increase in erythrocyte volume is considerable and averages 450 mL (Pritchard, 1960). Moderate erythroid hyperplasia develops in the bone marrow, and the reticulocyte count is elevated slightly during normal pregnancy. These changes are almost certainly related to the rise in maternal plasma erythropoietin levels (Appendix, p. 1227).

Because of great plasma augmentation, both hemoglobin concentration and hematocrit decline slightly during pregnancy. As a result, whole blood viscosity decreases (Huisman, 1987). Hemoglobin concentration at term averages 12.5 g/dL, and in approximately 5 percent of women it is below 11.0 g/dL. Thus, a concentration <11.0 g/dL, especially late in pregnancy, is considered abnormal and usually due to iron-deficiency anemia rather than pregnancy hypervolemia (Chap. 59, p. 1049).

Iron Metabolism

The total iron content of normal adult women ranges from 2.0 to 2.5 g, or approximately half that found normally in men. Most of this is incorporated in hemoglobin or myoglobin, and thus iron stores of normal young women approximate only 300 mg (Pritchard, 1964). Although the lower iron levels in women may be partly due to menstrual blood loss, other factors have a role. One is *hepcidin*—a peptide hormone that functions as a homeostatic regulator of systemic iron metabolism (Fisher, 2017). As shown in Figure 4-5, hepcidin levels drop early in pregnancy (Hedengran, 2016a,b). Lower hepcidin levels are associated with greater absorption of iron via ferroportin in enterocytes (Camaschella, 2015). Lower hepcidin levels also augment iron transport into the fetus via ferroportin in syncytiotrophoblast. Hepcidin levels rise with inflammation, but drop with iron deficiency and increased amount of several hormones, including testosterone, estrogen, vitamin D, and possibly prolactin (Liu, 2016).

Of the approximate 1000 mg of iron required for normal pregnancy, about 300 mg is actively transferred to the fetus and placenta, and another 200 mg is lost through various normal excretion routes, primarily the gastrointestinal tract. These are obligatory losses and accrue even when the mother is iron deficient. The average increase in the total circulating erythrocyte volume—about 450 mL—requires another 500 mg. Recall that each 1 mL of erythrocytes contains 1.1 mg of iron.

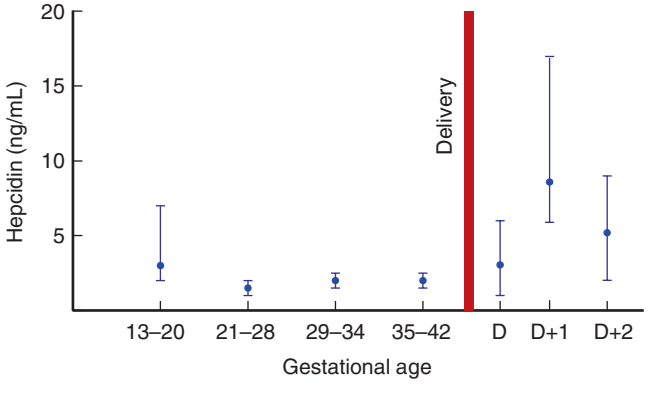

FIGURE 4-5 Hepcidin levels during pregnancy. Blue data points are median values and crossbars are the 25th and 75th percentiles. D is delivery and D + 1 and D + 2 are postpartum days 1 and 2.

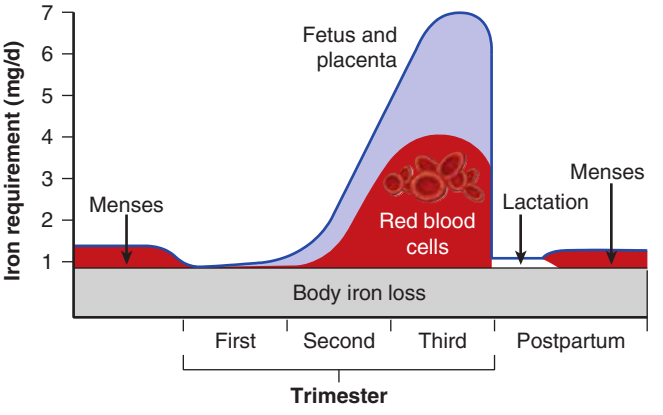

FIGURE 4-6 Estimated daily iron requirements during pregnancy in a 55-kg woman.

As shown in Figure 4-6, most iron is used during the latter half of pregnancy (Koenig, 2014). Thus, the iron requirement becomes large after midpregnancy and averages 6 to 7 mg/d (Pritchard, 1970). In most women, this amount is usually not available from iron stores or diet. If the nonanemic pregnant woman is not given supplemental iron, serum iron and ferritin concentrations decline after midpregnancy. Moreover, the optimal rise in maternal erythrocyte volume will not develop, and the hemoglobin concentration and hematocrit will fall appreciably as plasma volume rises. At the same time, fetal red cell production is not impaired because the placenta transfers iron even if the mother has marked iron-deficiency anemia. In severe cases, we have documented maternal hemoglobin values of 3 g/dL, and at the same time, fetuses had hemoglobin concentrations of 16 g/dL. The mechanisms of placental iron transport and regulation are complex (Koenig, 2014; McArdle, 2014).

With normal vaginal delivery, at least 500 to 600 mL of blood is typically lost, and thus not all the maternal iron added in the form of hemoglobin is spent. The excess hemoglobin iron postpartum becomes stored iron.

Immunological Functions

Pregnancy is associated with suppression of various humoral and cell-mediated immunological functions (Chap. 5, p. 93). This permits accommodation of the "foreign" semiallogeneic fetal graft that contains antigens of both maternal and paternal origin (Redman, 2015). The tolerance that exists at the maternal-fetal interface remains a great unsolved medical mystery. This tolerance is complex and involves certain immune system adaptations and crosstalk among the maternal microbiome, uterine decidua, and trophoblast. In particular, areas of the uterus that were previously considered sterile are colonized with bacteria. In most cases, these microbes are believed to be commensal and play a tolerizing and protective role. Indeed, commensal organisms may inhibit the proliferation of certain pathogens. Several reviewers have described these relationships (Mor, 2015; Racicot, 2014; Sisti, 2016).

One immune adaptation that promotes tolerance and protection at the maternal-fetal interface involves the expression of special major histocompatibility complex (MHC) molecules on the trophoblast. Another immune adaptation that promotes tolerance stems from important changes in CD4 T lymphocyte subpopulations in pregnancy. Specifically, immunity mediated by T-helper (Th) 1 cells shifts to Th2-mediated immunity. An important antiinflammatory component of pregnancy involves suppression of Th1 and T-cytotoxic (Tc) 1 cells, which lower secretion of interleukin 2 (IL-2), interferon α, and tumor necrosis factor (TNF).

In cervical mucus, peak levels of immunoglobulins A and G (IgA and IgG) are significantly higher during pregnancy, and the immunoglobulin-rich cervical mucus plug creates a barrier to ascending infection (Hansen, 2014; Wang, 2014). Similarly, IgG is transferred to the developing fetus in the third trimester as a form of passive immunity, ostensibly in anticipation of birth. Immunoglobulins secreted into breast milk during lactation augment neonatal defenses against infection (Chap. 36, p. 640).

Leukocytes and Lymphocytes

Normal leukocyte counts during pregnancy can be higher than nonpregnant values, and upper values approach 15,000/μL (Appendix, p. 1227). During labor and the early puerperium, values may markedly rise to attain levels ≥25,000/μL (Gat, 2019). The cause is unknown, but the same response occurs during and after strenuous exercise. The leukocytosis possibly represents the reappearance of leukocytes previously shunted out of active circulation.

The distribution of lymphocyte cell types also is altered during pregnancy. Specifically, B lymphocytes numbers are unchanged, but the absolute numbers of T lymphocytes rise and create a relative increase. Concurrently, the ratio of CD4 to CD8 T lymphocytes does not change (Kühnert, 1998).

Inflammatory Markers

Many tests performed to diagnose inflammation cannot be used reliably during pregnancy. For example, *leukocyte alkaline phosphatase* levels—used to evaluate myeloproliferative disorders—are elevated beginning early in pregnancy. The concentration of *C-reactive protein,* an acute-phase serum reactant, rises rapidly in response to tissue trauma or inflammation. Median C-reactive protein levels in pregnancy and labor are higher than for nonpregnant women (Anderson, 2013). Of nonlaboring gravidas, 95 percent had levels measuring ≤1.5 mg/dL, and gestational age did not affect serum levels.

Another marker of inflammation, the *erythrocyte sedimentation rate (ESR)*, is increased in normal pregnancy because of elevated plasma globulin and fibrinogen concentrations. *Complement factors C3* and *C4* levels also significantly rise during the second and third trimesters (Richani, 2005). Concentrations of *procalcitonin*, a normal precursor of calcitonin, are low to undetectable in midpregnancy but increase at the end of the third trimester and through the first few postpartum days (Bilinski, 2018). Procalcitonin levels rise with severe bacterial infections but remain low in viral infections and nonspecific inflammatory disease. However, measured levels poorly predict development of overt or subclinical chorioamnionitis after premature rupture of membranes (Thornburg, 2016; Tujula, 2018).

Coagulation and Fibrinolysis

During normal pregnancy, both coagulation and fibrinolysis are augmented but remain balanced to maintain hemostasis (Kenny, 2015). Evidence of activation includes increased concentrations of all clotting factors except factors XI and XIII (Table 4-4) (Cunningham, 2015).

Of procoagulants, the level and rate of thrombin generation throughout gestation progressively increase (McLean, 2012). In normal nonpregnant women, plasma fibrinogen (factor I) averages 300 mg/dL and ranges from 200 to 400 mg/dL. During normal pregnancy, the fibrinogen concentration rises approximately 50 percent. In late pregnancy, it averages 450 mg/dL, with a range from 300 to 600 mg/dL. As discussed, this contributes greatly to the striking elevation in the erythrocyte sedimentation rate. Also, levels of factor XIII—*fibrin stabilizing factor*—significantly drop as normal pregnancy advances (Sharief, 2014). Few studies describe thromboelastographic changes in normal pregnancy (Murray, 2018).

The end product of the coagulation cascade is fibrin formation, and the main function of the fibrinolytic system is to remove excess fibrin. Tissue plasminogen activator (tPA) converts plasminogen into plasmin, which is the enzyme that promotes fibrinolysis. It yields fibrin-degradation products such as D-dimers, and levels of these are increased in pregnancy (Hedengran, 2016b). Although somewhat conflicting, most evidence suggests that fibrinolytic activity is reduced in normal pregnancy (Kenny, 2015). As reviewed by Cunningham and

TABLE 4-4. Coagulation Factor Normal Values Across Pregnancy

Factor	Nonpregnant	Trimester		
		1st	2nd	3rd
Fibrinogen (mg/dL)	233–496	244–510	291–538	373–6.19
D-dimer (μg/mL)	0.22–0.74	0.05–0.95	0.32–1.29	0.13–1.7
Factor (% activity)				
V	50–150	75–95	72–96	60–88
VII	50–150	100–146	95–153	149–211
VIII	50–150	90–110	97–312	143–353
Protein C, functional (%)	70–130	78–121	83–133	67–135
Protein S, functional (%)	65–140	57–95	42–68	16–42

Nelson (2015), these changes favor fibrin formation. Although this is countered by increased levels of plasminogen, the net result is that pregnancy is a procoagulant state. Amnionic fluid is a potent activation of coagulation (Oda, 2018). Such changes serve to ensure hemostatic control during pregnancy, particularly during delivery when a certain amount of blood loss is expected.

Regulatory Proteins

Several proteins are natural inhibitors of coagulation, including proteins C and S and antithrombin. Inherited or acquired deficiencies of these and other natural regulatory proteins—collectively referred to as *thrombophilias*—account for many thromboembolic episodes during pregnancy. They are discussed in Chapter 55 (p. 976).

Activated protein C, along with the cofactors protein S and factor V, functions as an anticoagulant by neutralizing the procoagulants factor Va and factor VIIIa. During pregnancy, resistance to activated protein C grows progressively and is related to a concomitant drop in free protein S levels and greater factor VIII concentrations. Between the first and third trimesters, activated protein C levels decline from 2.4 to 1.9 U/mL, and free protein S concentrations diminish from 0.4 to 0.16 U/mL (Cunningham, 2015; Walker, 1997). Antithrombin levels drop by 13 percent between midpregnancy and term and fall 30 percent from this baseline until 12 hours after delivery. By 72 hours after delivery, there is a return to baseline (James, 2014).

Platelets

In a study of more than 7000 women, and as shown in Figure 4-7, the average platelet count declined across pregnancy and returned to normal nonpregnant values by 4 to 12 weeks postpartum (Reese, 2018). The platelet counts were lower for twin pregnancies. Lower platelet concentrations are partially due to hemodilution. In addition, platelet consumption is likely augmented and creates a greater proportion of younger and therefore larger platelets (Han, 2014). Further, clinically insignificant levels of several markers of platelet activation rise with gestational age but drop postpartum (Blomqvist, 2018). Because of splenic enlargement, an element of "hypersplenism," may sequester and prematurely destroy platelets (Kenny, 2015).

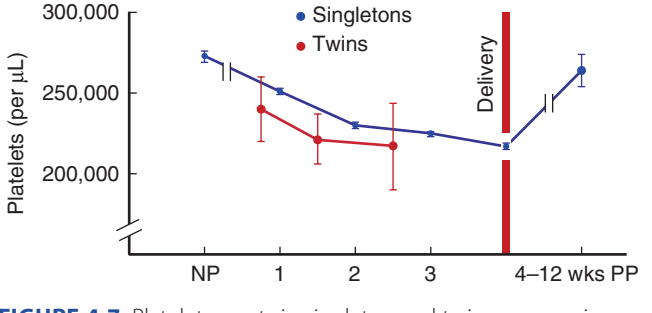

FIGURE 4-7 Platelet counts in singleton and twin pregnancies determined during 1st, 2nd, and 3rd trimester, at delivery, and then at 4–12 weeks postpartum. NP = nonpregnant. Values are means and 95% confidence intervals.

Spleen

By the end of normal pregnancy, the spleen enlarges up to 50 percent compared with that in the first trimester (Maymon, 2007). Moreover, Gayer and coworkers (2012) found that splenic size was 68-percent greater compared with that of nonpregnant controls. The cause of this splenomegaly is unknown, but it might follow the increased blood volume and/or the hemodynamic changes of pregnancy.

CARDIOVASCULAR SYSTEM

Changes in cardiac function become apparent during the first 8 weeks of pregnancy (Hibbard, 2015). Cardiac output is increased as early as the fifth week and reflects a reduced systemic vascular resistance and an increased heart rate. Compared with prepregnancy measurements, brachial systolic blood pressure, diastolic blood pressure, and central systolic blood pressure are all significantly lower 6 to 7 weeks from the last menstrual period (Mahendru, 2012). The resting pulse rate rises approximately 10 beats/min during pregnancy. Nelson and associates (2015) found that for both normal and overweight women, heart rate rose significantly between 12 and 16 weeks' and between 32 and 36 weeks' gestation. Between weeks 10 and 20, plasma volume expansion begins, and preload rises. This augmented preload results in a significantly larger left atrial volume and ejection fraction (Cong, 2015).

Ventricular performance during pregnancy is influenced by both the decline in systemic vascular resistance and changes in pulsatile arterial flow. Multiple factors contribute to this overall altered hemodynamic function, which allows the physiological demands of the fetus to be met while maintaining maternal cardiovascular integrity (Hibbard, 2015). These changes in stroke volume during the last half of pregnancy and the effects of maternal posture are summarized in Figure 4-8 (Nelson, 2015). Bijl and colleagues (2019) offer a detailed review of methods to measure cardiac function in gravidas.

Heart

As the diaphragm becomes progressively elevated, the heart is displaced to the left and upward and is rotated on its long

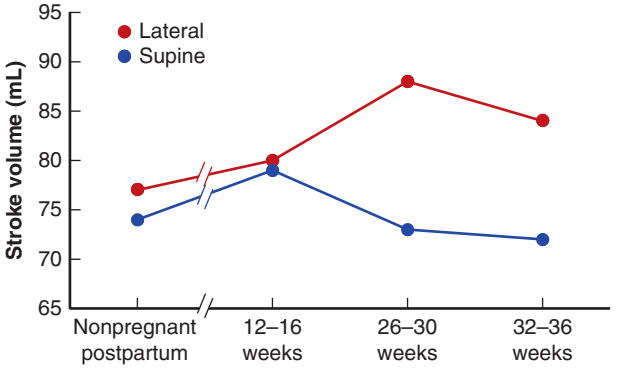

FIGURE 4-8 Left ventricular stroke volume across pregnancy compared with 12-week postpartum (nonpregnant) values for normal-weight women in the supine and lateral positions.

axis. As a result, the apex is moved somewhat laterally from its usual position and produces a larger cardiac silhouette in chest radiographs. Furthermore, gravidas normally have some degree of benign pericardial effusion, which may enlarge the cardiac silhouette (Enein, 1987). These factors make it difficult to precisely identify moderate degrees of cardiomegaly by simple radiographic studies.

Normal pregnancy induces some characteristic electrocardiographic (ECG) changes, and the most common is slight left-axis deviation due to the altered heart position. Q waves in leads II, III, and avF and flat or inverted T waves in leads III and V1–V3 also may be seen (Sunitha, 2014).

During pregnancy, many of the normal *cardiac sounds* are modified. These include: (1) an exaggerated splitting of the first heart sound and increased loudness of both components, (2) no definite changes in the aortic and pulmonary elements of the second sound, and (3) a loud, easily heard third sound (Cutforth, 1966). In most gravidas, a systolic murmur is intensified during inspiration in some or with expiration in others. Less often, a soft diastolic murmur can be noted transiently, and continuous murmurs arising from the breast vasculature may be heard (Fig. 52-1, p. 917).

Structurally, the expanding plasma volume seen during normal pregnancy is reflected by enlarging cardiac end-systolic and end-diastolic dimensions. Concurrently, however, septal thickness or ejection fraction does not change. This is because these dimensional changes are accompanied by substantive ventricular remodeling, which is characterized by left-ventricular mass expansion of 30 to 35 percent near term. In the nonpregnant state, the heart is capable of remodeling in response to stimuli such as hypertension and exercise. Such cardiac *plasticity* likely is a continuum that encompasses physiological growth as with exercise, and pathological hypertrophy as with hypertension (Hill, 2008; Osol, 2019).

Stewart and colleagues (2016) used cardiac MR imaging to prospectively evaluate cardiac remodeling during pregnancy. Compared with the first trimester, left ventricular mass significantly grew beginning at 26 to 30 weeks' gestation, and this continued until delivery (Fig. 4-9) (Stewart, 2016). This remodeling is concentric and proportional to maternal size for both normal and overweight women and resolved within 3 months of delivery. Certainly for clinical purposes,

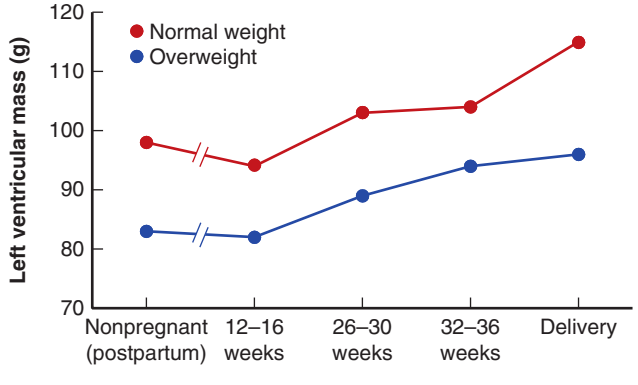

FIGURE 4-9 Left ventricular mass of normal-weight and overweight women across pregnancy compared with 12-week postpartum (nonpregnant) values.

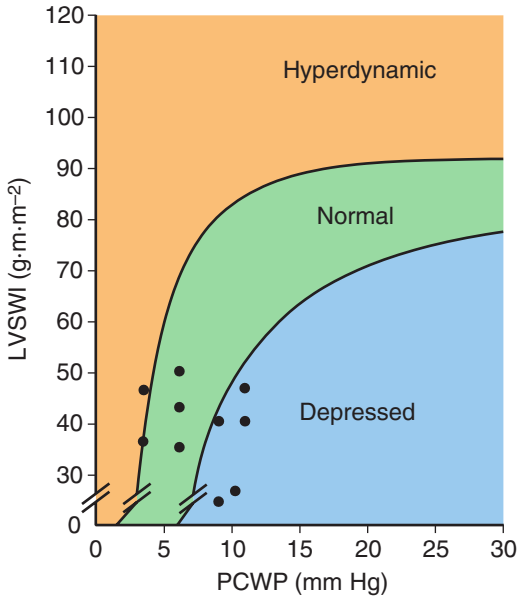

FIGURE 4-10 Relationship between left ventricular stroke work index (LVSWI), cardiac output, and pulmonary capillary wedge pressure (PCWP) in 10 normal pregnant women in the third trimester.

ventricular function during pregnancy is normal, as estimated by the *Braunwald ventricular function* graph (Fig. 4-10) (Clark, 1989). For the given filling pressures, cardiac output is appropriate and thus cardiac function during pregnancy is eudynamic. Of the metabolic changes that occur in the heart during pregnancy, the efficiency of cardiac work—which is the product of cardiac output × mean arterial pressure—is estimated to rise by approximately 25 percent. The associated increase in oxygen consumption is primarily accomplished via increased coronary blood flow rather than increased extraction (Liu, 2014).

Cardiac Output

When measured in the lateral recumbent position at rest, cardiac output increases significantly beginning in early pregnancy. It continues to rise and remains elevated during the remainder. In a supine woman, a large uterus consistently compresses veins and diminishes venous return from the lower body. It may also compress the aorta. In response, cardiac filling is limited, and cardiac output lessened. Specifically, cardiac MR imaging shows that a woman rolling from her back onto her left side raises her cardiac output at 26 to 30 weeks' gestation by approximately 20 percent and at 32 to 34 weeks by 10 percent (see Fig. 4-7). Consistent with this, Simpson and James (2005) found that fetal oxygen saturation is approximately 10 percent higher if a laboring woman lies in a lateral recumbent position compared with supine. Upon standing, cardiac output falls to the same degree as in the nonpregnant woman (Easterling, 1988).

In multifetal pregnancies, compared with singletons, maternal cardiac output is augmented further by almost another 20 percent. Ghi and coworkers (2015) used transthoracic echocardiography to show that first-trimester cardiac output with twins (mean 5.5 L/min) was more than 20 percent greater than postpartum values. Cardiac output values in the second (6.3 L/min)

and third (6.3 L/min) trimesters rose an additional 15 percent compared with first-trimester output. Due to augmented preload, left atrial and left ventricular end-diastolic diameters also grow with twins (Orabona, 2021). The augmented heart rate and inotropic contractility imply that cardiovascular reserve is reduced in multifetal gestations (Orabona, 2019).

During first-stage labor, cardiac output rises moderately. During the second stage, with vigorous expulsive efforts, it is appreciably greater. The pregnancy-induced increase is lost after delivery, at times dependent on blood loss.

Hemodynamic Function in Late Pregnancy

Clark and associates (1989) conducted invasive studies to measure hemodynamic function late in pregnancy (Table 4-5). Right heart catheterization was performed in 10 healthy nulliparas at 35 to 38 weeks' gestation, and again at 11 to 13 weeks postpartum. Late pregnancy was associated with the expected increases in heart rate, stroke volume, and cardiac output. Systemic vascular and pulmonary vascular resistance both dropped significantly, as did colloid osmotic pressure. Pulmonary capillary wedge pressure and central venous pressure did not change appreciably. Thus, although cardiac output rises, left ventricular function as measured by stroke work index remains similar to the nonpregnant normal range (see Fig. 4-10). Put another way, normal pregnancy is not a continuous "high-output" state (Herrera, 2018).

Circulation and Blood Pressure

Arterial pressure usually declines to a nadir at 24 to 26 weeks' gestation and rises thereafter. Diastolic pressure decreases more than systolic. Changes in posture affect arterial blood pressure (Fig. 4-11) (Wilson, 1980). Brachial artery pressure when sitting is lower than that when in the lateral recumbent supine position (Bamber, 2003). Additionally, systolic blood pressure is lower in the lateral positions compared with either the flexed sitting or supine positions (Armstrong, 2011). In approximately

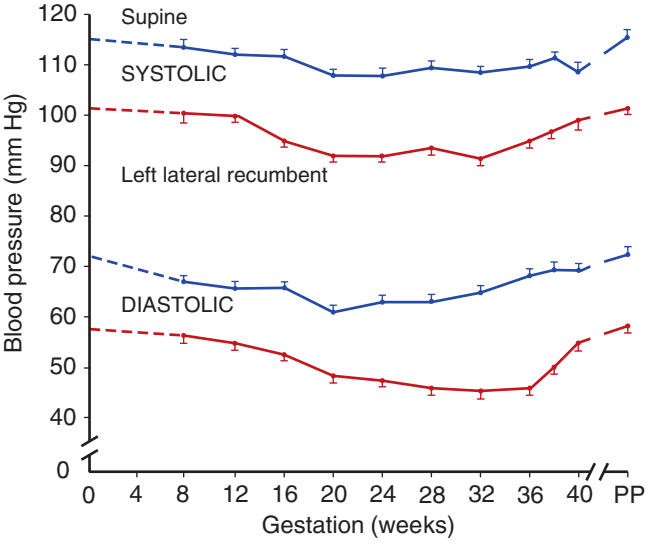

FIGURE 4-11 Sequential changes (± SEM) in blood pressure throughout pregnancy in 69 women in supine (*blue lines*) and left lateral recumbent positions (*red lines*). PP = postpartum.

10 percent of women, supine compression of the great vessels by the uterus causes significant arterial hypotension, sometimes referred to as the supine hypotensive syndrome. Also when supine, uterine arterial pressure—and thus uterine blood flow—is significantly lower than that in the brachial artery. Evidence to support whether this directly affects fetal heart rate patterns in uncomplicated low-risk pregnancies is conflicting (Armstrong, 2011; Ibrahim, 2015). Similar changes can also be seen with hemorrhage or with spinal analgesia.

Studies have assessed vascular compliance before pregnancy, during pregnancy, and postpartum (Morris, 2015; Osman, 2017). Compared with healthy nonpregnant controls, significant declines in mean arterial pressure and arterial stiffness were observed between prepregnant and postpartum time periods. These findings suggest that pregnancy confers a favorable effect on maternal cardiovascular remodeling.

TABLE 4-5. Central Hemodynamic Changes in 10 Normal Nulliparous Women Near Term and Postpartum

	Pregnant[a] (35–38 wk)	Postpartum (11–13 wk)	Change[b]
Mean arterial pressure (mm Hg)	90 ± 6	86 ± 8	NSC
Pulmonary capillary wedge pressure (mm Hg)	8 ± 2	6 ± 2	NSC
Central venous pressure (mm Hg)	4 ± 3	4 ± 3	NSC
Heart rate (beats/min)	83 ± 10	71 ± 10	+17%
Cardiac output (L/min)	6.2 ± 1.0	4.3 ± 0.9	+43%
Systemic vascular resistance (dyn/sec/cm^{-5})	1210 ± 266	1530 ± 520	−21%
Pulmonary vascular resistance (dyn/sec/cm^{-5})	78 ± 22	119 ± 47	−34%
Serum colloid osmotic pressure (mm Hg)	18.0 ± 1.5	20.8 ± 1.0	−14%
COP-PCWP gradient (mm Hg)	10.5 ± 2.7	14.5 ± 2.5	−28%
Left ventricular stroke work index (g/m/m^2)	48 ± 6	41 ± 8	NSC

[a]Measured in lateral recumbent position.
[b]Changes significant unless NSC = no significant change.
COP = colloid osmotic pressure; PCWP = pulmonary capillary wedge pressure.

The venous system is a high-flow, low-resistance circulation during pregnancy (Gyselaers, 2018). While antecubital venous pressure remains unchanged, in the supine position, femoral venous pressure rises steadily, from approximately 8 mm Hg early in pregnancy to 24 mm Hg at term. Venous blood flow in the legs is retarded except when the lateral recumbent position is assumed. This tendency toward blood stagnation in the lower extremities during later pregnancy is attributable to occlusion of the pelvic veins and inferior vena cava by the enlarged uterus. The elevated venous pressure returns to normal when the pregnant woman lies on her side and immediately after delivery. These alterations contribute to the dependent edema frequently experienced and to development of hemorrhoids and varicose veins in the legs and vulva. These changes also predispose to deep-vein thrombosis and pulmonary embolism.

Renin, Angiotensin II, and Plasma Volume

The renin-angiotensin-aldosterone axis is intimately involved in blood pressure control via sodium and water balance. All components of this system show increased levels in normal pregnancy. Renin is produced by both the maternal kidney and the placenta, and greater amounts of renin substrate (angiotensinogen) are produced by both maternal and fetal liver. Elevated angiotensinogen levels result, in part, from augmented estrogen production during normal pregnancy and are important in first-trimester blood pressure maintenance (West, 2016).

Gant and associates (1973) reported that nulliparas who remained normotensive became and stayed refractory to the pressor effects of infused angiotensin II. Conversely, those who ultimately became hypertensive developed, but then lost, this refractoriness. The diminished vascular responsiveness to angiotensin II may be progesterone related. Placental growth factor (PlGF) also blunts this response (Espinoza, 2019). Normally, pregnant women lose their acquired vascular refractoriness to angiotensin II within 15 to 30 minutes after the placenta is delivered. Large amounts of intramuscular progesterone given during late labor delay this diminishing responsiveness.

Cardiac Natriuretic Peptides

At least two species of these—*atrial natriuretic peptide (ANP)* and *brain natriuretic peptide (BNP)*—are secreted by cardiomyocytes in response to chamber-wall stretching. These peptides regulate blood volume by provoking natriuresis, diuresis, and vascular smooth-muscle relaxation. In nonpregnant and pregnant patients, levels of BNP and of amino-terminal pro–brain natriuretic peptide (Nt pro-BNP), as well as newer analytes such as suppressor of tumorigenicity 2 (ST2), may be useful in screening for depressed left ventricular systolic function and determining chronic heart failure prognosis (Cunningham, 2019; Ker, 2018).

During normal pregnancy, plasma ANP and BNP levels are maintained in the nonpregnant range despite greater plasma volume (Yurteri-Kaplan, 2012). In one study, median BNP levels were stable across pregnancy with values <20 pg/mL (Resnik, 2005). BNP levels are elevated in severe preeclampsia, and this may be caused by cardiac strain from increased afterload. It would appear that ANP-induced physiological adaptations participate in extracellular fluid volume expansion and in the elevated plasma aldosterone concentrations characteristic of normal pregnancy.

Prostaglandins

Elevated prostaglandin production during pregnancy is thought to have a central role in control of vascular tone, blood pressure, and sodium balance. Renal medullary prostaglandin E_2 synthesis is markedly elevated during late pregnancy and is presumed to be natriuretic. Levels of prostacyclin (PGI_2), the principal prostaglandin of endothelium, also rise during late pregnancy. PGI_2 regulates blood pressure and platelet function. It helps maintain vasodilation during pregnancy, and its deficiency is associated with pathological vasoconstriction (Shah, 2015). The ratio of PGI_2 to thromboxane in maternal urine and blood may be important indicators of preeclampsia pathogenesis.

Endothelin

Pregnancy generates several endothelins, which are vasoconstricting peptides. Endothelin-1 is a potent vasoconstrictor produced in endothelial and vascular smooth muscle cells and regulates local vasomotor tone (Lankhorst, 2016). Its production is stimulated by angiotensin II, arginine vasopressin, and thrombin. Endothelins, in turn, stimulate secretion of ANP, aldosterone, and catecholamines. Vascular sensitivity to endothelin 1 is not altered during normal pregnancy. Pathologically elevated levels may play a role in preeclampsia (Saleh, 2016).

Nitric Oxide

This potent vasodilator is released by endothelial cells and may modify vascular resistance during pregnancy. As discussed earlier (p. 52), nitric oxide is an important mediator of placental vascular tone and development (West, 2016). Abnormal nitric oxide synthesis has been linked to preeclampsia (Laskowska, 2015; Vignini, 2016).

RESPIRATORY TRACT

Of anatomical changes, the diaphragm rises approximately 4 cm during pregnancy (Fig. 4-12). The subcostal angle widens appreciably as the transverse diameter of the thoracic cage lengthens approximately 2 cm. The thoracic circumference increases about 6 cm, but not sufficiently to prevent reduced residual lung volumes created by the elevated diaphragm. Even so, diaphragmatic excursion is greater in pregnancy. Dyspnea is common (Rudder, 2021).

Pulmonary Function

Of physiological lung changes, *functional residual capacity (FRC)* decreases by approximately 20 to 30 percent or 400 to 700 mL during pregnancy (Fig. 4-13). This capacity is composed of *expiratory reserve volume*—which drops 15 to 20 percent or 200 to 300 mL—and *residual volume*—which decreases 20 to 25 percent or 200 to 400 mL. FRC and residual volume decline

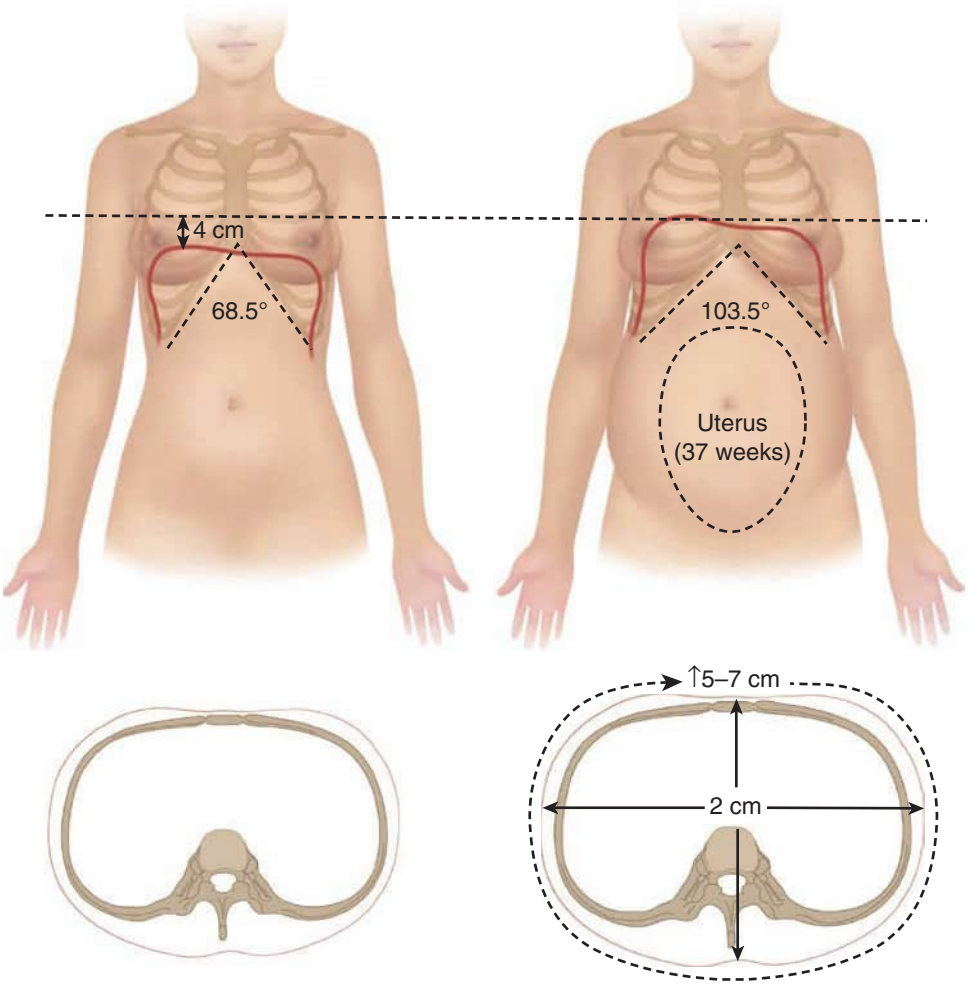

FIGURE 4-12 Chest wall measurements in nonpregnant (*left*) and pregnant women (*right*). The subcostal angle increases, as does the anteroposterior and transverse diameters of the chest wall and chest wall circumference. These changes compensate for the 4-cm elevation of the diaphragm so that total lung capacity is not significantly reduced. (Redrawn from Hegewald MJ, Crapo RO. Respiratory physiology in pregnancy, Clin Chest Med 2011 Mar;32(1):1–13.)

progressively across pregnancy due to diaphragm elevation. Significant reductions are observed by the sixth month. *Inspiratory capacity*, the maximum volume that can be inhaled from FRC, rises by 5 to 10 percent or 200 to 350 mL during pregnancy. *Total lung capacity*—the combination of FRC and inspiratory capacity—is unchanged or declines by <5 percent at term (Hegewald, 2011).

The respiratory rate is essentially unchanged, but *tidal volume* and *resting minute ventilation* increase significantly as pregnancy advances. Kolarzyk and coworkers (2005) reported significantly greater mean tidal volumes—0.66 to 0.8 L/min—and resting minute ventilations—10.7 to 14.1 L/min—compared with those of nonpregnant women. The elevated minute ventilation is caused by several factors. These include enhanced respiratory drive primarily due to the stimulatory action of progesterone, low expiratory reserve volume, and compensated respiratory alkalosis (Heenan, 2003). Also, decreased plasma osmolality can result in less respiratory depression (Moen, 2014).

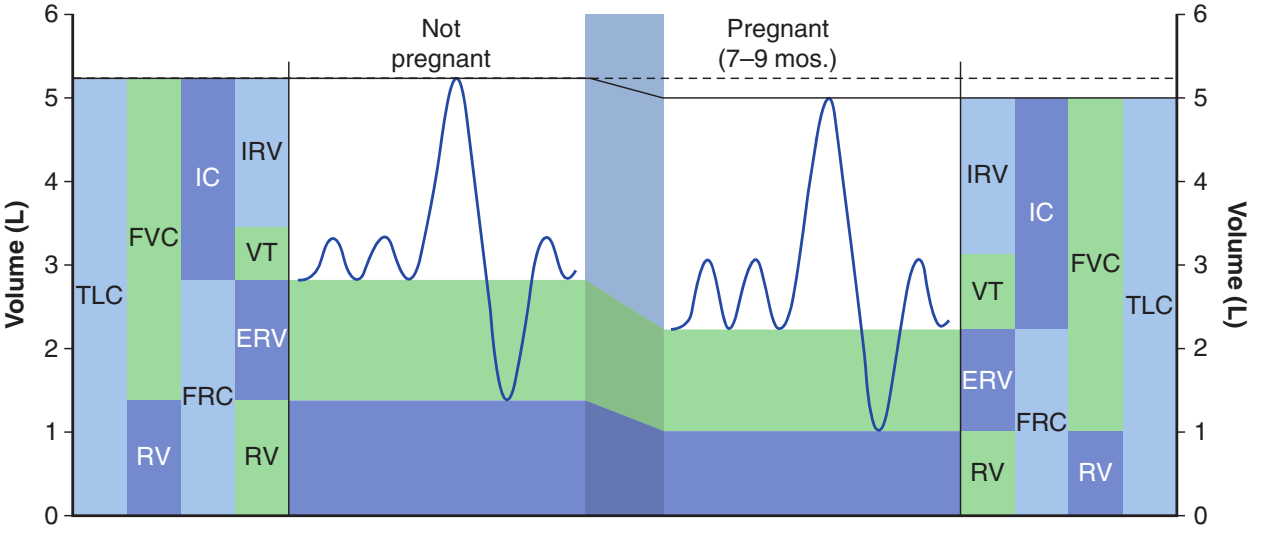

FIGURE 4-13 Changes in lung volumes with pregnancy. The most significant changes are reduction in functional residual capacity (FRC) and its subcomponents, expiratory reserve volume (ERV) and residual volume (RV), as well as increases in inspiratory capacity (IC) and tidal volume (VT). (Reproduced with permission from Hegewald MJ, Crapo RO. Respiratory physiology in pregnancy, Clin Chest Med 2011 Mar;32(1):1–13.)

Regarding pulmonary function, *peak expiratory flow rates* rise progressively as gestation advances (Grindheim, 2012). *Lung compliance* is unaffected by pregnancy. *Airway conductance* is increased and *total pulmonary resistance* reduced, possibly as a result of progesterone. The *maximum breathing capacity* and *forced* or *timed vital capacity* are not altered appreciably. It is unclear whether the critical *closing volume*—the lung volume at which airways in the dependent parts of the lung begin to close during expiration—is higher in pregnancy (Hegewald, 2011). Pulmonary function with a singleton pregnancy does not significantly differ from that with twins (Siddiqui, 2014). Importantly, the greater oxygen requirements and perhaps the increased critical closing volume imposed by pregnancy make respiratory diseases more serious.

Demir and colleagues (2015) studied nasal physiology in 85 pregnant women. Although the minimal cross-sectional area decreased between the first and third trimesters, subjective reports of nasal congestion or total nasal resistance did not significantly differ among trimesters or compared with nonpregnant controls.

Oxygen Delivery

The amount of oxygen delivered into the lungs by the increased tidal volume clearly exceeds oxygen requirements imposed by pregnancy. Moreover, the total hemoglobin mass and, in turn, total oxygen-carrying capacity rise appreciably during normal pregnancy, as does cardiac output. Consequently, the *maternal arteriovenous oxygen* difference is diminished. Oxygen consumption grows approximately 20 percent during pregnancy, and it is approximately 10 percent higher in multifetal gestations (Ajjimaporn, 2014). During labor, oxygen consumption increases 40 to 60 percent (Bobrowski, 2010).

Acid–Base Equilibrium

A greater awareness of a desire to breathe is common even early in pregnancy (Milne, 1978). This may be interpreted as dyspnea, which may suggest pulmonary or cardiac abnormalities when none exist. This physiological dyspnea, which should not interfere with normal physical activity, is thought to result from greater tidal volume that lowers the partial pressure of carbon dioxide (CO_2) in blood ($Paco_2$) slightly and paradoxically causes dyspnea. The increased respiratory effort during pregnancy, and in turn the reduction in the $Paco_2$, is likely induced in large part by progesterone and to a lesser degree by estrogen. Progesterone acts centrally. Here, it lowers the threshold and raises the sensitivity of the chemoreflex response to carbon dioxide (Jensen, 2005).

To compensate for the resulting respiratory alkalosis, plasma bicarbonate levels normally drop from 26 to 22 mmol/L. Although blood pH is increased only minimally, it does shift the oxygen dissociation curve to the left. This shift increases the affinity of maternal hemoglobin for oxygen—the *Bohr effect*—thereby lowering the oxygen-releasing capacity of maternal blood. This is offset because the slight pH rise also stimulates an increase in 2,3-diphosphoglycerate in maternal erythrocytes. This shifts the curve back to the right (Tsai, 1982). Thus, reduced $Paco_2$ from maternal hyperventilation aids CO_2 (waste) transfer from the fetus to the mother while also aiding oxygen release to the fetus.

URINARY SYSTEM

Kidney

The urinary system undergoes several remarkable changes in pregnancy (Table 4-6) (Lindheimer, 2000). *Kidney size* grows

TABLE 4-6. Renal Changes in Normal Pregnancy

Parameter	Alteration	Clinical Relevance
Kidney size	Approximately 1 cm longer on radiograph	Size returns to normal postpartum
Dilatation	Resembles hydronephrosis on sonogram or IVP (more marked on right)	Can be confused with obstructive uropathy; retained urine leads to collection errors; renal infections are more virulent; may be responsible for "distention syndrome"; elective pyelography should be deferred to at least 12 weeks postpartum
Renal function	Glomerular filtration rate and renal plasma flow increase ~50%	Serum creatinine decreases during normal gestation; >0.8 mg/dL (>72 μmol/L) creatinine already borderline; protein, amino acid, and glucose excretion all increase
Maintenance of acid-base	Decreased bicarbonate threshold; progesterone stimulates respiratory center	Serum bicarbonate decreased by 4–5 mEq/L; Pco_2 decreased 10 mm Hg; a Pco_2 of 40 mm Hg already represents CO_2 retention
Plasma osmolality	Osmoregulation altered; osmotic thresholds for AVP release and thirst decrease; hormonal disposal rates increase	Serum osmolality decreases 10 mOsm/L (serum Na^+ ~5 mEq/L) during normal gestation; increased placental metabolism of AVP may cause transient diabetes insipidus during pregnancy

AVP = vasopressin; IVP = intravenous pyelography; Pco_2 = partial pressure carbon dioxide.

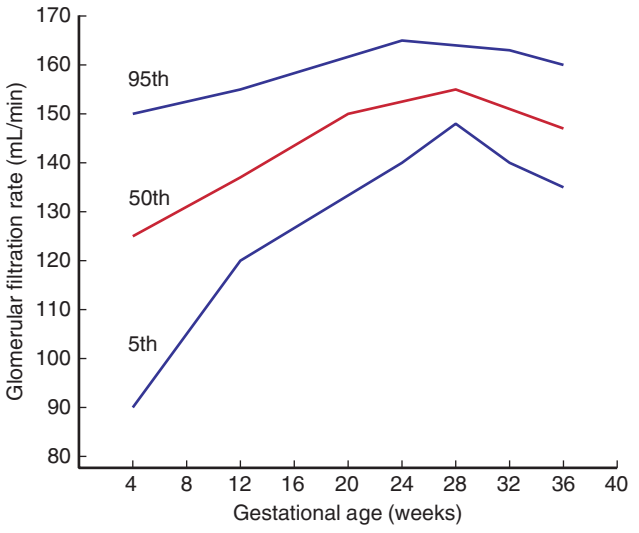

FIGURE 4-14 Glomerular filtration rate across pregnancy as measured by inulin clearance. The solid line is the 50th percentile and the dashed lines are the 5th and 95th percentiles.

approximately 1.0 cm (Cietak, 1985). Both the *glomerular filtration rate (GFR)* and *renal plasma flow* increase early in pregnancy. The GFR rises as much as 25 percent by the second week after conception and 50 percent by the beginning of the second trimester (Fig. 4-14) (Lopes van Balen, 2019). This hyperfiltration results from two principal factors. First, hypervolemia-induced hemodilution lowers the protein concentration and oncotic pressure of plasma entering the glomerular microcirculation. Second, renal plasma flow rises by approximately 80 percent before the end of the first trimester (Conrad, 2015; Lopes van Balen, 2019). Elevated GFR persists until term, even though renal plasma flow declines during late pregnancy. Primarily as a consequence of this elevated GFR, approximately 60 percent of nulliparas during the third trimester experience urinary frequency, and 80 percent experience nocturia (Frederice, 2013).

During the puerperium, a marked GFR persists during the first postpartum day, principally from the reduced glomerular capillary oncotic pressure. The gestational hypervolemia and hemodilution, still evident on the first postpartum day, resolves by the second week postpartum.

Studies suggest that relaxin, discussed earlier (p. 54), may mediate both increased GFR and renal blood flow during pregnancy (Conrad, 2015). Relaxin boosts renal nitric oxide production, which leads to renal vasodilation and lowered renal afferent and efferent arteriolar resistance. This augments renal blood flow and GFR (Bramham, 2016). Relaxin may also increase vascular gelatinase activity during pregnancy, which leads to renal vasodilation, glomerular hyperfiltration, and reduced myogenic reactivity of small renal arteries (Odutayo, 2012).

As with blood pressure, maternal posture may considerably influence several aspects of renal function. Late in pregnancy, the sodium excretion rate in the supine position averages less than half that in the lateral recumbent position. The effects of posture on GFR and renal plasma flow vary.

One unusual feature of the pregnancy-induced changes in renal excretion is the remarkably higher amounts of some nutrients lost in the urine. Amino acids and water-soluble vitamins are excreted in much greater amounts (Shibata, 2013).

Renal Function Tests

The mean nonpregnancy serum creatinine level of 0.7 mg/dL declines during normal pregnancy to 0.5 mg/dL. *Values ≥0.9 mg/dL suggest underlying renal disease and prompt further evaluation.* Creatinine clearance in pregnancy averages 30 percent higher than the 100 to 115 mL/min in nonpregnant women. This is a useful test to estimate renal function, provided that complete urine collection is made during an accurately timed period. If this is not done precisely, results are misleading (Lindheimer, 2010). During the day, pregnant women tend to accumulate water as dependent edema. When recumbent at night, they mobilize this fluid with diuresis. This reversal of the usual nonpregnant diurnal pattern of urinary flow causes nocturia, and urine is more dilute than in nonpregnant women. Failure of a pregnant woman to excrete concentrated urine after withholding fluids for approximately 18 hours does not necessarily signify renal damage. In fact, the kidneys in these circumstances function perfectly normally by excreting mobilized extracellular fluid of relatively low osmolality.

Urinalysis

Glucosuria during pregnancy may not be abnormal. The appreciably increased GFR, together with impaired tubular reabsorptive capacity for filtered glucose, accounts for most cases of glucosuria. Chesley (1963) calculated that approximately one sixth of gravidas will spill glucose in the urine. As discussed in Chapter 56 (p. 994), although the sensitivity is low, glucosuria may be an indicator of gestational diabetes mellitus. For women with glucosuria, no guidelines in the United States direct practice, but in the United Kingdom, early oral glucose testing is considered for those with an isolated 2+ or repetitive 1+ urine dipstick readings (National Institute for Health And Clinical Excellence, 2015).

Hematuria most often suggests urinary tract disease or infection. Evaluation of this finding is outlined in Chapter 56 (p. 995). Hematuria is common after difficult labor and delivery because of trauma to the bladder and urethra.

Proteinuria is typically defined in nonpregnant subjects as a protein excretion rate of more than 150 mg/d. Because of the aforementioned hyperfiltration and possible reduction of tubular reabsorption, proteinuria during pregnancy is usually considered significant once a protein excretion threshold of at least 300 mg/d is reached (Odutayo, 2012). Higby and coworkers (1994) measured protein excretion in 270 normal women throughout pregnancy (Fig. 4-15). Mean 24-hour excretion for all three trimesters was 115 mg, and the upper 95-percent confidence limit was 260 mg/d without significant differences by trimester. They showed that albumin excretion is minimal and ranges from 5 to 30 mg/d. Proteinuria increases with gestational age, which corresponds with the peak in GFR (Benzing, 2021).

Measuring Urine Protein

The three most commonly employed approaches for assessing proteinuria are the qualitative classic dipstick, the quantitative

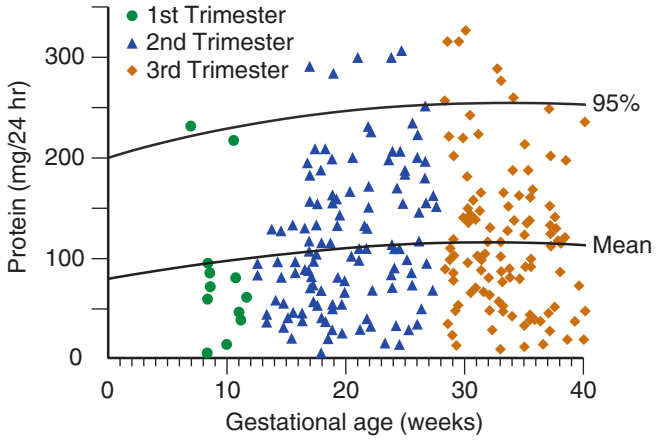

FIGURE 4-15 Scatter plot of women showing 24-hour urinary total protein excretion by gestational age. Mean and 95-percent confidence limits are outlined. (Modified with permission from Higby K, Suiter CR, Phelps JY, et al: Normal values of urinary albumin and total protein excretion during pregnancy, Am J Obstet Gynecol 1994 Oct;171(4):984–989.)

24-hour collection, and the albumin/creatinine or protein/creatinine ratio of a single voided urine specimen. The pitfalls of each approach have been reviewed (Bramham, 2016; Conrad, 2015).

With dipstick assessment, the principal problem is its failure to account for renal concentration or dilution of urine. For example, with polyuria and extremely dilute urine, a negative or trace dipstick could actually be associated with excessive protein excretion.

The 24-hour urine collection is affected by urinary tract dilation, discussed in the next section. The dilated tract may lead to errors related both to retention—hundreds of milliliters of urine remaining in the dilated tract—and to timing—the remaining urine may have formed hours before the collection. To minimize these pitfalls, the patient is first hydrated and positioned in lateral recumbency—the definitive nonobstructive posture—for 45 to 60 minutes. After this, she is asked to void, and this specimen is discarded. Immediately following this void, her 24-hour collection begins. During the final hour of collection, the patient is again placed in the lateral recumbent position. But, at the end of this hour, the final collected urine is incorporated into the total collected volume (Lindheimer, 2010).

Last, the protein:creatinine ratio is a promising approach because data can be obtained quickly and collection errors are avoided. Disadvantageously, the amount of protein per unit of creatinine excreted during a 24-hour period is not constant, and the thresholds to define abnormal vary. Nomograms for urinary microalbumin and creatinine ratios during uncomplicated pregnancies have been developed. The ratio is unreliable postpartum (Aziz, 2018).

■ Ureters

After the uterus completely rises out of the pelvis, it rests on the ureters. This laterally displaces and compresses them at the pelvic brim. Above this level, elevated intraureteral tonus results, and ureteral dilation (hydroureter) and hydronephrosis is impressive. It is greater on the right side as shown in Figure 4-16

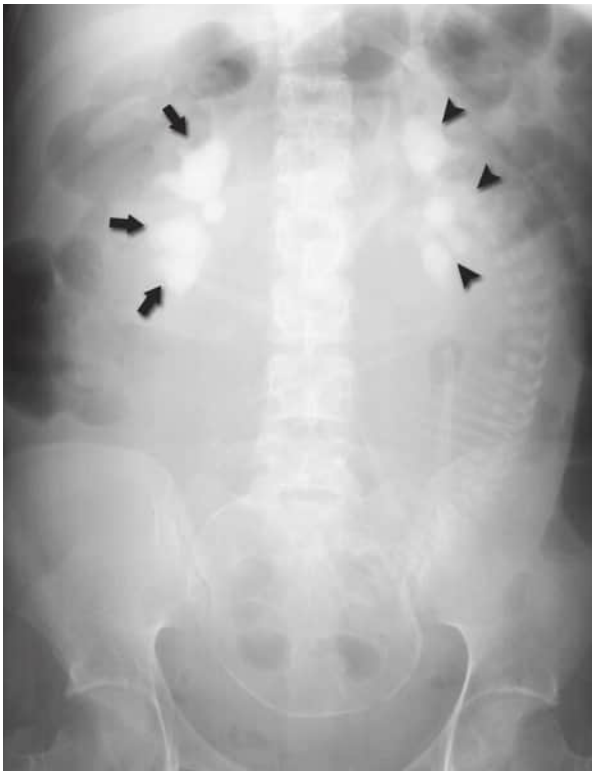

FIGURE 4-16 Hydronephrosis. Plain film from the 15-minute image of an intravenous pyelogram (IVP). Moderate hydronephrosis on the right (*arrows*) and mild hydronephrosis on the left (*arrowheads*) are both normal for this 35-week gestation.

(Wadasinghe, 2016). It is right sided in 86 percent of women. This unequal dilation may result from cushioning provided to the left ureter by the sigmoid colon and perhaps from greater right ureteral compression exerted by the dextrorotated uterus. The right ovarian vein complex, which is remarkably dilated during pregnancy, lies obliquely over the right ureter and may also contribute to ureteral compression and proximal dilation.

Progesterone likely has some additional effect. Van Wagenen and Jenkins (1939) described continued ureteral dilation after removal of the monkey fetus but with the placenta left in situ. The relatively abrupt onset of dilation in women at midpregnancy, however, seems more consistent with ureteral compression.

Ureteral elongation accompanies distention, and the ureter is frequently thrown into curves of varying size, and smaller curves may be sharply angulated. These so-called kinks are poorly named, because the term connotes obstruction. They are usually single or double curves that, when viewed in a radiograph taken in the same plane as the curve, may appear as acute angulations. Another exposure at right angles nearly always identifies them to be gentle curves. Despite these anatomical changes, complication rates associated with ureteroscopy in pregnant and nonpregnant patients do not differ significantly (Semins, 2014).

■ Bladder

The bladder shows few significant anatomical changes before 12 weeks' gestation. Subsequently, however, increased uterine size, the hyperemia that affects all pelvic organs, and hyperplasia

of bladder muscle and connective tissues together elevate the trigone and thicken its intraureteric margin. Continuation of this process to term produces marked deepening and widening of the trigone. The bladder mucosa is unchanged other than an increase in the size and tortuosity of its blood vessels.

Bladder pressure in primigravidas rises from 8 cm H_2O early in pregnancy to 20 cm H_2O at term (Iosif, 1980). To compensate for reduced bladder capacity, absolute and functional urethral lengths increase by 6.7 and 4.8 mm, respectively. Concurrently, maximal intraurethral pressure rises from 70 to 93 cm H_2O, and thus continence is maintained. Still, at least half of women experience some degree of urinary incontinence by the third trimester (Abeysekera, 2016). Indeed, this is always considered in the differential diagnosis of ruptured membranes. Near term—particularly in nulliparas, in whom the presenting part often engages before labor—the entire base of the bladder is pushed ventral and cephalad. This converts the normally convex surface into a concavity. As a result, diagnostic and therapeutic procedures are more difficult. Moreover, pressure from the presenting part impairs blood and lymph drainage from the bladder base, often rendering the area edematous, easily traumatized, and possibly more susceptible to infection.

GASTROINTESTINAL TRACT

As pregnancy progresses, the stomach and intestines are displaced cephalad by the enlarging uterus. Consequently, the physical findings in certain diseases are altered. The appendix, for instance, is usually displaced upward and somewhat laterally. At times, it may reach the right flank.

Pyrosis (heartburn) is common during pregnancy and is most likely caused by reflux of acidic secretions into the lower esophagus. Although the altered stomach position probably contributes to its frequency, lower esophageal sphincter tone also is diminished. In addition, intraesophageal pressures are lower and intragastric pressures higher in pregnant women. Concurrently, esophageal peristalsis has lower wave speed and lower amplitude (Ulmsten, 1978).

Gastric emptying time is essentially unchanged across pregnancy in gravidas compared with nonpregnant women. In fasting women at term, gastric volume is not different than that in nonpregnant controls (Van de Putte, 2019). At term, during labor, and especially after administration of analgesics, however, gastric emptying time may be appreciably prolonged (Barboni, 2016). As a result, one danger of general anesthesia for delivery is regurgitation and aspiration of either food-laden or highly acidic gastric contents.

Some reports describe maternal gut microbiome changes during pregnancy (Smid, 2018). Currently, however, the vaginal and gut microbiome profiles and their influence on pregnancy are unclear (Taddei, 2018).

Hemorrhoids are common during pregnancy (Shin, 2015). They are caused in large measure by constipation and elevated pressure in rectal veins below the level of the enlarged uterus.

Liver

Liver size does not enlarge during human pregnancy. Hepatic arterial and portal venous blood flow, however, rise substantively (Clapp, 2000). Liver stiffness increases from the second to third trimester and returns to baseline postpartum (Ammon, 2018).

Some laboratory test results of hepatic function are altered in normal pregnancy (Appendix, p. 1229). Total alkaline phosphatase activity almost doubles, but much of the rise is attributable to heat-stable placental alkaline phosphatase isozymes. Serum aspartate transaminase (AST), alanine transaminase (ALT), γ-glutamyl transpeptidase (GGT), and bilirubin levels are slightly lower compared with nonpregnant values (Cattozzo, 2013).

The serum albumin concentration declines during pregnancy. By late pregnancy, albumin levels may be near 3.0 g/dL compared with approximately 4.3 g/dL in nonpregnant women (Mendenhall, 1970). Total body albumin levels rise, however, because of pregnancy-associated expansion of plasma volume. Serum globulin levels also are slightly higher.

Leucine aminopeptidase is a proteolytic liver enzyme whose serum levels may be elevated with liver disease. Its activity is markedly higher in pregnant women. The rise, however, results from a pregnancy-specific enzyme(s) with distinct substrate specificities (Song, 1968). Pregnancy-induced aminopeptidase has oxytocinase and vasopressinase activity that occasionally causes transient diabetes insipidus (Chap. 61, p. 1104).

Gallbladder

During normal pregnancy, gallbladder volume expands by approximately 50 percent, contractility declines, and both lead to greater residual volume (Braverman, 1980). Progesterone potentially impairs gallbladder contraction by inhibiting cholecystokinin-mediated smooth muscle stimulation, which is the primary regulator of gallbladder contraction. Impaired emptying, subsequent stasis, and the greater cholesterol saturation of bile in pregnancy contribute to the increased prevalence of cholesterol gallstones in multiparas. In one study, approximately 8 percent of women had gallbladder sludge or stones (Ko, 2014).

The pregnancy effects on maternal serum bile acid concentrations are still incompletely characterized. This is despite the long-acknowledged propensity for pregnancy to cause intrahepatic cholestasis from retained bile salts. Cholestasis of pregnancy is described in Chapter 58 (p. 1032).

ENDOCRINE SYSTEM

Pituitary Gland

During normal pregnancy, the pituitary gland enlarges by approximately 135 percent (Woodmansee, 2019). This expansion may sufficiently compress the optic chiasma to reduce visual fields. Impaired vision from this is rare and usually due to macroadenomas (Lee, 2014). Pituitary enlargement is primarily caused by estrogen-stimulated hypertrophy and hyperplasia of the lactotrophs (Feldt-Rasmussen, 2011). As discussed subsequently, maternal serum prolactin levels parallel this growth. Gonadotroph number decline, and corticotroph and thyrotroph populations remain constant. Somatotroph function is generally suppressed due to negative feedback by the placental production of growth hormone.

Peak pituitary size may reach 12 mm in MR images in the first days postpartum. The gland involutes rapidly and reaches normal size by 6 months postpartum (Woodmansee, 2019). The incidence of pituitary prolactinomas is not increased during pregnancy. When these tumors are large before pregnancy, such as with macroadenomas that by definition measure ≥10 mm, then growth during pregnancy is more likely (Chap. 61, p. 1103).

The maternal pituitary gland is not essential for pregnancy maintenance. Many women have undergone hypophysectomy, completed pregnancy successfully, and entered spontaneous labor while receiving compensatory glucocorticoids, thyroid hormone, and vasopressin.

Of pituitary gland hormones, *growth hormone* during the first trimester is secreted predominantly from the maternal pituitary gland, and concentrations in serum and amnionic fluid lie within the nonpregnant range. As early as 6 weeks' gestation, growth hormone secreted from the placenta becomes detectable, and by approximately 20 weeks, the placenta is the principal source of growth hormone secretion (Woodmansee, 2019). During this time, maternal serum values rise slowly from approximately 3.5 ng/mL at 10 weeks to plateau at about 14 ng/mL after 28 weeks' gestation. Growth hormone in amnionic fluid peaks at 14 to 15 weeks' gestation and slowly declines thereafter to reach baseline values after 36 weeks.

Placental growth hormone—which differs from pituitary growth hormone by 13 amino acid residues—is secreted by syncytiotrophoblast (Newbern, 2011). Its regulation and physiological effects are incompletely understood, but it influences fetal growth via upregulation of insulin-like growth factor 1 (IGF-1). That said, fetal growth still progresses in the complete absence of this hormone. Although not absolutely essential, the hormone may act in concert with placental lactogen to regulate fetal growth (Newbern, 2011).

Prolactin levels rise markedly in maternal plasma during normal pregnancy. Concentrations are usually tenfold greater at term—approximately 150 ng/mL—compared with those of nonpregnant women. Paradoxically, plasma levels drop after delivery even in women who are breastfeeding. During early lactation, pulsatile bursts of prolactin secretion are a response to suckling.

The principal function of maternal prolactin is to ensure lactation. Early in pregnancy, prolactin acts to initiate DNA synthesis and mitosis of glandular epithelial cells and presecretory alveolar cells of the breast. Prolactin also augments the number of estrogen and prolactin receptors in these cells. Last, prolactin promotes mammary alveolar cell RNA synthesis, galactopoiesis, and production of casein, lactalbumin, lactose, and lipids (Andersen, 1982). A woman with isolated prolactin deficiency failed to lactate after two pregnancies (Kauppila, 1987). This establishes prolactin as a requisite for lactation but not for pregnancy.

Grattan (2015) has reviewed the numerous physiological roles of prolactin to aid maternal adaptations to pregnancy. The prolactin receptor in the maternal pancreas indicates that prolactin may function to mediate pancreatic adaptations to pregnancy (Nteeba, 2019). A possible role is proposed for a prolactin fragment in the genesis of peripartum cardiomyopathy (Chap. 52, p. 933) (Cunningham, 2019; Koenig, 2018).

Prolactin is present in amnionic fluid in high concentrations. Levels of up to 10,000 ng/mL are found at 20 to 26 weeks' gestation. Thereafter, levels decline and reach a nadir after 34 weeks. Uterine decidua is the synthesis site of amnionic fluid prolactin. The exact function of this hormone is unknown, but water transfer from the fetus into the maternal compartment to prevent fetal dehydration is one suggestion.

Oxytocin and *antidiuretic hormone* are hormones secreted from the posterior pituitary gland. The roles of oxytocin in parturition and lactation are discussed in Chapters 21 (p. 413) and 36 (p. 640), respectively. Brown and colleagues (2013) have reviewed the complex mechanisms that promote quiescence of oxytocin systems during pregnancy. Levels of antidiuretic hormone, also called vasopressin, do not change during pregnancy. As discussed earlier (p. 56), osmolality is slightly higher in maternal compared with fetal blood, and the gradient favors water transport to the fetus (Moen, 2018).

Thyroid Gland

The maternal and fetal thyroid glands are intricately interrelated. On the maternal side, *thyrotropin-releasing hormone (TRH)* is secreted by the hypothalamus and stimulates thyrotrope cells of the anterior pituitary to release *thyroid-stimulating hormone (TSH),* also called *thyrotropin*. TRH levels do not rise during normal pregnancy. However, TRH does cross the placenta and may serve to stimulate the fetal pituitary to secrete TSH.

Serum TSH and hCG levels vary with gestational age (Fig. 4-17) (Burrow, 1994). As discussed in Chapter 5 (p. 96), the α-subunits of the two glycoproteins are identical, whereas the β-subunits, although similar, differ in their amino acid sequence. As a result of this structural similarity, hCG has intrinsic thyrotropic activity, and thus, high serum hCG levels cause thyroid stimulation. Indeed, TSH levels in the first trimester decline in more than 80 percent of pregnant women, however, they still remain in the normal range for nonpregnant women.

The thyroid gland boosts production of thyroid hormones by 40 to 100 percent to meet maternal and fetal needs (Korevaar, 2017). To accomplish this, the thyroid gland undergoes moderate enlargement during pregnancy caused by glandular hyperplasia and greater vascularity. Mean thyroid volume expands from 12 mL in the first trimester to 15 mL at term (Glinoer, 1990). That said, normal pregnancy does not typically cause significant thyromegaly, and thus any goiter warrants evaluation.

Early in the first trimester, levels of the principal carrier protein—*thyroid-binding globulin (TBG)*—rise. They reach their zenith at about 20 weeks' gestation. Concentrations stabilize at approximately double baseline values for the remainder of pregnancy (see Fig. 4-17). The greater TBG concentrations result from both higher hepatic synthesis rates—due to estrogen stimulation—and lower metabolism rates due to increased TBG sialylation and glycosylation. These elevated TBG levels increase total serum T_4 and triiodothyronine (T_3) concentrations, but do not affect the physiologically important serum *free* T_4 and *free* T_3 levels. Specifically, total serum T_4 levels rise sharply beginning between 6 and 9 weeks' gestation and reach a plateau at 18 weeks. Serum free T_4 levels rise only slightly and peak along with hCG levels, and then they return to normal.

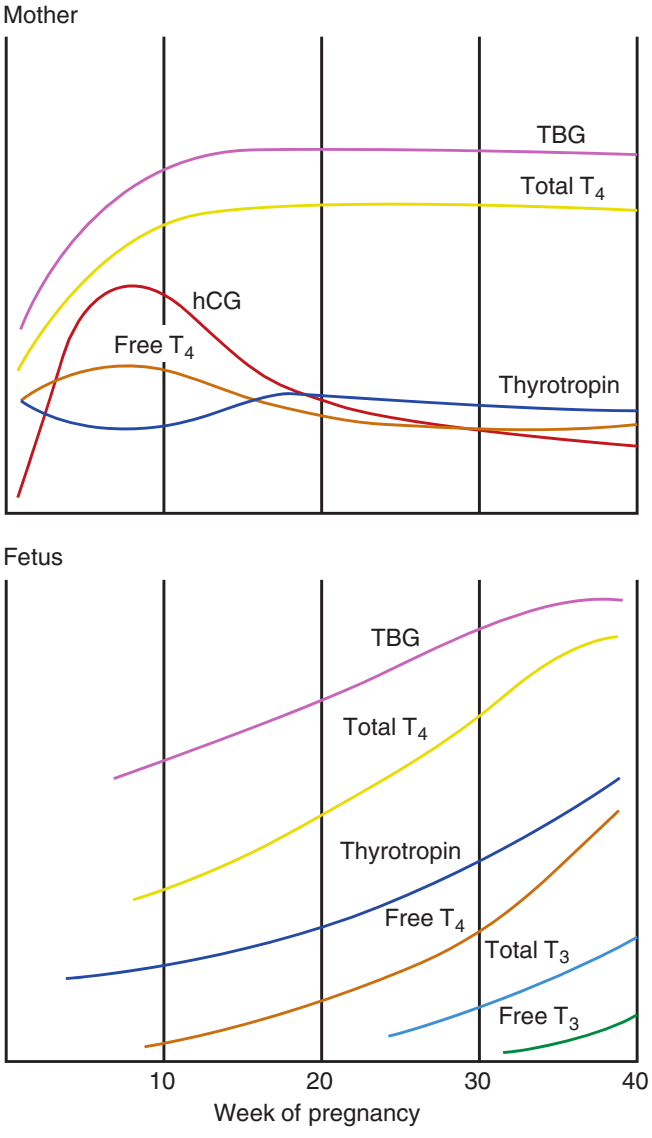

FIGURE 4-17 Relative changes in maternal and fetal thyroid function across pregnancy. Maternal changes include a marked and early increase in hepatic production of thyroxine-binding globulin (TBG) and placental production of human chorionic gonadotropin (hCG). Elevated TBG increases serum thyroxine (T_4) concentrations. hCG has thyrotropin-like activity and stimulates maternal free T_4 secretion. This transient hCG-induced increase in serum T_4 levels inhibits maternal secretion of thyrotropin. Except for minimally increased free T_4 levels when hCG peaks, these levels are essentially unchanged. Fetal levels of all serum thyroid analytes increase incrementally across pregnancy. Fetal triiodothyronine (T_3) does not increase until late pregnancy.

Interestingly, T_4 and T_3 secretion is not similar for all pregnant women. Approximately a third of women experience relative hypothyroxinemia, preferential T_3 secretion, and higher, albeit normal, serum TSH levels (Korevaar, 2017). Thus, thyroidal adjustments during normal pregnancy may vary considerably.

The fetus relies on maternal T_4, which crosses the placenta in small quantities to maintain normal fetal thyroid function (Chap. 61, p. 1089). Recall that the fetal thyroid does not begin to concentrate iodine until 10 to 12 weeks' gestation. The synthesis and secretion of thyroid hormone by fetal pituitary TSH

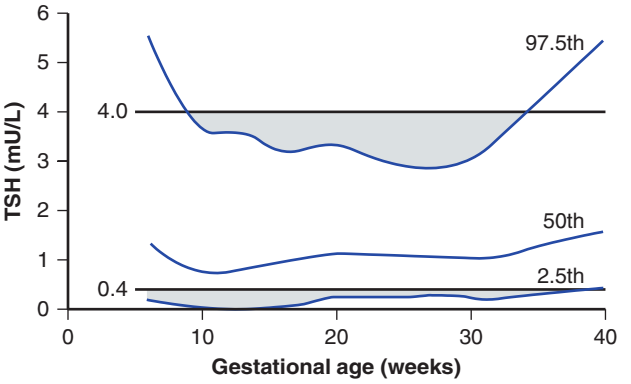

FIGURE 4-18 Gestational age-specific thyroid-stimulating hormone (TSH) nomogram derived from 13,599 singleton pregnancies. The nonpregnant reference values of 4.0 and 0.4 mU/L are represented as solid black lines. Upper shaded area represents the 28 percent of singleton pregnancies with TSH values above the 97.5th percentile threshold that would not have been identified as abnormal based on the assay reference value of 4.0 mU/L. Lower shaded area represents singleton pregnancies that would have been (falsely) identified as having TSH suppression based on the assay reference value of 0.4 mU/L.

ensues at approximately 20 weeks. At birth, approximately 30 percent of the T_4 in umbilical cord blood is of maternal origin (Leung, 2012).

Thyroid Function Tests

As detailed in Chapter 61 (p. 1095), a substantial proportion of otherwise normal pregnancies are found to have subclinical hypothyroidism or isolated hypothyroxinemia. The effects of thyroxine replacement in these women is currently controversial (Korevaar, 2017). Normal suppression of TSH during pregnancy may lead to a misdiagnosis of subclinical hyperthyroidism. Of greater concern is the potential failure to identify women with early hypothyroidism because of suppressed TSH concentrations. To mitigate the likelihood of such misdiagnoses, Dashe and coworkers (2005), and others, have developed gestational-age-specific TSH normal curves for both singleton and twin pregnancies (Fig. 4-18).

These complex alterations of thyroid regulation do not appear to alter maternal thyroid status as measured by metabolic studies. Although basal metabolic rate rises progressively by as much as 25 percent during normal pregnancy, most of this greater oxygen consumption can be attributed to fetal metabolic activity. If fetal body surface area is considered along with that of the mother, the predicted and observed basal metabolic rates are similar to those in nonpregnant women.

Iodine Status

As discussed earlier (p. 59), iodine requirements increase during normal pregnancy (Chap. 61, p. 1097). In women with low or marginal intake, deficiency may manifest as low T_4 and higher TSH levels. Importantly, more than one third of the world population lives in areas where iodine intake is marginal. Even in modernized countries, iodine deficiency is commonplace (Snart, 2019). For the fetus, early exposure to thyroid hormone is essential for the nervous system. Yet, despite public health programs

to supplement iodine, severe deficiency that results in cretinism affects more than 2 million people globally (Syed, 2015).

Parathyroid Glands

During pregnancy, levels of calcitriol, which is the bioactive form of vitamin D, increase twofold and enhance intestinal calcium absorption (Khan, 2019). In an earlier longitudinal investigation of 20 women, all markers of bone turnover rose during normal pregnancy and failed to reach baseline levels by 12 months postpartum (More, 2003). Investigators concluded that the calcium needed for fetal growth and lactation may be drawn at least in part from the maternal skeleton. The factors affecting bone turnover create a net yield that favors fetal skeletal formation at the expense of the mother. As a result, pregnancy is a vulnerable period for osteoporosis (Sanz-Salvador, 2015).

Parathyroid hormone (PTH) release is stimulated by acute or chronic declines in plasma calcium or acute drops in magnesium levels. Conversely, greater calcium and magnesium levels suppress PTH levels. The action of this hormone on bone resorption, intestinal absorption, and kidney reabsorption is to raise extracellular fluid calcium concentrations and lower phosphate levels.

As discussed earlier (p. 59), fetal skeleton mineralization requires approximately 30 g of calcium, primarily during the third trimester. Although this amounts to only 3 percent of the total calcium held within the maternal skeleton, calcium demands still challenge the mother (Degennaro, 2021). Augmented maternal calcium absorption provides the additional calcium. During pregnancy, the amount of calcium absorbed rises gradually and reaches approximately 400 mg/d in the third trimester. Greater calcium absorption appears to be mediated by elevated maternal 1,25-dihydroxyvitamin D concentrations. This occurs despite decreased PTH levels during early pregnancy, which is the normal stimulus for active vitamin D production within the kidney. Indeed, PTH plasma levels decline during the first trimester and then rise progressively throughout the remainder of pregnancy (Pitkin, 1979).

The increased production of active vitamin D is likely due to placental production of either PTH or a PTH-related protein (PTH-rP). Outside pregnancy and lactation, PTH-rP is usually detectable only in serum of women with hypercalcemia due to malignancy. During pregnancy, however, PTH-rP concentrations rise significantly. This protein is synthesized in both fetal tissues and maternal breasts.

Calcitonin is secreted by C cells that are located predominantly in the perifollicular areas of the thyroid gland. Calcitonin opposes actions of PTH and vitamin D and protects the maternal skeleton during times of calcium stress. As discussed, pregnancy and lactation cause profound maternal calcium stress. Indeed, fetal calcitonin levels are at least twofold higher than maternal levels (Ohata, 2016). Although maternal calcitonin levels fall during pregnancy, they generally rise postpartum.

Calcium and magnesium promote the biosynthesis and secretion of calcitonin. Various gastric hormones—gastrin, pentagastrin, glucagon, and pancreozymin—and food ingestion also promote calcitonin plasma levels.

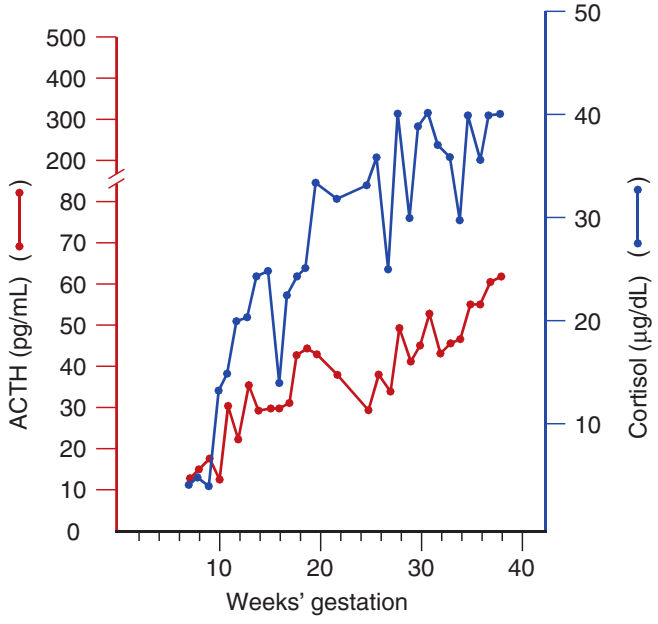

FIGURE 4-19 Serial increases in serum cortisol (*blue line*) and adrenocorticotropic hormone (ACTH) (*red line*) across normal pregnancy.

Adrenal Glands

Cortisol

In normal pregnancy, unlike their fetal counterparts, the maternal adrenal glands undergo little, if any, morphological change. The serum concentration of circulating cortisol rises, but much of it is bound by *transcortin*, the cortisol-binding globulin. The adrenal secretion rate of this principal glucocorticoid is not elevated, and it is probably lower than in the nonpregnant state. The metabolic clearance rate of cortisol, however, is diminished during pregnancy because its half-life is nearly doubled compared with that for nonpregnant women (Migeon, 1957). Administration of estrogen, including most oral contraceptives, causes changes in serum cortisol levels and transcortin similar to those of pregnancy (Jung, 2011).

During early pregnancy, the levels of circulating *adrenocorticotropic hormone* (*ACTH*), also known as *corticotropin*, are dramatically reduced. As pregnancy progresses, ACTH and free cortisol levels rise equally and strikingly (Fig. 4-19) (Carr, 1981). This apparent paradox is not understood completely. Some suggest that greater free cortisol levels in pregnancy result from a "resetting" of the maternal feedback mechanism to higher thresholds (Nolten, 1981). This might result from *tissue refractoriness* to cortisol. Others assert that these incongruities stem from an antagonistic action of progesterone on mineralocorticoids (Keller-Wood, 2001). Thus, in response to elevated progesterone levels during pregnancy, an elevated free cortisol is needed to maintain homeostasis. Other theories include possible roles for higher free cortisol in preparation for the stress of pregnancy, delivery, and lactation.

Aldosterone

As early as 15 weeks' gestation, the maternal adrenal glands secrete considerably higher amounts of aldosterone, the principal mineralocorticoid. By the third trimester, approximately 1 mg/d is

released. If sodium intake is restricted, aldosterone secretion is even further elevated. Concurrently, levels of renin and angiotensin II substrate normally rise, especially during the latter half of pregnancy. This scenario promotes greater plasma levels of angiotensin II, which acts on the zona glomerulosa of the maternal adrenal glands and accounts for the markedly elevated aldosterone secretion. Some suggest the increased aldosterone secretion during normal pregnancy affords protection against the natriuretic effect of progesterone and atrial natriuretic peptide. Gennari-Moser and colleagues (2011) provide evidence that aldosterone and cortisol may modulate trophoblast growth and placental size.

Deoxycorticosterone

Maternal plasma levels of this potent mineralocorticosteroid progressively increase during pregnancy. Indeed, plasma levels of deoxycorticosterone rise to near 1500 pg/mL by term, a more than 15-fold increase (Parker, 1980). This marked elevation does not derive from adrenal secretion but instead represents augmented kidney production resulting from estrogen stimulation. The levels of deoxycorticosterone and its sulfate in fetal blood are appreciably higher than those in maternal blood, which suggests transfer of fetal deoxycorticosterone into the maternal compartment.

Androgens

In balance, androgenic activity rises during pregnancy, and both maternal plasma levels of *androstenedione* and *testosterone* are increased. This finding is not totally explained by alterations in their metabolic clearance. Both androgens are converted to estradiol in the placenta, which increases their clearance rates. Conversely, greater plasma sex hormone–binding globulin levels in gravidas retard testosterone clearance. Thus, the production rates of maternal testosterone and androstenedione during human pregnancy are increased. The source of this higher C_{19}-steroid production is unknown, but it likely originates in the ovary. Interestingly, little or no testosterone in maternal plasma enters the fetal circulation as testosterone. Even when massive testosterone levels are found in the circulation of pregnant women, as with androgen-secreting tumors, testosterone concentrations in umbilical cord blood are likely to be undetectable. This results from the near complete trophoblastic conversion of testosterone to 17β-estradiol.

Maternal serum and urine levels of *dehydroepiandrosterone sulfate* are lower during normal pregnancy. This stems from a greater metabolic clearance through extensive maternal hepatic 16α-hydroxylation and placental conversion to estrogen (Chap. 5, p. 101).

MUSCULOSKELETAL SYSTEM

Progressive lordosis is characteristic of pregnancy. Compensating for the anterior position of the enlarging uterus, lordosis shifts the center of gravity dorsally and over the lower extremities. The sacroiliac, sacrococcygeal, and pubic joints have greater mobility during pregnancy. However, as discussed earlier, increased joint laxity and associated discomfort during pregnancy do not correlate with increased maternal serum levels of estradiol, progesterone, or relaxin. Most relaxation takes place in the first half of pregnancy. It may contribute to maternal posture alterations and in turn create lower back discomfort. As discussed in Chapter 36 (p. 644), although some symphyseal separation likely accompanies many deliveries, those greater than 1 cm may cause significant pain (Shnaekel, 2015).

Aching, numbness, and weakness also occasionally are experienced in the upper extremities. This may result from the marked lordosis and associated anterior neck flexion and shoulder girdle slumping. These can produce traction on the ulnar and median nerves. The latter may give rise to symptoms mistaken for the *carpal tunnel syndrome* (Chap. 63, p. 1137). Joint strengthening begins immediately following delivery and is usually complete within 3 to 5 months. Pelvic dimensions measured by MR imaging up to 3 months postpartum are not significantly different from prepregnancy values (Huerta-Enochian, 2006).

CENTRAL NERVOUS SYSTEM

Changes to the central nervous system during pregnancy are relatively few and mostly subtle. Zeeman and coworkers (2003) used MR imaging to measure cerebral blood flow across pregnancy. They found that mean blood flow in the middle and posterior cerebral arteries declined progressively from 147 and 56 mL/min when nonpregnant to 118 and 44 mL/min late in pregnancy, respectively. Others have found similar middle cerebral artery blood flow changes with ultrasound (Batur Caglayan, 2019). Mechanisms and significance of the decline are unknown. It appears that pregnancy does not affect cerebrovascular autoregulation (Cipolla, 2015).

Memory

Women often report problems with attention, concentration, and memory throughout pregnancy and the early puerperium. Systematic studies of memory in pregnancy, however, are limited and often anecdotal. In a metaanalysis, Davies and coworkers (2018) reported pregnancy-related memory decline was worst in the third trimester. This decline was not attributable to depression, anxiety, sleep deprivation, or other physical changes associated with pregnancy. It was transient and quickly resolved following delivery. In follow up studies, preeclampsia and eclampsia were found to lead to both short- and long-term cognitive disability (Aukes, 2007; Dayan, 2018).

Eyes

Intraocular pressure declines during pregnancy and is attributed partly to greater vitreous outflow. Corneal sensitivity is decreased, and the greatest changes are late in gestation. Most pregnant women demonstrate a measurable but slight increase in corneal thickness, thought to be due to edema. Consequently, they may have difficulty with previously comfortable contact lenses. Brownish-red opacities on the posterior surface of the cornea—*Krukenberg spindles*—are observed with a higher than expected frequency during pregnancy. Hormonal

effects similar to those observed for skin lesions are believed to cause this increased pigmentation. Other than transient loss of accommodation reported during both pregnancy and lactation, visual function is unaffected by pregnancy. These changes during pregnancy and pathological eye aberrations were reviewed by Gilbert and colleagues (2019).

Sleep

Beginning as early as 12 weeks' gestation and extending through the first 2 months postpartum, women have difficulty with falling asleep, frequent awakenings, fewer hours of night sleep, and reduced sleep efficiency. These symptoms are part of the spectrum of sleep-disordered breathing, the most severe of which is obstructive sleep apnea (Ayyar, 2018; Dominguez, 2018). The greatest disruption of sleep is encountered postpartum and may contribute to *postpartum blues* or to frank depression and suicidal ideation (Palagini, 2019).

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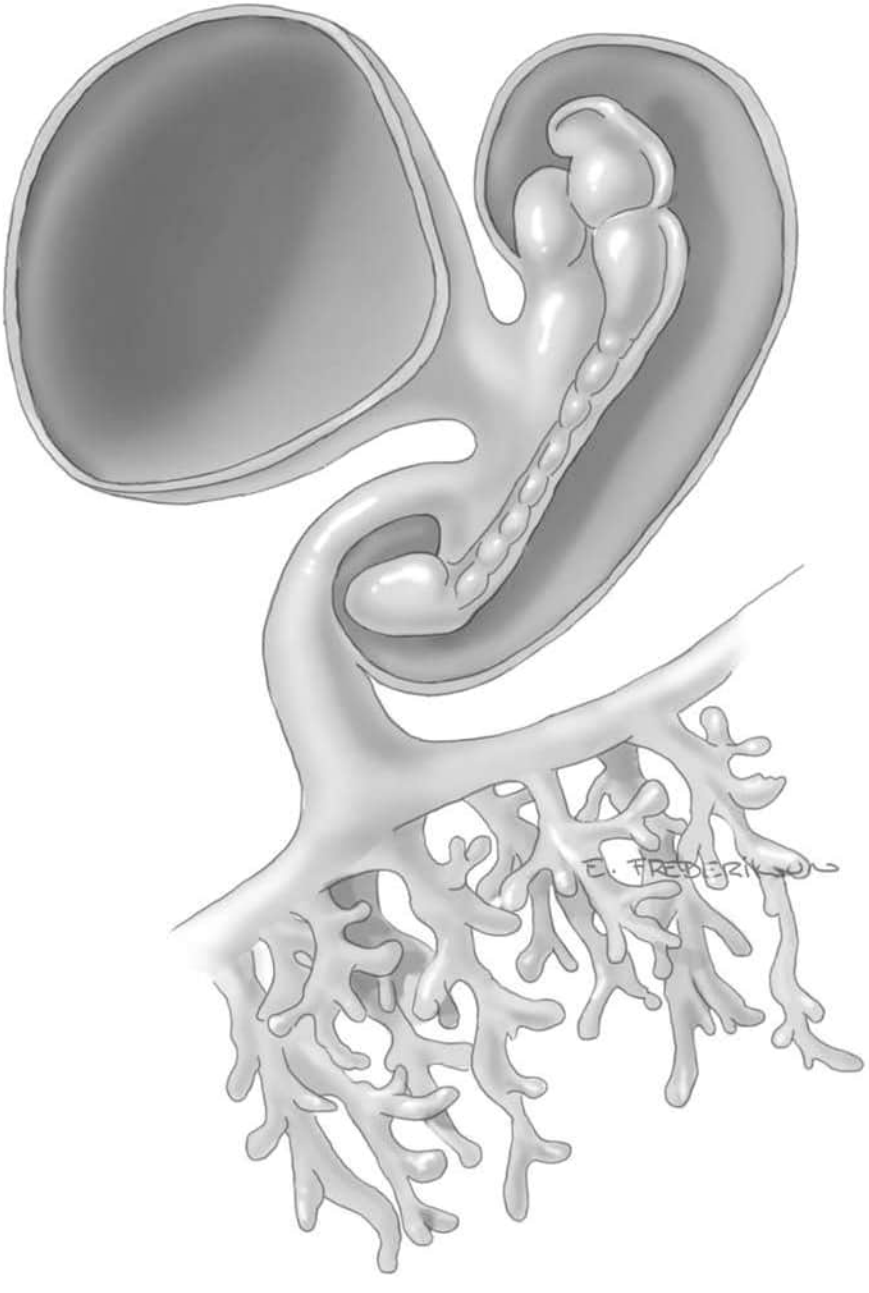
SECTION 3

PLACENTATION, EMBRYOGENESIS, AND FETAL DEVELOPMENT



CHAPTER 5

Implantation and Placental Development

All obstetricians should understand the basic biological steps required for women to achieve pregnancy. Moreover, abnormalities affecting these steps can lead to infertility or pregnancy loss. The biological and molecular changes involved in human zygote implantation and subsequent fetal and placental development are intricate. In the past 50 years, researchers have delineated many of these molecular and physiological events. Yet, much work remains in the continual challenge to improve clinical outcomes.

OVARIAN-ENDOMETRIAL CYCLE

In most women, cyclical ovulation continues during the almost 40 years between menarche and menopause. Thus, without contraception, approximately 400 opportunities for pregnancy exist, and these are tightly regulated by complex interactions of the hypothalamic-pituitary-ovarian axis. Concurrently, endometrium undergoes faithfully reproduced cyclical changes to prepare for pregnancy (Fig. 5-1). Essential contributors in this process include gonadotropin-releasing hormone (GnRH), the gonadotropin hormones follicle-stimulating hormone (FSH) and luteinizing hormone (LH), and the ovarian sex steroid hormones estrogen and progesterone. For a detailed description of menstrual cycle physiology, the reader is referred to Chapter 16 in *Williams Gynecology*, 4th edition (Halvorson, 2020).

Ovulation

This defining event separates the follicular and luteal phases of the menstrual cycle. Following ovulation, the corpus luteum develops from the remains of the graafian follicle in a process referred to as *luteinization*. The basement membrane separating the granulosa-lutein and theca-lutein cells breaks down, and by day 2 postovulation, blood vessels and capillaries invade the granulosa cell layer. During luteinization, these cells undergo hypertrophy and increase their capacity to synthesize hormones. LH is the primary luteotropic factor responsible for corpus luteum maintenance (Vande Wiele, 1970).

The hormone secretion pattern of the corpus luteum differs from that of the follicle. First, the greater capacity of granulosa-lutein cells to produce progesterone results from enhanced access to blood-borne, low-density lipoprotein (LDL)-derived cholesterol, which is a steroidogenic precursor (Carr, 1981). Ovarian progesterone production peaks at 25 to 50 mg/d during the midluteal phase. With pregnancy, the corpus luteum continues progesterone production in response to placental human chorionic gonadotropin (hCG). LH and hCG both act via the same LH-hCG receptor.

The human corpus luteum is a transient endocrine organ. In the absence of pregnancy, it rapidly undergoes apoptosis 9 to 11 days after ovulation (Vaskivuo, 2002). The dramatic drop in

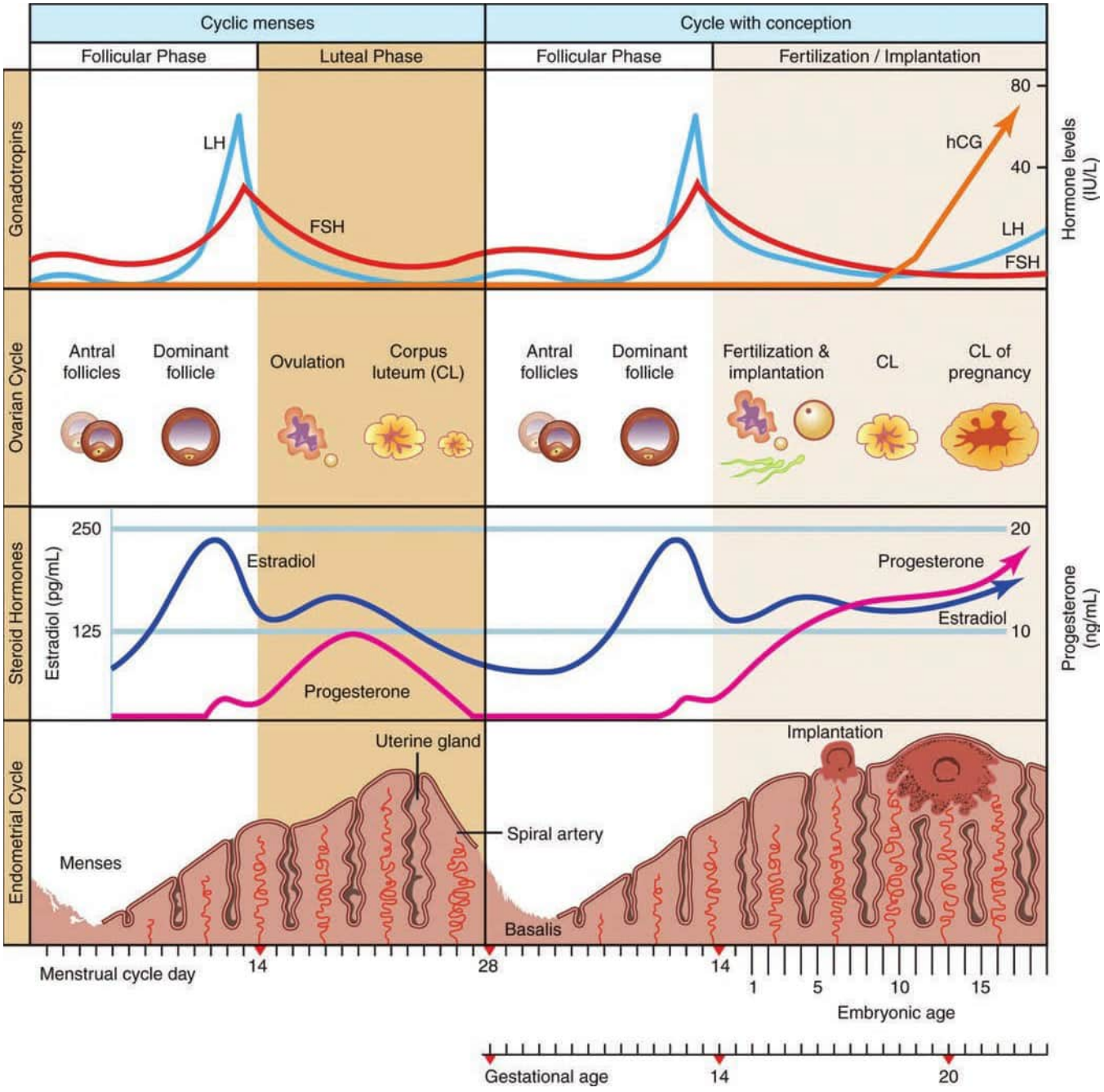


FIGURE 5-1 Gonadotropin control of the ovarian and endometrial cycles. The ovarian-endometrial cycle is structured as a 28-day cycle. The follicular phase (days 1 to 14) is characterized by rising estrogen levels, endometrial thickening, and selection of the dominant "ovulatory" follicle. During the luteal phase (days 14 to 21), the corpus luteum (CL) produces estrogen and progesterone, which prepare the endometrium for implantation. If implantation occurs, the developing blastocyst begins to produce human chorionic gonadotropin (hCG) and rescues the corpus luteum, thus maintaining progesterone production. FSH = follicle-stimulating hormone; LH = luteinizing hormone.

circulating estradiol and progesterone levels initiate molecular events that lead to menstruation.

Between days 22 and 25 after ovulation, the secretory-phase endometrium undergoes striking changes associated with predecidual transformation of the upper two thirds of the functionalis layer. The glands exhibit extensive coiling, and luminal secretions become visible. Changes within the endometrium can also mark the *window of implantation* seen on days 20 to 24. Epithelial surface cells show fewer microvilli and cilia, but luminal protrusions appear on the apical cell surface (Nikas, 2003). These *pinopodes* help prepare for blastocyst implantation. They also coincide with changes in the surface glycocalyx that allow acceptance of a blastocyst (Aplin, 2003).

Another highlight of the secretory phase is the continuing growth and development of the spiral arteries. These vessels arise from the radial arteries, which are myometrial branches of the arcuate and, ultimately, uterine vessels. The morphological and functional properties of the spiral arteries are unique and essential to blood flow changes seen during menstruation or implantation. During endometrial growth, spiral arteries lengthen at

a rate appreciably greater than the rate of endometrial tissue thickening. This growth discordance obliges even greater coiling. Spiral artery development reflects a marked induction of angiogenesis, reflected by widespread vessel sprouting and extension.

At this juncture with hormonal withdrawal, menstruation follows. With blastocyst implantation, however, the endometrium is converted to the decidua.

DECIDUA

This is a specialized, highly modified endometrium of pregnancy. It is essential for *hemochorial placentation*, that is, one in which maternal blood contacts trophoblast. This relationship requires trophoblast invasion, and considerable research has focused on the interaction between decidual cells and invading trophoblasts. *Decidualization* transforms proliferating endometrial stromal cells into specialized secretory cells. This process depends on estrogen, progesterone, androgens, and factors secreted by the implanting blastocyst (Gibson, 2016). The decidua produces factors that regulate endometrial receptivity and that modulate immune and vascular cell functions within the maternal–fetal microenvironment. The special immunomodulatory relationship between the decidua and invading trophoblasts is largely mediated by decidual natural killer (NK) cells and ensures success of the pregnancy semiallograft.

Decidual Structure

The decidua is classified into three parts based on anatomical location. Decidua directly beneath the implanted blastocyst is modified by trophoblast invasion and becomes the *decidua basalis*. The *decidua capsularis* overlies the enlarging blastocyst and initially separates the conceptus from the rest of the uterine cavity (Fig. 5-2). This portion is most prominent during the second month of pregnancy and consists of stromal decidual cells covered by a single layer of flattened epithelial cells. The other side of the capsularis contacts the avascular, extraembryonic fetal membrane—the chorion laeve. The remainder of the uterus is lined by *decidua parietalis*. During early pregnancy, a space lies between the decidua capsularis and parietalis because the gestational sac does not fill the entire uterine cavity. The gestational sac is the *extraembryonic coelom* and also called the chorionic cavity. By 14 to 16 weeks' gestation, the expanding sac has enlarged to completely fill the uterine cavity. The resulting apposition of the decidua capsularis and parietalis creates the *decidua vera*, and the uterine cavity is functionally obliterated.

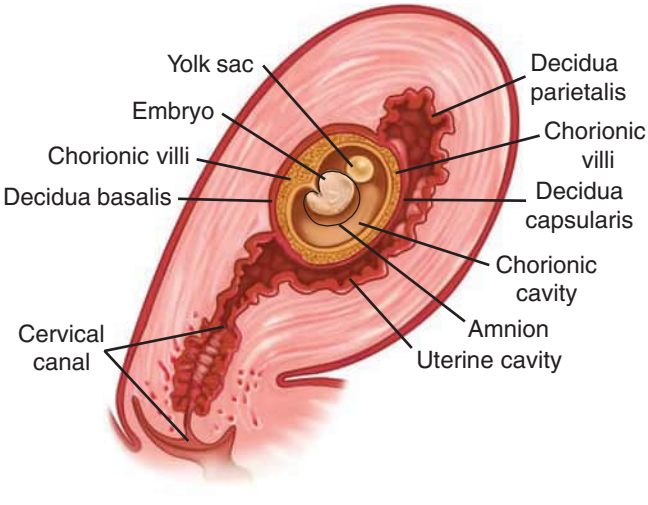


FIGURE 5-2 Three portions of the decidua—the basalis, capsularis, and parietalis—are illustrated.

In early pregnancy, the decidua begins to thicken, eventually attaining a depth of 5 to 10 mm. With magnification, furrows and numerous small openings, representing the mouths of uterine glands, can be detected. Later in pregnancy, the decidua becomes thinner, presumably because of pressure exerted by the expanding uterine contents.

The decidua parietalis and basalis are composed of three layers. There is a surface or compact zone—*zona compacta*; a middle portion or spongy zone—*zona spongiosa*—that has remnants of glands and numerous small blood vessels; and a basal zone—*zona basalis*. The zona compacta and spongiosa together form the *zona functionalis*. The basal zone remains after delivery and gives rise to new endometrium.

The decidual reaction is completed only with blastocyst implantation. Predecidual changes, however, commence first during the midluteal phase in endometrial stromal cells adjacent to the spiral arteries and arterioles. Thereafter, these alterations spread in waves throughout the uterine endometrium. The endometrial stromal cells enlarge to form polygonal or round decidual cells. The nuclei become vesicular, and the cytoplasm becomes clear, slightly basophilic, and surrounded by a translucent membrane.

As the embryo–fetus grows, the blood supply to the decidua capsularis is lost. However, spiral arteries persist to supply the decidua parietalis. These arteries retain smooth muscle and endothelium and thereby remain responsive to vasoactive agents.

In contrast, the spiral arteries that supply the decidua basalis and ultimately the placental intervillous space are altered remarkably. Trophoblastic cells invade the spiral arterioles and arteries and replace their endothelial cells. The vessel wall smooth muscle is destroyed, and the resulting uteroplacental vessels become unresponsive to vasoactive agents. Defective trophoblastic invasion of spiral arteries is thought to be one underlying cause of preeclampsia (Chap. 40, p. 692). Conversely, the fetal chorionic vessels, which transport blood between the placenta and the fetus, contain smooth muscle and thus do respond to vasoactive agents.

Decidual Histology

Early in pregnancy, the decidual zona spongiosa consists of large distended glands, often exhibiting marked hyperplasia and separated by minimal stroma. At first, the glands are lined by typical cylindrical uterine epithelium with abundant secretory activity that contributes to blastocyst nourishment. With advanced pregnancy, the glandular elements largely disappear, and the spongy zone of the decidua basalis consists mainly of arteries and widely dilated veins.

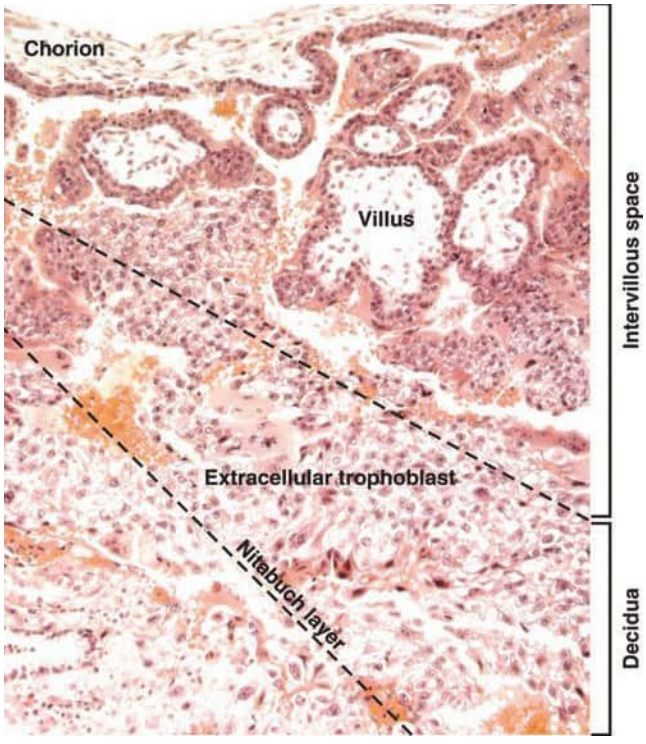


FIGURE 5-3 Section through a junction of chorion, villi, and decidua basalis in early first-trimester pregnancy. (Reproduced with permission from Dr. Kurt Benirschke.)

The decidua basalis contributes to formation of the placental basal plate (Fig. 5-3). As such, it is invaded by many interstitial trophoblasts. The *Nitabuch layer* is a zone of fibrinoid degeneration in which invading trophoblasts meet the decidua basalis. If the decidua is defective, as in placenta accreta, the Nitabuch layer is usually absent (Chap. 43, p. 759). Normally, there is also a more superficial, but inconsistent, deposition of fibrin—*Rohr stria*—at the bottom of the intervillous space and surrounding the anchoring villi. Decidual necrosis is a common phenomenon in the first and probably second trimesters (McCombs, 1964). Thus, necrotic decidua obtained through curettage after spontaneous abortion should not necessarily be interpreted as either a cause or an effect of the pregnancy loss.

Both decidual layers contain numerous cell groups whose composition varies with gestational stage (Loke, 1995). The primary cellular components are the true decidual cells, which differentiated from the endometrial stromal cells, and numerous maternal bone marrow-derived cells. Of the latter, lymphocytes with unique properties accumulate at the maternal–fetal interface and are essential to evoke immune tolerance between mother and fetus. These include regulatory T cells, decidual macrophages, and decidual NK cells. Collectively, these cells not only provide immunotolerance but also play an important role in trophoblast invasion and vasculogenesis (PrabhuDas, 2015).

■ Decidual Prolactin

The decidua produces prolactin, which is present in enormous amounts in amnionic fluid (Golander, 1978; Riddick, 1979). Decidual prolactin is a product of the same gene that encodes for anterior pituitary prolactin, but the exact physiological role of decidual prolactin is unknown. Signaling by prolactin can lead to the production of proangiogenic factors. Prolactin can also be cleaved by proteases to form vasoinhibins (Nakajima, 2015; Triebel, 2015). These compounds have antiangiogenic properties and may contribute to peripartum cardiomyopathy, whose pathogenesis and treatment are discussed in Chapter 52 (p. 933).

Decidual prolactin preferentially enters amnionic fluid and may reach extraordinarily high levels of 10,000 ng/mL at 20 to 24 weeks' gestation (Tyson, 1972). In contrast, maternal serum levels are relatively low at 150 to 200 ng/mL. As discussed in Chapter 4 (p. 57), prolactin inhibits maternal insulin action and results in increased glucose levels for fetal growth.

IMPLANTATION AND EARLY TROPHOBLAST FORMATION

■ Fertilization

With ovulation, the ovary releases the secondary oocyte and surrounding cells of the cumulus–oocyte complex. The oocyte complex is quickly engulfed by the fallopian tube infundibulum. Directional movement of cilia and tubal peristalsis moves the ovum within the tubal lumen. Fertilization takes place in the lumen within a few hours, and no more than a day after ovulation. Because of this narrow window, spermatozoa must be present in the fallopian tube at the time of oocyte arrival. Almost all pregnancies result when intercourse occurs during the 2 days preceding or on the day of ovulation.

Fertilization is highly complex. Molecular mechanisms allow spermatozoa to pass between cumulus cells; through the zona pellucida, which is a thick glycoprotein layer surrounding the oocyte cell membrane; and into the oocyte cytoplasm. Fusion of the two nuclei and intermingling of maternal and paternal chromosomes creates the *zygote*.

Early human development is described by days or weeks postfertilization, that is, postconceptional (Chap. 7, p. 121). By contrast, in most chapters of this book, clinical pregnancy dating is calculated from the first day of the last menstrual period (LMP). Thus, 1 week postfertilization corresponds to approximately 3 weeks from the LMP in women with regular 28-day cycles. This convention is clinically important for dating pregnancies conceived by in vitro fertilization (IVF), in which the gestational age is 14 days greater than the day of fertilization. As an example, 8 weeks' gestation refers to 8 completed weeks following the LMP but corresponds to 6 weeks postfertilization.

After fertilization, the zygote—a diploid cell with 46 chromosomes—undergoes cleavage, and zygote cells produced by this division are *blastomeres* (Fig. 5-4). In the two-cell zygote, the blastomeres and polar body continue to be surrounded by the zona pellucida. The zygote undergoes slow cleavage for 3 days while still in the fallopian tube. As the blastomeres continue to divide, a solid mulberry-like ball of cells—the *morula*—is produced. The morula enters the uterine cavity approximately 3 days after fertilization. Gradual accumulation of fluid between the morula cells leads to formation of the early *blastocyst*.

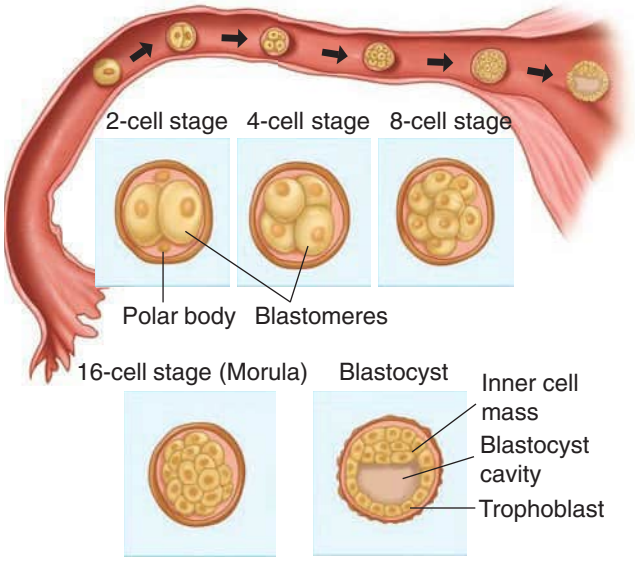


FIGURE 5-4 Zygote cleavage and blastocyst formation. The morula period begins at the 12- to 16-cell stage and ends when the blastocyst forms, which occurs when there are 50 to 60 blastomeres present. The polar bodies, shown in the 2-cell stage, are small nonfunctional cells that degenerate.

Blastocyst

As early as 4 to 5 days after fertilization, the 58-cell blastocyst differentiates into five embryo-producing cells—the *inner cell mass* (see Fig. 5-4). The remaining 53 outer cells, called the *trophectoderm*, are destined to form *trophoblasts* (Hertig, 1962).

In the 107-cell blastocyst, the eight formative, embryo-producing cells are surrounded by 99 trophoblastic cells. The blastocyst is released from the zona pellucida secondary to secretion of specific proteases from the secretory-phase endometrial glands (O'Sullivan, 2002). Release from the zona pellucida allows blastocyst-produced cytokines and hormones to directly influence endometrial receptivity (Lindhard, 2002). The blastocyst secretes interleukin-1α (IL-1α) and IL-1β, which are cytokines that likely directly influence the endometrium. Embryos also secrete hCG, which may influence endometrial receptivity (Licht, 2001; Lobo, 2001).

The receptive endometrium is thought to respond by producing leukemia inhibitory factor (LIF), follistatin, and colony-stimulating factor-1 (CSF-1). LIF and follistatin activate signaling pathways that collectively inhibit proliferation and promote differentiation of the endometrial epithelia and stroma to enable uterine receptivity (Rosario, 2016b). At the maternal–fetal interface, CSF-1 has proposed immunomodulatory and proangiogenic actions that are required for implantation (Rahmati, 2015).

■ Implantation

The blastocyst implants into the uterine wall 6 or 7 days after fertilization. This process can be divided into three phases: (1) *apposition*—initial contact of the blastocyst to the uterine wall; (2) *adhesion*—increased physical contact between the blastocyst and decidua; and (3) *invasion*—penetration and invasion of syncytiotrophoblast and cytotrophoblasts into the decidua, inner third of the myometrium, and uterine vasculature. Successful implantation requires a receptive endometrium appropriately primed with estrogen and progesterone by the corpus luteum. Such uterine receptivity is limited to days 20 to 24 of the endometrial cycle. Adherence is mediated by cell-surface receptors at the implantation site that interact with blastocyst receptors (Carson, 2002; Lessey, 2002). If the blastocyst approaches the endometrium after cycle day 24, the potential for adhesion declines because antiadhesive glycoprotein synthesis prevents receptor interactions (Navot, 1991). A mismatch between uterine receptivity and timing of embryo transfer can lead to repeated implantation failure in some IVF patients. This has stimulated efforts to define receptivity by gene expression profiles to improve clinical outcomes (Ruiz-Alonso, 2013).

At the time of its interaction with the endometrium, the blastocyst is composed of 100 to 250 cells. The blastocyst trophectoderm loosely adheres to the decidua by apposition. This appears to be closely regulated by paracrine interactions between these two tissues and most commonly occurs on the upper posterior uterine wall.

Successful endometrial blastocyst adhesion involves modified expression of cellular adhesion molecules (CAMs). The integrins—one of four families of CAMs—are cell-surface receptors that mediate cell adhesion to extracellular matrix proteins (Lessey, 2002). Endometrial integrins are hormonally regulated, and a specific set of integrins is expressed at implantation (Lessey, 1995). Recognition-site blockade of the integrins needed for binding will prevent blastocyst attachment (Kaneko, 2013).

■ Trophoblast Development

The fetus depends on the placenta for pulmonary, hepatic, and renal functions. These are accomplished through the anatomical relationship of the placenta and its uterine interface. In overview, maternal blood flows from uteroplacental vessels into the placental intervillous space and bathes the syncytiotrophoblast, which surround villi. Here, gases, nutrients, and other substances are exchanged with fetal capillary blood within the core of each placental villus. Thus, fetal and maternal blood do not normally mix in this hemochorial placenta.

Human placental formation begins with the trophectoderm, which gives rise to a trophoblast cell layer encircling the blastocyst. Trophoblast exhibits the most variable structure, function, and developmental pattern of all placental components. Its invasiveness promotes implantation, its nutritional role for the conceptus is reflected in their name, and its endocrine function is essential to maternal physiological adaptations and to pregnancy maintenance.

By the eighth day postfertilization, after initial implantation, the trophoblast has differentiated into an outer multinucleated syncytium—the primitive *syncytiotrophoblast*, and an inner layer of primitive mononuclear cells—*cytotrophoblasts*. The latter are solely germinal cells for the syncytium. As cytotrophoblasts differentiate, they express an endogenous envelope protein called *syncytin*, which aids their cell fusion with the expanding outer layer of syncytiotrophoblast. Each cytotrophoblast has a well-demarcated cell border, a single nucleus, and ability to undergo DNA synthesis and mitosis (Arnholdt, 1991). These are lacking

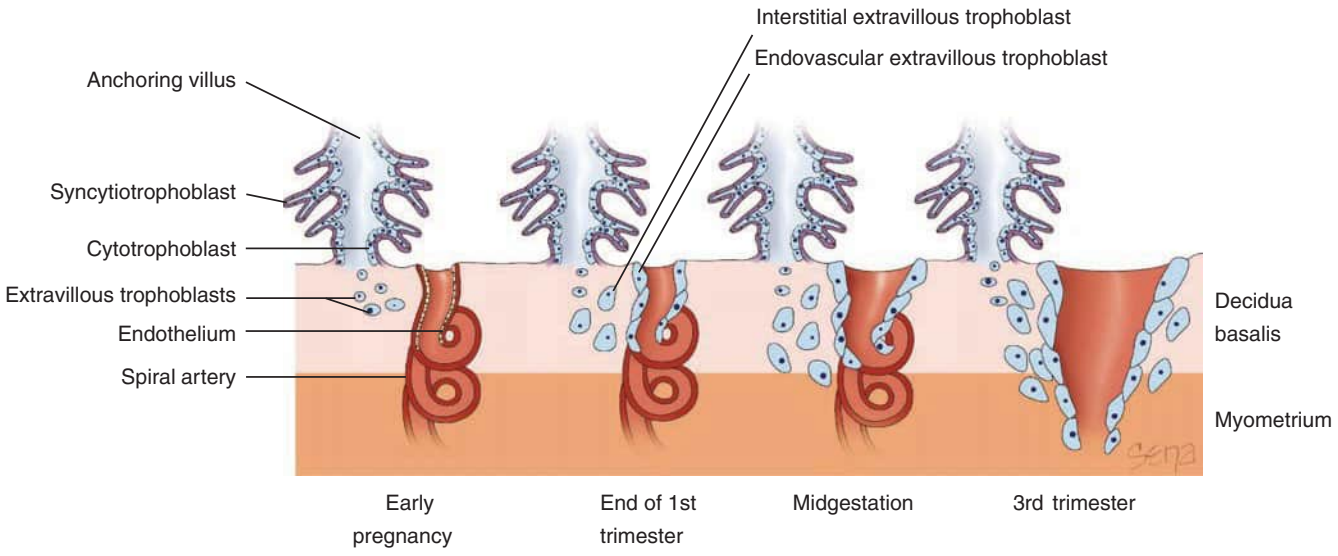


FIGURE 5-5 Endovascular and interstitial extravillous trophoblasts are found outside the villus. Endovascular trophoblasts invade and transform spiral arteries during pregnancy to create low-resistance blood flow that is characteristic of the placenta. Interstitial trophoblasts invade the decidua and surround spiral arteries.

in the syncytiotrophoblast, which provides transport functions of the placenta. It is so named because instead of individual cells, it has an amorphous cytoplasm without cell borders, nuclei that are multiple and diverse in size and shape, and a continuous syncytial lining.

Following implantation, trophoblasts differentiate along two main pathways that give rise to either villous or extravillous trophoblasts. As shown in Figure 5-5, both have distinct functions (Loke, 1995). *Villous trophoblasts* generate chorionic villi, which primarily transport oxygen, nutrients, and other compounds between the fetus and mother. *Extravillous trophoblasts* migrate into the decidua and myometrium (Fig. 5-6). They also penetrate maternal vasculature and thus directly contact various maternal cell types (Pijnenborg, 1994). Extravillous trophoblasts are further classified as *interstitial trophoblasts* and *endovascular trophoblasts*. The interstitial trophoblasts invade the decidua and eventually penetrate the myometrium to form placental-bed giant cells. These trophoblasts also surround spiral arteries. The endovascular trophoblasts penetrate the spiral artery lumens (Pijnenborg, 1983).

Recently, single-cell RNA sequencing technology has enabled inference of trophoblast differentiation lineages (Liu, 2018; Tsang, 2017). This has also yielded insights into the communication between trophoblasts and maternal decidual and immune cell populations (Vento-Tormo, 2018). Furthermore, human trophoblast stem cells, long hypothesized to exist, have been isolated from early gestations (Okae, 2018). Culture of these cells will likely aid greater understanding of early trophoblast differentiation and invasion (Haider, 2018; Turco, 2018).

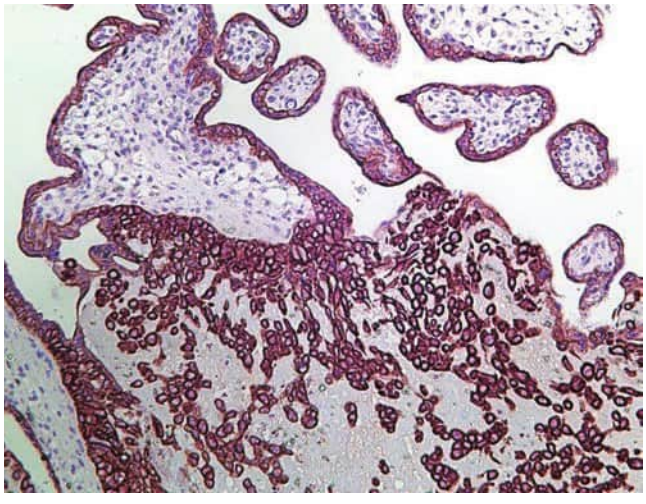


FIGURE 5-6 Photomicrograph of extravillous trophoblast invasion of the decidua basalis.

Early Invasion

After gentle erosion between epithelial cells of the surface endometrium, invading trophoblasts burrow deeper. At 9 days of development, the blastocyst wall facing the uterine lumen is a single layer of flattened cells. By the 10th day, the blastocyst becomes totally encased within the endometrium (Fig. 5-7). The blastocyst wall opposite the uterine lumen is thicker and comprises two zones—the trophoblasts and the embryo-forming inner cell mass. As early as 7.5 days postfertilization, the inner cell mass or embryonic disc differentiates into a thick plate of primitive ectoderm and an underlying layer of endoderm. Some small cells appear between the embryonic disc and the trophoblasts and enclose a space that will become the amnionic cavity.

Extraembryonic mesenchyme first appears as groups of isolated cells within the blastocyst cavity, and later this mesoderm completely lines the cavity. Within this mesoderm, spaces form and then fuse to form the chorionic cavity, that is, the extraembryonic coelom. The *chorion* is composed of trophoblasts and mesenchyme. Some mesenchymal cells eventually will condense to form the *body stalk*. This stalk joins the embryo to the nutrient chorion and later develops into the umbilical cord. The body stalk can be recognized at an early stage at the caudal end of the embryonic disc (Fig. 7-3, p. 123).

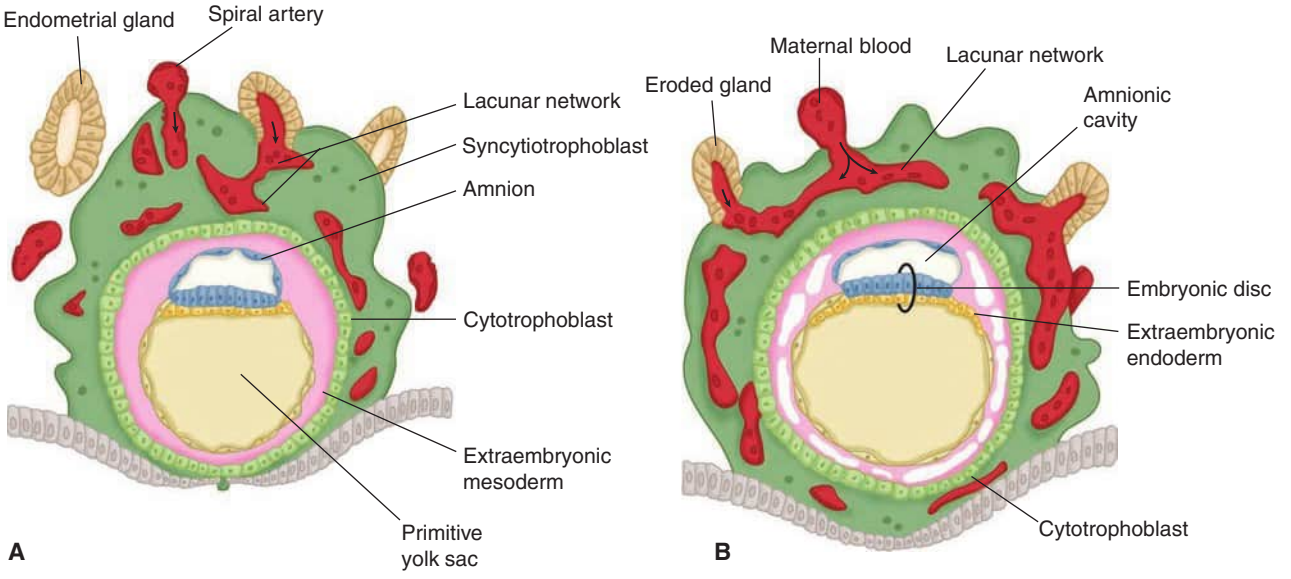


FIGURE 5-7 Drawing of sections through implanted blastocysts. **A.** At 10 days. **B.** At 12 days after fertilization. This stage is characterized by the intercommunication of the lacunae filled with maternal blood. Note in (B) that large cavities have appeared in the extraembryonic mesoderm, forming the beginning of the extraembryonic coelom. Also, extraembryonic endodermal cells have begun to form on the inside of the primitive yolk sac. (Redrawn from Moore KL, Persaud, TV, Torchia, MG (eds): The Developing Human. Clinically Oriented Embryology, 9th ed. Philadelphia, PA: Saunders; 2013.)

As the embryo enlarges, more maternal decidua basalis is invaded by syncytiotrophoblast. Beginning approximately 12 days after conception, the syncytiotrophoblast is permeated by a system of intercommunicating channels called *trophoblastic lacunae*. After invasion of superficial decidual capillary walls, lacunae become filled with maternal blood. At the same time, the decidual reaction, characterized by decidual stromal cell enlargement and glycogen storage, intensifies (p. 84).

Chorionic Villi

With deeper invasion into the decidua, solid primary villi arise from buds of cytotrophoblasts that protrude into the primitive syncytium before 12 days postfertilization. Primary villi are composed of a cytotrophoblast core covered by syncytiotrophoblast. As the lacunae merge, a complicated labyrinth is formed that is partitioned by these solid cytotrophoblastic columns. The trophoblast-lined channels form the *intervillous space*, and the solid cellular columns form the *primary villous stalks*.

Beginning on the 12th day after fertilization, mesenchymal cords derived from extraembryonic mesoderm invade the solid trophoblast columns. These then form *secondary villi*. Once angiogenesis begins in the mesenchymal cords, *tertiary villi* are created. Although maternal venous sinuses are tapped early in implantation, maternal arterial blood does not enter the intervillous space until around day 15. By the 17th day, however, fetal blood vessels are functional, and a placental circulation is established. The fetal–placental circulation is completed when the blood vessels of the embryo are connected with chorionic vessels. In some villi, angiogenesis fails from lack of circulation. The most striking exaggeration of this is seen with hydatidiform mole (Fig. 13-1, p. 236).

Villi are covered by an outer layer of syncytiotrophoblast and an inner layer of cytotrophoblasts. Proliferation of cytotrophoblast at the villous tips produces the trophoblastic cell columns that form *anchoring villi*. They are not invaded by fetal mesenchyme, and they are anchored to the decidua at the *basal plate*, which is the maternal side of the intervillous space. The *chorionic plate* forms the roof of the intervillous space. It consists of the two layers of trophoblasts, which line the intervillous space, and fibrous mesoderm on the opposite side. The final chorionic plate is formed by 8 to 10 weeks as the amnionic and primary chorionic plate mesenchyme fuse together. This formation is accomplished by expansion of the amnionic sac.

Early electron microscopic studies demonstrate prominent microvilli on the syncytial surface (Fig. 5-8) (Wislocki, 1955).

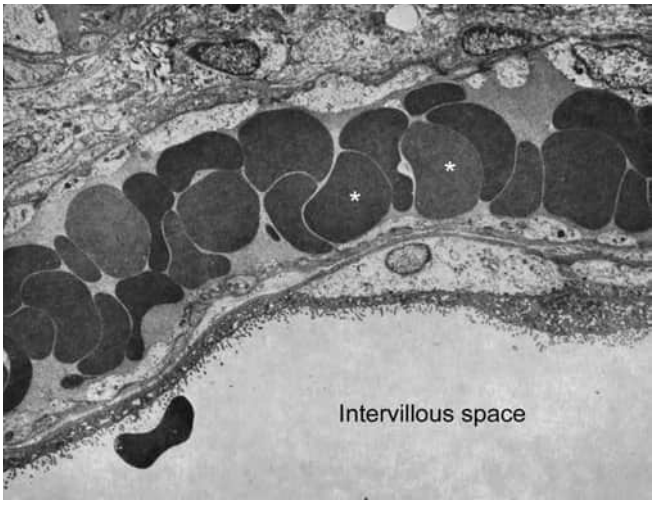


FIGURE 5-8 Electron micrograph of term human placenta villus. A villus capillary filled with fetal red blood cells (*asterisks*) is seen in close proximity to the microvilli border. (Reproduced with permission from Boyd JD, Hamilton WJ: The Human Placenta. Cambridge, Heffer, 1970.)

Associated pinocytotic vacuoles and vesicles are involved in both absorptive and secretory placental functions. Microvilli increase trophoblast surface area in direct contact with maternal blood, the defining characteristic of a hemochorial placenta.

PLACENTA AND CHORION

Chorion Development

In early pregnancy, the villi are distributed over the entire periphery of the chorionic membrane (Fig. 5-9). As the blastocyst with its surrounding trophoblasts grows and expands into the decidua, one pole faces the endometrial cavity. The opposite pole will form the placenta. Here, chorionic villi in contact with the decidua basalis proliferate to form the *chorion frondosum*—or leafy chorion. As growth of embryonic and extraembryonic tissues continues, the blood supply to the chorion facing the endometrial cavity is restricted. Because of this, villi in contact with the decidua capsularis cease to grow and then degenerate. This portion of the chorion becomes the avascular fetal membrane that abuts the decidua parietalis and is called the *chorion laeve*—or smooth chorion. This smooth chorion is composed of cytotrophoblasts and fetal mesodermal mesenchyme. A paracrine system between the decidua and chorion also links mother and fetus. This is an extraordinarily important arrangement for maternal–fetal communication and for maternal immunological acceptance of the conceptus (Guzeloglu-Kayisli, 2009).

Until near the end of the third month, the chorion laeve is separated from the amnion by the exocoelomic cavity. Thereafter, they are in intimate contact to form the avascular amniochorion. These two structures are important sites of molecular transfer and metabolic activity. Moreover, they constitute an important paracrine arm of the fetal–maternal communication system.

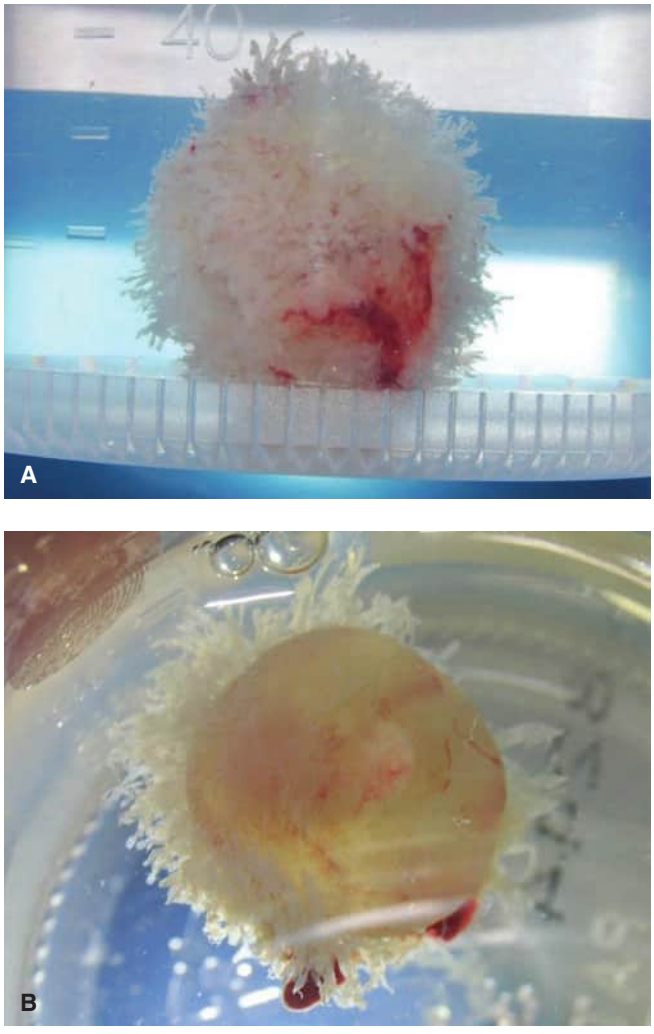


FIGURE 5-9 Complete abortion specimens. **A.** Initially, the entire chorionic sac is covered with villi, and the embryo within is not visible **B.** Stretch and pressure from further growth prompt partial regression of the villi. The remaining villi form the future placenta, whereas the smooth portion is the chorion.

Regulators of Trophoblast Invasion

Implantation and endometrial decidualization activate a unique population of maternal immune cells that play critical functions in trophoblast invasion, angiogenesis, spiral artery remodeling, and maternal tolerance to fetal alloantigens. Decidual natural killer cells (dNK) make up 70 percent of decidual leukocytes in the first trimester and directly contact trophoblasts. In contrast to NK cells in peripheral blood, dNK cells lack cytotoxic functions. They produce specific cytokines and angiogenic factors to regulate trophoblast invasion and spiral artery remodeling (Hanna, 2006). dNK cells promote phagocytosis of cell debris (Faas, 2017). These and other unique properties distinguish dNK cells from circulating NK cells and from NK cells in the endometrium before pregnancy (Fu, 2013; Winger, 2013). dNK cells express both IL-8 and interferon-inducible protein 10, which bind to receptors on invasive trophoblastic cells to promote their decidual invasion toward the spiral arteries. dNK cells also produce proangiogenic factors, including VEGF and placental growth factor (PlGF), which both promote vascular growth in the decidua.

Trophoblasts also secrete specific chemokines that attract the dNK cells to the maternal–fetal interface. Thus, both cell types simultaneously attract each other. Decidual macrophages account for approximately 20 percent of leukocytes in the first trimester and elicit an M2-immunomodulatory phenotype (Williams, 2009). Recall that while M1 macrophages are proinflammatory, M2 macrophages counter proinflammatory responses and promote tissue repair.

Concurrently, T cell subsets aid tolerance toward the allogenic fetus. Regulatory T cells (Tregs) are essential for promoting immune tolerance. Other T cell subsets are present, such as Th1, Th2, and Th17, although their functions are tightly regulated (Ruocco, 2014).

Endometrial Invasion

Extravillous trophoblasts of the first-trimester placenta are highly invasive. This process occurs under low-oxygen conditions, and regulatory factors that are induced under hypoxic conditions are contributory (Soares, 2012). Invasive trophoblasts

secrete numerous proteolytic enzymes that digest extracellular matrix and activate proteinases already present in the decidua. Trophoblasts produce urokinase-type plasminogen activator, which converts plasminogen into the broadly acting serine protease, plasmin. This in turn both degrades matrix proteins and activates MMPs. One member of the MMP family, MMP-9, appears to be critical. The timing and extent of trophoblast invasion is regulated by a balanced interplay between pro- and anti-invasive factors.

Low estradiol levels in the first trimester are critical for trophoblast invasion and spiral artery remodeling. Animal studies suggest that the rise in second-trimester estradiol levels suppresses and limits vessel remodeling by reducing trophoblast expression of VEGF and specific integrin receptors (Bonagura, 2012). Namely, extravillous trophoblasts express integrin receptors that recognize the extracellular matrix proteins collagen IV, laminin, and fibronectin. Binding of these matrix proteins and integrin receptors initiates signals to promote trophoblast cell migration and differentiation. However, as pregnancy advances, rising estradiol levels downregulate VEGF and integrin receptor expression. This represses and controls the extent of uterine vessel transformation.

Spiral Artery Invasion

One of the most remarkable features of human placental development is the extensive modification of maternal vasculature by trophoblasts, which are fetal in origin. These events occur in the first half of pregnancy and are essential to uteroplacental blood flow. They are also integral to conditions such as preeclampsia, fetal-growth restriction, and preterm birth. Spiral artery modifications are carried out by two populations of extravillous trophoblasts—*endovascular trophoblasts*, which penetrate the spiral-artery lumen, and *interstitial trophoblasts*, which surround the arteries (see Fig. 5-5).

Interstitial trophoblasts constitute a major portion of the placental bed. They penetrate the decidua and adjacent myometrium and aggregate around spiral arteries, where they may aid endovascular trophoblast invasion.

Endovascular trophoblasts first enter the spiral artery lumens and initially form cellular plugs. They then promote apoptosis of the native endothelium and replace the vessel lumen with cells of fetal origin. Fibrinoid material replaces smooth muscle and connective tissue of the vessel media. This decreases resistance of blood flow into the intervillous space. Invading endovascular trophoblasts can extend several centimeters along the vessel lumen, and they must migrate against arterial flow. Of note, invasion by trophoblasts involves only the decidual spiral arteries and not decidual veins.

Uteroplacental vessel development proceeds in two waves or stages (Ramsey, 1980). First, before 12 weeks' postfertilization, spiral arteries are invaded and modified up to the border between the decidua and myometrium. The second wave, between 12 and 16 weeks, involves some invasion of the intramyometrial segments of spiral arteries. Remodeling converts narrow-lumen, muscular spiral arteries into dilated, low-resistance uteroplacental vessels. Molecular mechanisms of these crucial events and their significance for preeclampsia and fetal-growth restriction have been reviewed (Pereira de Sousa, 2017; Xie, 2016).

Although early placenta development occurs in a low-oxygen-tension environment (2 to 3 percent O_2), this vascular remodeling increases blood flow and oxygenation such that the oxygen concentration more than doubles around the end of the first trimester (Chang, 2018).

Villus Branching

Although certain villi of the chorion frondosum extend from the chorionic plate to the decidua to serve as anchoring villi, most villi arborize and end freely within the intervillous space. As gestation proceeds, the short, thick, early stem villi branch to form progressively finer subdivisions and greater numbers of increasingly smaller villi (Fig. 5-10). This increasing villous surface area correlates with gestational age and aids fetal growth. In cases of restricted blood flow, more highly branched villi than expected for gestational age is a compensatory mechanism.

Each truncal or main stem villus and its ramifications constitutes a placental lobule or cotyledon. Each lobule has a single chorionic artery and vein, such that lobules constitute the functional units of placental architecture.

Placental Growth and Maturation

In the first trimester, placental growth is more rapid than that of the fetus. However, by 17 weeks' gestation, placental and fetal weights are nearly equal. By term, placental weight approximates one sixth of fetal weight.

The mature placenta and its variant forms are discussed in detail in Chapter 6 (p. 108). Briefly, viewed from the maternal surface, which attaches to the uterine wall, the number of slightly elevated convex areas, called lobes, varies from 10 to 38. Lobes are incompletely separated by grooves of variable depth. These tissue grooves form in response to placental septa, which rise up as projections of decidua. The total number of placental lobes remains the same throughout gestation, and individual lobes continue to grow—although less actively in late pregnancy (Crawford, 1959). Although grossly visible lobes are commonly referred to as cotyledons, this is inaccurate. Correctly used, lobules or cotyledons are the functional units supplied by each main stem villus.

As villi continue to branch and the terminal ramifications become more numerous and smaller, the volume of cytotrophoblasts decline. This layer attenuates, and by 16 weeks' gestation, the apparent continuity of the cytotrophoblasts is lost. As the syncytium also thins, the fetal vessels become more prominent within the villus and lie closer to the intervillous space (see Fig. 5-8). At term, villi may be focally reduced to a thin layer of syncytium covering minimal villous connective tissue in which thin-walled fetal capillaries abut the trophoblast and dominate the villi.

The villous stroma also exhibits changes as gestation progresses. In early pregnancy, the branching connective-tissue

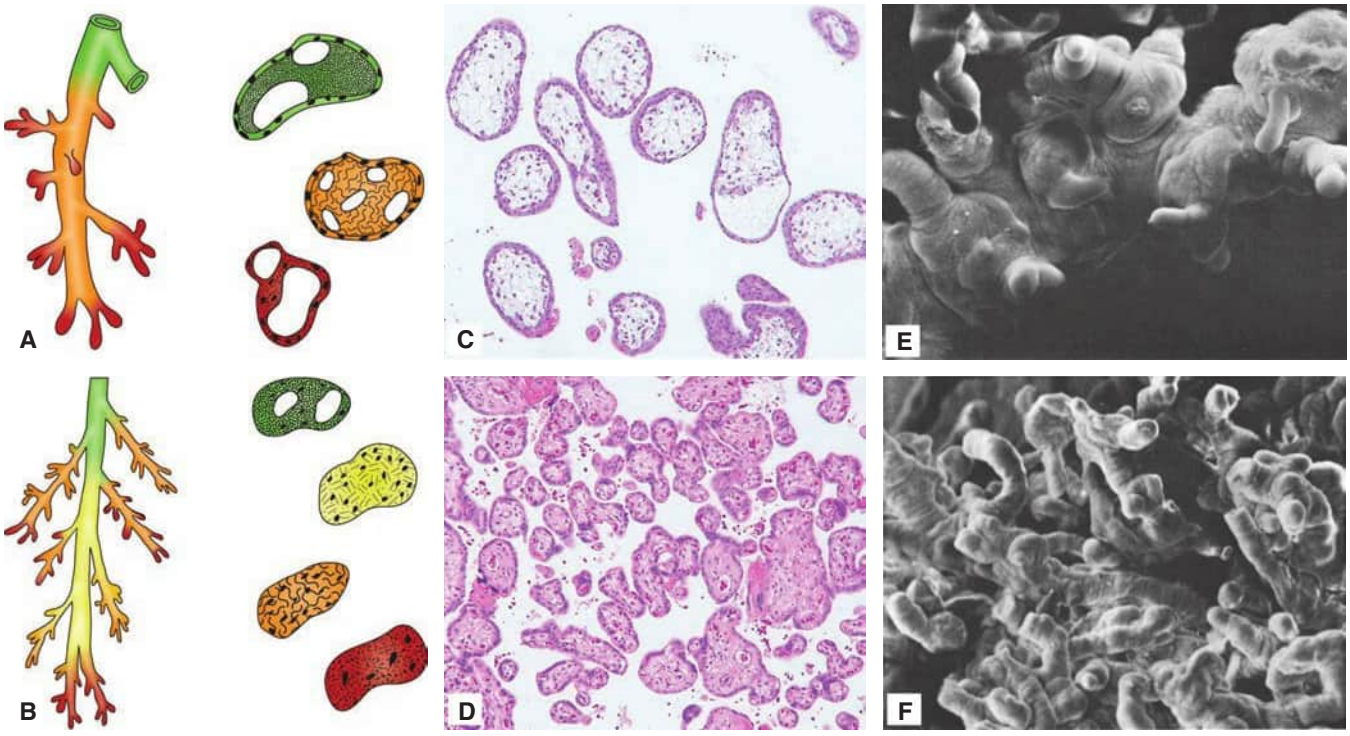


FIGURE 5-10 Illustration **(A, B)**, histology **(C, D)**, and electron microscopy **(E, F)** of early (top panel) and late (bottom panel) human placenta villi. Limited branching of villi is seen in the early placenta. With maturation, increasing villous arborization is seen, and villous capillaries lie closer to the surface of each villus. (Electron micrographs reproduced with permission from King BF, Menton DN: Scanning electron microscopy of human placental villi from early and late in gestation. Am J Obstet Gynecol 122:824, 1975.)

cells are separated by an abundant loose intercellular matrix. Later, the villous stroma becomes denser, and the cells are more spindly and closely packed. Another stromal change involves infiltration of *Hofbauer cells*, which are fetal macrophages. These are round with vesicular, often eccentric nuclei and with very granular or vacuolated cytoplasm. They grow in number and maturational state throughout pregnancy and appear to be important mediators of protection at the maternal–fetal interface (Johnson, 2012). These macrophages are phagocytic, have an immunosuppressive phenotype, produce various cytokines, and provide paracrine regulation of trophoblastic functions (Cervar, 1999; Reyes, 2017).

Some architectural changes, if substantive, can lower placental exchange efficiency. These include thickening of the basal lamina of trophoblast or capillaries, obliteration of certain fetal vessels, greater villous stroma, and fibrin deposition on the villous surface (Chap. 6, p. 109).

■ Placental Circulation

The gross anatomy of the placenta reflects the intimate approximation of the fetal capillary bed to maternal blood. The fetal surface is covered by the transparent amnion, beneath which chorionic vessels course. A section through the placenta includes amnion, chorion, chorionic villi and intervillous space, decidual (basal) plate, and myometrium (Figs. 5-11 and 5-12).

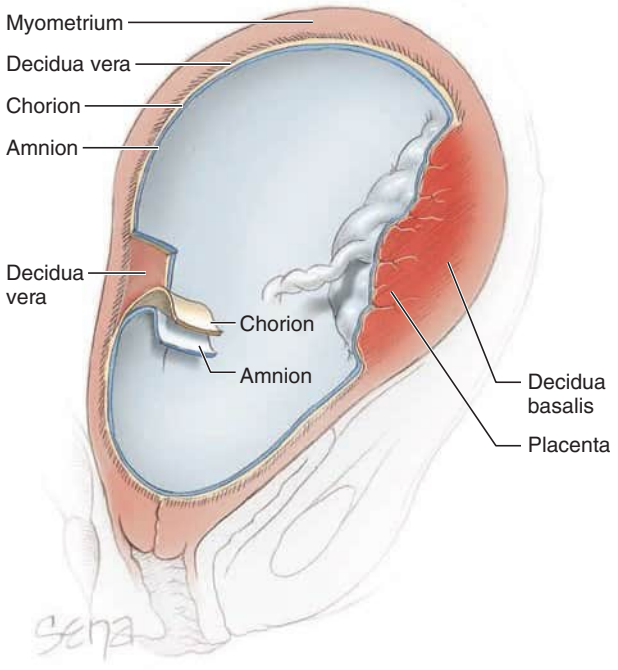


FIGURE 5-11 Uterus showing a normal placenta and its membranes in situ.

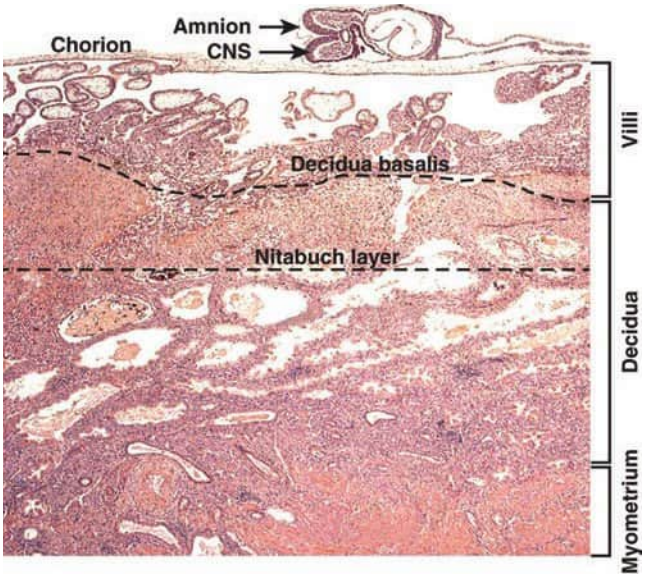


FIGURE 5-12 Photomicrograph of implantation site with partial section of an early embryo. Anchoring villi are seen with extravillous trophoblasts invading the decidua basalis. CNS = central nervous system. (Reproduced with permission from Dr. Kurt Benirschke.)

Fetal Circulation

Deoxygenated venous-like fetal blood flows to the placenta through the two umbilical arteries. As the cord joins the placenta, these umbilical vessels branch repeatedly beneath the amnion as they run across the chorionic plate. Branching continues within the villi to ultimately form capillary networks in the terminal villous branches. Blood with significantly higher oxygen content returns from the placenta via a single umbilical vein to the fetus.

The branches of the umbilical vessels that traverse along the chorionic plate are called placental surface vessels or chorionic vessels. They respond to vasoactive substances, but anatomically, morphologically, histologically, and functionally, they are unique. Chorionic arteries always cross over chorionic veins. Vessels are most readily recognized by this anatomical relationship, but they are difficult to distinguish by histological criteria.

Truncal arteries are perforating branches of the surface arteries and pass through the chorionic plate. Each truncal artery supplies one main stem villus and thus one cotyledon. As the artery penetrates the chorionic plate, its wall loses smooth muscle, and its caliber increases. The loss of muscle continues as the truncal arteries and veins branch into their smaller rami.

Before 10 weeks' gestation, end-diastolic flow is not detected within the umbilical artery at the end of the fetal cardiac cycle (Fisk, 1988; Loquet, 1988). After 10 weeks, however, end-diastolic flow appears and is maintained throughout normal pregnancy. Clinically, these flow patterns are studied with Doppler sonography to assess fetal well-being (Chap. 4, p. 262).

Maternal Circulation

Mechanisms of placental blood flow must allow blood to leave maternal circulation; flow into an amorphous space lined by syncytiotrophoblast; and return through maternal veins without producing arteriovenous-like shunts that would prevent adequate exchange between maternal blood and fetal villi. For this, maternal blood enters through the basal plate and is driven high up toward the chorionic plate by arterial pressure before laterally dispersing (Fig. 5-13). After bathing the external microvillous surface, maternal blood drains back through venous orifices in the basal plate and enters uterine veins. Thus, maternal blood traverses the placenta randomly without preformed channels. Trophoblast invasion of the spiral arteries creates low-resistance vessels that can accommodate massive increase in uterine perfusion during gestation. Generally, spiral arteries are perpendicular to, but veins are parallel to, the uterine wall. This arrangement aids closure of veins during a uterine contraction and prevents the exit of maternal blood from the intervillous space. The number of arterial openings into the intervillous space is gradually reduced by cytotrophoblastic invasion to approximately 120 entry sites at term (Brosens, 1963). These discharge blood in spurts to bath

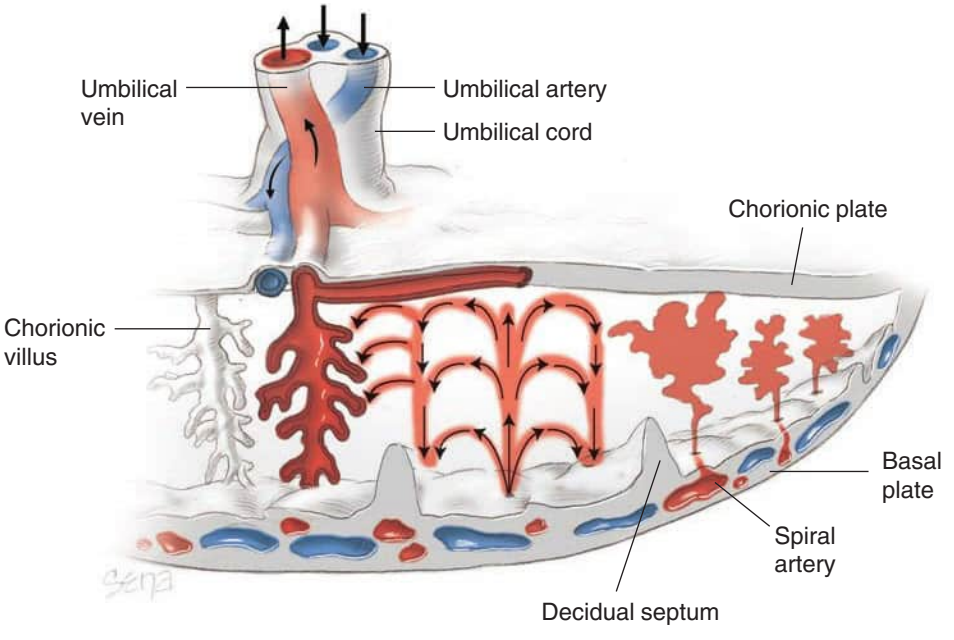


FIGURE 5-13 Schematic drawing of a section through a full-term placenta. Maternal blood flows into the intervillous spaces in funnel-shaped spurts, and umbilical arteries carry deoxygenated fetal blood to the placenta. Exchanges between the maternal and fetal systems occur as maternal blood flows around the villi. The umbilical vein carries oxygenated blood back to the fetus. Inflowing arterial blood pushes maternal venous blood into the endometrial veins, which are scattered over the entire surface of the decidua basalis. Placental lobes are separated from each other by placental (decidual) septa.

the adjacent villi (Borell, 1958). After the 30th week, a prominent venous plexus lies between the decidua basalis and myometrium and helps develop the cleavage plane needed for placental separation after delivery.

Both inflow and outflow are curtailed during uterine contractions. Bleker and associates (1975) used serial sonography during normal labor and found that placental length, thickness, and surface area grew during contractions. They attributed this to distention of the intervillous space by impairment of venous outflow compared with arterial inflow. During contractions, therefore, a somewhat larger volume of blood is available for exchange even though the rate of flow is decreased. Similarly, Doppler velocimetry has shown that diastolic flow velocity in spiral arteries is diminished during uterine contractions. Thus, principal factors regulating intervillous space blood flow are arterial blood pressure, intrauterine pressure, uterine contraction pattern, and factors that act specifically on arterial walls.

Breaks in the Placental "Barrier"

The placenta does not maintain absolute integrity of the fetal and maternal circulations, and cells traffic between mother and fetus in both directions. This situation is best exemplified clinically by erythrocyte D-antigen alloimmunization (Chap. 18, p. 353). Fetal cell transfer is small in most cases, although rarely the fetus exsanguinates into the maternal circulation.

Fetal cells can also engraft in the mother during pregnancy and still be detected decades later. Fetal lymphocytes, mesenchymal stem cells, and endothelial colony-forming cells all reside in maternal blood, bone marrow, or uterine vasculature (Huu, 2006; Piper, 2007; Sipos, 2013). This frequent phenomenon, termed *microchimerism*, is implicated in the disparate female: male ratio of autoimmune disorders (Greer, 2011; Stevens, 2006). As discussed in Chapter 62 (p. 1109), fetal cell engraftment has been associated with the pathogenesis of lymphocytic thyroiditis, scleroderma, and systemic lupus erythematosus.

Maternal–Fetal Interface

This maternal–fetal interface is an active hub of immunological interactions that allows implantation, appropriate placental development, and immunotolerance of the fetus. At the same time, a functional immune system must be maintained to protect the mother.

Immunogenicity of the Trophoblasts

Trophoblastic cells are the only fetus-derived cells in direct contact with maternal tissues and blood. Fetal syncytiotrophoblast synthesizes and secretes numerous factors that regulate the immune responses of maternal cells both at the implantation site and systemically.

Human leukocyte antigens (HLAs) are the human analogue of the major histocompatibility complex (MHC) (Hunt, 1992). There are 17 HLA class I genes and include three classic genes, *HLA-A*, *-B*, and *-C*, that encode the major class I (class Ia) transplantation antigens. Three other class I genes, designated *HLA-E*, *-F*, and *-G*, encode class Ib HLA antigens. MHC class I and II antigens are absent from villous trophoblasts, which appear to be immunologically inert at all gestational stages (Weetman, 1999). Invasive extravillous trophoblasts do express MHC class I molecules but avoid rejection by the maternal immune system.

Moffett-King (2002) reasoned that normal implantation depends on controlled trophoblastic invasion of maternal decidua and spiral arteries. Such invasion must proceed far enough to provide for normal fetal growth and development but avoid the pathogenic invasion seen in placenta accreta spectrum disorders (Chap. 43, p. 759). She suggests that dNK cells combined with extravillous trophoblasts' unique expression of three specific HLA class I genes act in concert to permit and subsequently limit trophoblast invasion.

Extravillous trophoblasts express the class Ia antigen HLA-C and nonclassic class Ib molecules HLA-E and HLA-G. HLA-G antigen is expressed only in humans and is restricted to extravillous trophoblasts in contact with maternal tissues. Expressed in both membrane-bound and soluble isoforms detectable in maternal circulation, HLA-G is thought to protect extravillous trophoblasts from immune rejection by modulating the function of both decidual and circulating NK populations (Apps, 2011; Rajagopalan, 2012). The importance of this molecule is highlighted by the observation that IVF embryos fail to implant if they do not express a soluble HLA-G isoform (Fuzzi, 2002). Thus, HLA-G may act through multiple mechanisms to aid tolerance of the maternal–fetal antigen mismatch (LeBouteiller, 1999). Abnormal HLA-G expression in extravillous trophoblasts from women with preeclampsia suggests immune dysregulation as one etiology (Goldman-Wohl, 2000).

Decidual Immune Cells

Of leukocytes, NK cells predominate in midluteal phase endometrium and in first-trimester decidua, but numbers decline by term (Johnson, 1999). In first-trimester decidua, dNK cells lie close to extravillous trophoblasts and purportedly regulate invasion. Their infiltration is increased by progesterone and by stromal cell production of IL-15 and decidual prolactin (Dunn, 2002; Gubbay, 2002). Although dNK cells have the capacity for cytotoxicity, they are not cytotoxic toward fetal trophoblasts. Their cytotoxic potential is prevented by molecular cues from decidual macrophages. As noted, specific HLA molecule expression protects against dNK cells' damaging actions.

Decidual macrophages are another decidual immune cell type and are distinct from proinflammatory M1 or antiinflammatory M2 macrophages. These cells regulate adaptive T cell responses; control dNK differentiation, activation, and cytotoxicity; and produce antiinflammatory cytokines such as IL-10.

Dendritic cells are antigen-presenting cells that educate maternal T cells. They affect development of a receptive endometrium for implantation.

Maternal T cells, as part of the adaptive immune response, increase in number and function after encounter with a specific antigen. These cells subsequently retain the ability to respond rapidly in a subsequent encounter with the same antigen. In contrast, Tregs are immunosuppressive, and during pregnancy systemic maternal populations expand. Specific Treg cell populations persist and protect against aberrant immune responses.

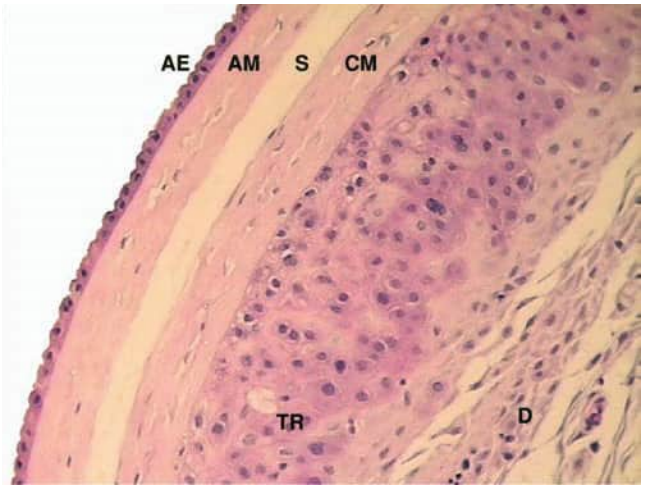


FIGURE 5-14 Photomicrograph of fetal membranes. From left to right: AE = amnion epithelium; AM = amnion mesenchyme; S = zona spongiosa; CM = chorionic mesenchyme; TR = trophoblast; D = decidua. (Reproduced with permission from Dr. Judith R. Head.)

AMNION

At term, the amnion is a tough and tenacious but pliable membrane. This innermost avascular fetal membrane is contiguous with amniotic fluid and provides almost all of the tensile strength of the fetal membranes. Its resilience to rupture is vital to successful pregnancy outcomes. Indeed, preterm rupture of fetal membranes is a major cause of preterm delivery (Chap. 45, p. 787).

Bourne (1962) described five separate amnion layers. Here, progression of discussed layers moves from amniotic fluid to the chorion. The innermost layer, which is bathed by amniotic fluid, is a single-layer *cuboidal epithelium* (Fig. 5-14). This epithelium attaches firmly to a distinct *basement membrane*. Next, an acellular *compact layer* composed primarily of interstitial collagens is followed by the *fibroblast-like mesenchymal cell layer*. The outermost layer is the relatively acellular *zona spongiosa*, which is contiguous with the chorion laeve. The amnion also contains a few fetal macrophages, which predominate in the outer two layers. The amnion lacks smooth muscle cells, nerves, lymphatics, and importantly, blood vessels.

Amnion Development

Early during implantation, a space develops between the embryonic cell mass and adjacent trophoblastic cells (see Fig. 5-7). Small cells that line this inner surface of trophoblasts are precursors of amniotic epithelium, and the amnion is first identifiable on the 7th or 8th day of embryo development. It is initially a minute vesicle, which then develops into a small sac that covers the dorsal embryo surface. As the amnion enlarges, it gradually engulfs the growing embryo, which prolapses into its cavity (Benirschke, 2012).

Distention of the amniotic sac eventually brings it into contact with the interior surface of the chorion laeve. Apposition of the chorion laeve and amnion near the end of the first trimester obliterates the extraembryonic coelom. The amnion and chorion laeve, although slightly adhered, are never intimately connected and can be separated easily. Placental amnion covers the placental surface and thereby is in contact with the chorionic vessels. Umbilical amnion covers the umbilical cord. As discussed in Chapter 48 (p. 842), with monochorionic-diamnionic placentas, no tissue intervenes between the fused amnions. With dichorionic-diamnionic twin placentas, amnions are separated by fused chorion laeves.

Amniotic fluid fills the amniotic sac. As pregnancy progresses, this normally clear fluid increases in volume until approximately 34 weeks' gestation. After this, the volume declines. At term, it averages 1000 mL, although this may vary widely in normal and especially abnormal conditions. Amniotic fluid origin, composition, circulation, and function of are discussed further in Chapter 14 (p. 256).

Amnion Cell Histogenesis

Amniotic epithelium derives from fetal ectoderm of the embryonic disc and not from trophoblasts. This is an important consideration both embryologically and functionally. For example, HLA class I gene expression in amnion is more akin to that in embryonic cells than to that in trophoblasts.

The fibroblast-like mesenchymal cell layer likely originates from embryonic mesoderm. Early in human embryogenesis, the amniotic mesenchymal cells lie immediately adjacent to the basal surface of the amnion epithelium. At this time, the amnion has two-cell layers and approximately equal numbers of epithelial and mesenchymal cells. Simultaneously with growth and development, interstitial collagens are deposited between these two cell layers. This marks formation of the amnion compact layer, which separates the two early layers.

Amniotic epithelium early in pregnancy replicates at a rate appreciably faster than mesenchymal cells. Thus, as the amniotic sac expands, its epithelial cells form a continuous, uninterrupted layer. Instead, mesenchymal cells become more sparsely distributed. Connected by a lattice network of extracellular matrix, they appear as long, slender fibrils.

Amnion Epithelial Cells

The apical surface of the amniotic epithelium is replete with highly developed microvilli. This structure reflects its function as a major site of transfer between amniotic fluid and amnion layers. This epithelium is metabolically active, and its cells synthesize tissue inhibitor of MMP-1, prostaglandin E_2 (PGE_2), and fetal fibronectin (fFN) (Rowe, 1997). Although epithelia produce fFN, studies suggest that fFN acts in the underlying mesenchymal cells. Here, fFN promotes synthesis of MMPs that break down strength-bearing collagens. It also enhances prostaglandin synthesis to prompt uterine contractions (Mogami, 2013). This pathway is upregulated with premature rupture of membranes induced by thrombin or infection-induced release of fFN (Chigusa, 2016; Mogami, 2014).

Epithelial cells may respond to signals derived from the fetus or the mother, and they are responsive to various endocrine or paracrine modulators. Examples include oxytocin and vasopressin, both of which increase PGE_2 production in vitro (Moore, 1988). These cells may also produce cytokines such as IL-8 during labor initiation (Elliott, 2001).

Amnionic epithelium also synthesizes vasoactive peptides, which function in both maternal and fetal tissues in diverse physiological processes. These peptides include endothelin and parathyroid hormone-related protein (Economos, 1992; Germain, 1992). Others are brain natriuretic peptide (BNP) and corticotropin-releasing hormone, which are peptides that invoke smooth-muscle relaxation (Riley, 1991; Warren, 1995). BNP production is positively regulated by mechanical stretch in fetal membranes and is proposed to function in uterine quiescence. Epidermal growth factor, a negative regulator of BNP, is upregulated in the membranes at term and leads to a decline in BNP-regulated uterine quiescence (Carvajal, 2013).

Amnion Mesenchymal Cells

These cells are responsible for other major functions. Mesenchymal cells synthesize the interstitial collagens that compose the amnionic compact layer—the major source of its tensile strength (Casey, 1996). At term, the generation of cortisol by 11β-hydroxysteroid dehydrogenase may contribute to membrane rupture by reducing collagen abundance (Mi, 2017). Mesenchymal cells also synthesize cytokines that include IL-6, IL-8, and MCP-1. Cytokine synthesis rises in response to bacterial toxins and IL-1. This ability of amnion mesenchymal cells to synthesize chemokines is an important consideration in interpreting studies of labor-associated accumulation of inflammatory mediators in amnionic fluid (Garcia-Velasco, 1999). Last, mesenchymal cells may be a greater source of PGE_2 than epithelial cells, especially in the case of premature membrane rupture (Mogami, 2013; Whittle, 2000).

■ Tensile Strength

During tests of tensile strength, the decidua and then the chorion laeve give way long before the amnion ruptures. Indeed, the membranes are elastic and can expand to twice normal size during pregnancy (Benirschke, 2012). The amnion tensile strength resides almost exclusively in the compact layer, which is composed of cross-linked interstitial collagens I and III, and lesser amounts of collagens V and VI.

Amnion tensile strength is regulated in part by fibrillar collagen assembly. This process is influenced by the interaction between fibrils and proteoglycans such as decorin and biglycan (Chap. 21, p. 405). Reduction of these proteoglycans is reported to perturb fetal membrane function (Horgan, 2014; Wu, 2014). Fetal membranes overlying the cervix have a regional shift in gene expression and lymphocyte activation that set in motion an inflammatory cascade (Marcellin, 2017). This change may contribute to tissue remodeling and loss of tensile strength in the amnion (Moore, 2009).

■ Metabolic Functions

The amnion is metabolically active, is involved in solute and water transport for amnionic fluid homeostasis, and produces an impressive array of bioactive compounds. The amnion is responsive both acutely and chronically to mechanical stretch, which alters amnionic gene expression (Carvajal, 2013; Nemeth, 2000). This in turn may trigger both autocrine and paracrine responses that include production of MMPs, IL-8, and collagenase (Bryant-Greenwood, 1998; Mogami, 2013). Such factors may modulate changes in membrane properties during labor.

UMBILICAL CORD

The yolk sac and the umbilical vesicle into which it develops are prominent early in pregnancy. Initially, the embryo is a flattened disc interposed between amnion and yolk sac (see Fig. 5-7). The embryonic dorsal surface, in association with the elongation of its neural tube, grows faster than the ventral surface. As a result, the embryo bulges into the amnionic sac, and the embryo body incorporates the adjacent yolk sac to form the gut. The body stalk connects the caudal embryo to the chorion. The fetal allantois forms as a diverticulum from the caudal wall of the yolk sac and projects into the base of the body stalk.

As pregnancy advances, the yolk sac becomes smaller and its pedicle relatively longer. By the middle of the third month, the expanding amnion fuses with the chorion laeve to obliterate the extraembryonic coelom. In its expansion, the amnion covers the bulging placental disc and the lateral surface of the body stalk. The latter is then called the *umbilical cord* or *funis*. A more detailed description of this cord and potential abnormalities is found in Chapter 6 (p. 113).

The cord at term normally has two arteries and one vein. The right umbilical vein usually disappears early during fetal development, leaving only the original left vein. The umbilical cord extends from the fetal umbilicus to the fetal surface of the placenta, that is, the chorionic plate. As discussed in detail in Chapter 7 (p. 126), blood flows from the umbilical vein toward the fetus. Blood then takes a path of least resistance via two routes within the fetus. One is the ductus venosus, which empties directly into the inferior vena cava. The other route consists of numerous smaller openings into the hepatic circulation. Blood from the liver flows into the hepatic vein and then the inferior vena cava. Resistance in the ductus venosus is controlled by a sphincter situated at the origin of the ductus at the umbilical recess and is innervated by a vagus nerve branch.

Blood exits the fetus via the two umbilical arteries. These are anterior branches of the internal iliac artery and become obliterated after birth to form the medial umbilical ligaments.

PLACENTAL HORMONES

The production of steroid and protein hormones by human trophoblasts is greater in amount and diversity than that of any single endocrine tissue in all of mammalian physiology. Table 5-1 is a compendium of average production rates for various steroid hormones in nonpregnant and in near-term pregnant women. It demonstrates the remarkable increase in steroid hormone production during pregnancy. The human placenta also synthesizes an enormous amount of protein and peptide hormones, summarized in Table 5-2. The successful physiological adaptations of pregnant women to this unique endocrine milieu is discussed throughout Chapter 4.

TABLE 5-1. Steroid Production Rates in Nonpregnant and Near-Term Pregnant Women

Steroid[a]	Production Rates (mg/24 hr)	
	Nonpregnant	Pregnant
Estradiol	0.1–0.6	15–20
Estriol	0.02–0.1	50–150
Progesterone	0.1–40	250–600
Aldosterone	0.05–0.1	0.250–0.600
Deoxycorticosterone	0.05–0.5	1–12
Cortisol	10–30	10–20

[a]Estrogens and progesterone are produced by placenta. Aldosterone is produced by the maternal adrenal in response to the stimulus of angiotensin II. Deoxycorticosterone is produced in extraglandular tissue sites by way of the 21-hydroxylation of plasma progesterone. Cortisol production during pregnancy is not increased, even though the blood levels are elevated because of decreased clearance caused by increased cortisol-binding globulin.

Human Chorionic Gonadotropin

Biosynthesis

Chorionic gonadotropin is a glycoprotein with biological activity similar to that of LH, and both act via the LH-hCG receptor. hCG varies in molecular weight from 36,000 to 40,000 Da and is highly glycosylated with the most carbohydrate content of any human hormone—30 percent. This glycosylation protects the molecule from catabolism and results in a 36-hour plasma half-life for intact hCG compared with 2 hours for LH. The hCG molecule is composed of two dissimilar subunits, α and β. These are noncovalently linked but held together by electrostatic and hydrophobic forces. Isolated subunits are unable to bind the LH-hCG receptor and thus lack biological activity.

The hCG hormone is structurally related to three other glycoprotein hormones—LH, FSH, and thyroid-stimulating hormone (TSH). All four glycoproteins share a common α-subunit. However, each of their β-subunits is characterized by a distinct (although related) amino acid sequence.

Synthesis of the α- and β-chains of hCG is regulated separately from gene loci on different chromosomes. A single gene

TABLE 5-2. Protein Hormones Produced by the Human Placenta

Hormone	Primary Non-placental Site of Expression	Shares Structural or Function Similarity	Functions
Human chorionic gonadotropin (hCG)	—	LH, FSH, TSH	Maintains corpus luteum function Regulates fetal testis testosterone secretion Stimulates maternal thyroid
Placental lactogen (PL)	—	GH, prolactin	Aids maternal adaptation to fetal energy requirements
Adrenocorticotropin (ACTH)	Hypothalamus	—	
Corticotropin-releasing hormone (CRH)	Hypothalamus	—	Relaxes smooth-muscle; initiates parturition? Promotes fetal and maternal glucocorticoid production
Gonadotropin-releasing hormone (GnRH)	Hypothalamus	—	Regulates trophoblast hCG production
Thyrotropin (TRH)	Hypothalamus		Unknown
Growth hormone-releasing hormone (GHRH)	Hypothalamus	—	Unknown
Growth hormone variant (hGH-V)	—	GH variant not found in pituitary	Potentially mediates pregnancy insulin resistance
Neuropeptide Y	Brain		Potential regulates CRH release by trophoblasts
Parathyroid-releasing protein (PTH-rp)	—		Regulates transfer of calcium and other solutes; regulates fetal mineral homeostasis
Inhibin	Ovary/testis		Potentially inhibits FSH-mediated ovulation; regulates hCG synthesis
Activin	Ovary/testis		Regulates placental GnRH synthesis

GH = growth hormone; FSH = follicle-stimulating hormone; LH = luteinizing hormone; TSH = thyroid-stimulating hormone.

on chromosome 6 encodes the α-subunit. Chromosome 19 encodes the β-hCG–β-LH family of subunits with six genes for β-hCG and one for β-LH (Miller-Lindholm, 1997). Both subunits are synthesized as larger precursors and then cleaved by endopeptidases to their mature form. Intact hCG is assembled and released by secretory granule exocytosis (Morrish, 1987). Modifications during synthesis and subsequent enzymatic degradation give rise to multiple forms of hCG in maternal plasma and urine that vary enormously in bioactivity and immunoreactivity.

Before 5 weeks, hCG is expressed both in the syncytiotrophoblast and cytotrophoblasts (Maruo, 1992). Later in the first trimester, hCG is produced almost solely in the syncytiotrophoblast, peaks around 9 weeks' gestation, and then declines to a plateau for the remainder of gestation (Beck, 1986; Kurman, 1984). Dynamic changes in hCG concentration in the first trimester highlight the importance of accurate gestational age estimation when interpreting aneuploidy screening strategies that include hCG.

Circulating levels of free β-subunit are low to undetectable throughout pregnancy, and their concentration is the limiting factor for secretion of complete hCG molecules. Levels of the α-subunit rise gradually and roughly correspond to placental mass, until they plateau at approximately 36 weeks' gestation (Cole, 1997).

Concentrations in Serum and Urine

The combined hCG molecule is detectable in plasma of pregnant women 7 to 9 days after the midcycle LH surge preceding ovulation. Thus, hCG likely enters maternal blood at the time of blastocyst implantation. Plasma levels rise rapidly, doubling approximately every 2 days in the first trimester (Fig. 5-15). Appreciable fluctuations in levels for a given patient are observed on the same day.

Intact hCG circulates as multiple, highly related isoforms that have variable cross-reactivity between commercial assays. This emphasizes the need to use the same assay type when measuring serial hCG levels for clinical indications such as evaluating pregnancy of unknown location or medical management of ectopic pregnancy. Peak maternal plasma levels reach approximately 50,000 to 100,000 mIU/mL between the 60th and 80th days after menses. Plasma levels then decline, and a nadir is reached by approximately 16 weeks' gestation. Plasma levels remain at this lower level for the rest of pregnancy.

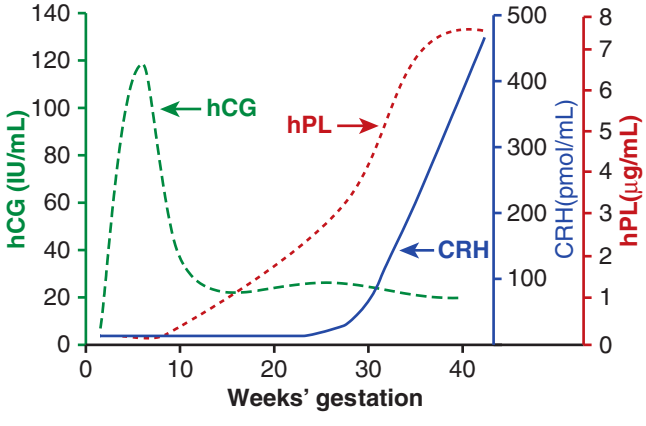


FIGURE 5-15 Distinct profiles for the concentrations of human chorionic gonadotropin (hCG), human placental lactogen (hPL), and corticotropin-releasing hormone (CRH) in serum of women throughout normal pregnancy.

Although maternal urine, like plasma, contains various hCG degradation products, the principal urinary form is the terminal product of hCG degradation, namely, the β-core fragment. Concentrations of this fragment follow the same general pattern as that in maternal plasma, peaking at approximately 10 weeks' gestation. Importantly, the β-subunit antibody used in most pregnancy tests reacts with both intact hCG (the major form in the plasma) and with fragments of hCG (the major form found in urine).

hCG Regulation

Placental GnRH is likely involved in the regulation of hCG formation. Both GnRH and its receptor are expressed by cytotrophoblasts and syncytiotrophoblast (Wolfahrt, 1998). GnRH administration elevates circulating hCG levels, and cultured trophoblasts respond to GnRH treatment with increased hCG secretion (Iwashita, 1993; Siler-Khodr, 1981). Pituitary GnRH production is regulated by inhibin and activin. Likewise, in cultured placental cells, activin stimulates and inhibin inhibits GnRH and hCG production (Petraglia, 1989; Steele, 1993).

hCG is cleared by the kidney (about 30 percent), and the remainder is likely cleared by liver metabolism (Wehmann, 1980). Thus, levels can be markedly altered in gravidas with chronic renal disease.

Biological Functions

Noted earlier, hCG maintains corpus luteum function—that is, continued progesterone production. Both hCG subunits are required for binding to the LH-hCG receptor in the corpus luteum. However, maximum plasma hCG concentrations are attained well after hCG-stimulated corpus luteum secretion of progesterone has ceased. Specifically, luteal progesterone synthesis begins to decline at approximately 6 weeks' gestation despite continued and increasing hCG production. Therefore, this incompletely explains the physiological function of hCG in pregnancy. LH-hCG receptors are present in various other tissues, and roles are discussed subsequently.

In pregnancies with male fetuses, hCG stimulates fetal testicular testosterone secretion. This reaches a maximum when hCG levels peak. Thus, at a critical time in male sexual differentiation, hCG enters fetal plasma from the syncytiotrophoblast. In the fetus, it acts as an LH surrogate to stimulate Leydig cell replication and testosterone synthesis to promote male sexual differentiation (Chap. 3, p. 35). Before approximately 110 days, the fetal anterior pituitary lacks vascularization from the hypothalamus and produces minimal LH secretion. Thereafter, as hCG levels fall, pituitary LH maintains modest testicular stimulation.

The maternal thyroid gland also is stimulated by large quantities of hCG. In women with gestational trophoblastic disease, biochemical and clinical evidence of hyperthyroidism sometimes develops (Chap. 13, p. 238). Some forms of

hCG bind to TSH receptors on thyrocytes (Hershman, 1999). The thyroid-stimulatory activity in plasma of first-trimester pregnant women varies appreciably from sample to sample. Modifications of hCG oligosaccharides likely are important in the capacity of hCG to stimulate thyroid function. Acidic isoforms stimulate thyroid activity, and some more basic isoforms stimulate iodine uptake (Kraiem, 1994; Tsuruta, 1995). Last, the LH-hCG receptor is also expressed by thyrocytes, which suggests that hCG stimulates thyroid activity via the LH-hCG receptor as well (Tomer, 1992).

LH-hCG receptors are found in myometrium and in uterine vascular tissue. It has been hypothesized that hCG may promote uterine vascular vasodilation and myometrial smooth muscle relaxation (Kurtzman, 2001). hCG also modulates maternal immune cell functions in the decidua during early stages of placentation (Schumacher, 2019; Silasi, 2020).

Abnormally High or Low Levels

Several clinical circumstances display substantively higher maternal plasma hCG levels. Some examples include multifetal pregnancy, erythroblastosis fetalis associated with fetal hemolytic anemia, and gestational trophoblastic disease. Relatively higher hCG levels may be found in women carrying a fetus with Down syndrome, and this has been incorporated into screening strategies (Table 17-4, p. 336). Various malignant tumors also produce hCG, sometimes in large amounts—especially trophoblastic neoplasms (Chap. 13, p. 241).

Relatively lower hCG plasma levels are found in women with failing early pregnancies and ectopic pregnancy (Chap. 12, p. 222). hCG is produced in very small amounts in normal tissues of men and nonpregnant women, perhaps primarily in the anterior pituitary gland. Nonetheless, the detection of hCG in blood or urine almost always indicates pregnancy (Chap. 10, p. 176).

Human Placental Lactogen

Biosynthesis

This single, nonglycosylated polypeptide chain shares a 96-percent amino-acid-sequence homology with human growth hormone (hGH) and a 67-percent homology with human prolactin (hPRL). Because of these similarities, it was called chorionic growth hormone or human placental lactogen. Currently, the latter term is used by most.

Five genes in the growth hormone–placental lactogen gene cluster are linked and located on chromosome 17: *GH1*, *GH2*, *CSHL1, CSH1*, and *CSH2*. Human placental lactogen (hPL) is encoded by the last two genes. hPL is concentrated in syncytiotrophoblast, but similar to hCG, hPL is demonstrated in cytotrophoblasts before 6 weeks (Grumbach, 1964; Maruo, 1992). Within 5 to 10 days after conception, hPL is demonstrable in the placenta and can be detected in maternal serum as early as 3 weeks. Levels of mRNA for hPL in syncytiotrophoblast remain relatively constant throughout pregnancy. This finding supports the idea that the hPL secretion rate is proportional to placental mass. Levels rise steadily until 34 to 36 weeks' gestation. The hPL production rate near term—approximately 1 g/d—is by far the greatest of any known hormone in humans. It is rapidly cleared and has a half-life between 10 and 30 minutes (Walker, 1991). In late pregnancy, maternal serum concentrations reach levels of 5 to 15 μg/mL (see Fig. 5-15).

Very little hPL is detected in fetal blood, and amnionic fluid levels are somewhat lower than that in maternal plasma. Thus, although hPL may have a direct effect on fetal tissues, such as modulating fetal vasculature formation, its primary role is to act on maternal physiology to ensure adequate nutrient delivery to the placenta (Corbacho, 2002).

Metabolic Actions

hPL has putative actions in several important maternal metabolic processes. First, hPL promotes lipolysis to raise circulating free fatty acid levels. This provides an energy source for maternal metabolism and fetal nutrition. In vitro studies suggest that hPL inhibits secretion by term syncytiotrophoblast of leptin (Coya, 2005). Prolonged maternal starvation in the first half of pregnancy leads to higher hPL plasma concentrations.

Second, hPL aids maternal adaptation to fetal energy requirements (Hill, 2018). For example, increased maternal insulin resistance ensures nutrient flow to the fetus. It also favors protein synthesis and provides a readily available amino acid source to the fetus. To counterbalance the greater insulin resistance and prevent maternal hyperglycemia, maternal insulin levels rise. Both hPL and prolactin signal through the prolactin receptor to increase maternal beta cell proliferation, which augments insulin secretion (Georgia, 2010). In animals, prolactin and hPL upregulate serotonin synthesis, which increases beta cell proliferation (Kim, 2010). Short-term changes in plasma glucose or insulin, however, have relatively little effect on plasma hPL levels. In vitro studies of syncytiotrophoblast suggest that hPL synthesis is stimulated by insulin and insulin-like growth factor-1 and inhibited by PGE_2 and $PGF_{2\alpha}$ (Bhaumick, 1987; Genbacev, 1977).

Other Placental Protein Hormones

The placenta has a remarkable capacity to synthesize numerous peptide hormones, including some that are analogous or related to hypothalamic and pituitary hormones. In contrast to their counterparts, some of these placental peptide/protein hormones are not subject to feedback inhibition.

Hypothalamic-Like Releasing Hormones

The known hypothalamic-releasing or -inhibiting hormones include GnRH, corticotropin-releasing hormone (CRH), thyrotropin-releasing hormone (TRH), growth hormone–releasing hormone (GHRH), and somatostatin. For each of these, the human placenta produces an analogous hormone (Petraglia, 1992; Siler-Khodr, 1988).

GnRH in the placenta shows its highest expression in the first trimester (Siler-Khodr, 1978, 1988). Interestingly, it is found in cytotrophoblasts but not syncytiotrophoblast. Placenta-derived GnRH functions to regulate trophoblast hCG production and extravillous trophoblast invasion via regulation of MMP-2 and MMP-9 (Peng, 2016). Placenta-derived GnRH is also the likely source of elevated maternal GnRH levels in pregnancy (Siler-Khodr, 1984).

CRH is a member of a larger family of CRH-related peptides that includes CRH and urocortins (Dautzenberg, 2002). Maternal serum CRH levels rise from 5 to 10 pmol/L in the nonpregnant woman to approximately 100 pmol/L in the early third trimester and then to almost 500 pmol/L abruptly during the last 5 to 6 weeks (see Fig. 5-15). After labor begins, maternal plasma CRH levels rise even further (Petraglia, 1989, 1990). Urocortin, involved in the stress response, is also produced by the placenta and secreted into the maternal circulation, but at much lower levels than that seen for CRH (Florio, 2002).

The function of CRH synthesized in the placenta, membranes, and decidua has been somewhat defined. For example, trophoblast, amniochorion, and decidua express both CRH-R1 and CRH-R2 receptors and several variant receptors (Florio, 2000). Both CRH and urocortin enhance trophoblast secretion of adrenocorticotropic hormone (ACTH), and this suggests an autocrine–paracrine role (Petraglia, 1999). Large amounts of trophoblast CRH enter maternal blood.

CRH receptors are also present in many tissues outside the placenta. Proposed biological roles include induction of smooth-muscle relaxation in vascular and myometrial tissue and immunosuppression. The physiological reverse, however, induction of myometrial contractions, has been proposed for the rising CRH levels seen near term. Some hypothesize that CRH may be involved with parturition initiation (Wadhwa, 1998).

Glucocorticoids act in the hypothalamus to inhibit CRH release. But, in the trophoblast, glucocorticoids stimulate CRH gene expression (Jones, 1989a; Robinson, 1988). Thus, a novel positive feedback loop in the placenta may allow placental CRH to stimulate placental ACTH and thereby prompt fetal and maternal adrenal glucocorticoid production, with subsequent stimulation of placental CRH expression (Nicholson, 2001; Riley, 1991).

GHRH is expressed in placenta, but its function is unclear (Berry, 1992). GHRH may play an autocrine role in trophoblast survival via the GHRH receptor (Liu, 2016). Ghrelin is another regulator of hGH secretion and is produced by placental tissue (Horvath, 2001). Trophoblast ghrelin expression peaks at midpregnancy and is a paracrine regulator of differentiation or is a potential regulator of human growth hormone variant production, described next (Fuglsang, 2005; Gualillo, 2001).

Pituitary-Like Hormones

A *human growth hormone variant (hGH-V)* that is not expressed in the pituitary is expressed in the placenta. The gene encoding hGH-V is located in the hGH–hPL gene cluster on chromosome 17. Sometimes referred to as placental growth hormone, hGH-V is a 191-amino-acid protein that differs in 15 amino acid positions from the sequence for hGH. Although hGH-V retains growth-promoting and antilipogenic functions that are similar to those of hGH, it has reduced diabetogenic and lactogenic functions relative to hGH (Vickers, 2009). Placental hGH-V presumably is synthesized in the syncytiotrophoblast. It is believed that hGH-V is present in maternal plasma by 21 to 26 weeks' gestation, rises in concentration until approximately 36 weeks, and remains relatively constant thereafter. hGH-V levels in maternal plasma and those of insulin-like growth factor 1 positively correlate. Moreover, hGH-V secretion by trophoblast in vitro is inhibited by glucose in a dose-dependent manner (Patel, 1995). Overexpression of hGH-V in mice causes severe insulin resistance, making it a likely candidate to mediate insulin resistance of pregnancy (Liao, 2016).

Pro-opiomelanocortin (POMC) is a polypeptide produced in the pituitary and other tissues including the placenta. It is proteolytically cleaved into numerous active hormones including ACTH, β-lipotropic hormone, melanocyte-stimulating hormone (α-, β-, and γ-MSH), and β–endorphin (Harno, 2018). These hormones play a role in maintaining energy balance. As discussed, placental CRH stimulates synthesis and release of placental ACTH, demonstrating the autocrine and paracrine functions of the placenta in addition to its systemic endocrine activity.

Relaxin

The peptide is expressed in human corpus luteum, decidua, and placenta (Bogic, 1995). Two of the three relaxin genes—*H2* and *H3*—are transcribed in the corpus luteum (Bathgate, 2002; Hudson, 1983, 1984). Decidua, placenta, and membranes express *H1* and *H2* (Hansell, 1991). Relaxin is synthesized as a single, 105-amino-acid preprorelaxin molecule that is cleaved to A and B molecules. Relaxin is structurally similar to insulin and insulin-like growth factor.

The rise in maternal circulating relaxin levels in early pregnancy is attributed to corpus luteum secretion, and levels parallel those of hCG. Relaxin, along with rising progesterone levels, may act on myometrium to promote relaxation and the quiescence of early pregnancy (Chap. 21, p. 404). In addition, the production of relaxin and relaxin-like factors within the placenta and fetal membranes may play an autocrine-paracrine role in postpartum regulation of extracellular matrix remodeling (Qin, 1997a,b). One important relaxin function is enhancement of the maternal glomerular filtration rate that is apparent early in gestation (Chap. 4, p. 68).

Parathyroid Hormone-Related Protein

Levels of this peptide are elevated within maternal but not fetal circulation (Bertelloni, 1994; Saxe, 1997). Parathyroid hormone-related protein (PTH-rP) synthesis is found in several normal adult tissues, especially in reproductive organs that include myometrium, endometrium, corpus luteum, and lactating mammary tissue. PTH-rP is not produced in the parathyroid glands of normal adults. Although yet undefined, placenta-derived PTH-rP may regulate genes involved in transfer of calcium and other solutes. It also contributes to mineral homeostasis in fetal bone, amnionic fluid, and the fetal circulation (Simmonds, 2010).

Leptin

This hormone is normally secreted by adipocytes, but cytotrophoblasts and syncytiotrophoblast also synthesize leptin (Henson, 2002). Relative contributions of leptin from maternal adipose tissue versus placenta are currently undefined. Leptin functions as an antiobesity hormone that decreases food

intake through its hypothalamic receptor. It also regulates bone growth and immune function (Cock, 2003; La Cava, 2004). Placental leptin promotes placental cell proliferation, protein synthesis, and activation of immune tolerance and antiapoptotic responses (Rosario, 2016a; Schanton, 2018). Maternal serum levels are significantly higher than those in nonpregnant women. Fetal leptin levels correlate positively with birthweight and likely function in fetal development and growth. Studies suggest that reductions in leptin availability contribute to adverse fetal metabolic programing in intrauterine growth-restricted offspring (Nusken, 2016, Perez-Perez, 2018).

Neuropeptide Y

This 36-amino-acid peptide is widely distributed in brain. It also is found in sympathetic neurons innervating the cardiovascular, respiratory, gastrointestinal, and genitourinary systems. Neuropeptide Y has been isolated from the placenta and localized in cytotrophoblasts (Petraglia, 1989). Trophoblasts possess neuropeptide Y receptors, and treatment of these with neuropeptide Y causes CRH release (Robidoux, 2000).

Transforming Growth Factor Beta Superfamily

This family of cytokines regulates various cellular functions that include placental development, trophoblast differentiation, and invasion into the decidua (Adu-Gyamafi, 2020). This process is finely tuned, and extreme invasion results in placenta accreta spectrum disorders, whereas shallow implantation can lead to early pregnancy loss or preeclampsia. Members of the family include transforming growth factor beta (TGF-β), activin, inhibin, nodal, bone morphogenic proteins (BMPs), antimüllerian hormone, and growth differentiation factors (GDFs).

These cytokines bind to a suite of receptors composed of a type 1 subunit and a type 2 receptor subunit to ultimately direct gene expression. This combinatorial diversity leads to divergent functions in the placenta and decidua. Activin A promotes syncytialization, extravillous trophoblast formation, and invasion. BMP2 enhances invasion, and BMP4 may direct embryonic stem cells toward a trophoblast lineage (Zhang 2018, Xu 2002). Inhibin A promotes syncytialization but inhibits invasion (Debiève, 2000; Jones, 2006). Nodal inhibits proliferation, extravillous trophoblast formation, and invasion. The complete role this superfamily in normal and abnormal placental development is yet to be fully defined.

■ Placental Progesterone Production

After 6 to 7 weeks' gestation, little progesterone is produced in the ovary (Diczfalusy, 1961). Surgical removal of the corpus luteum or even bilateral oophorectomy during the 7th to 10th week does not decrease excretion rates of urinary pregnanediol, the principal urinary metabolite of progesterone. Before this time, however, corpus luteum removal will lead to spontaneous abortion unless an exogenous progestin is given, and Chapter 66 (p. 1170) lists suitable dosing. After approximately 8 weeks, the placenta assumes progesterone secretion, and maternal serum levels throughout pregnancy gradually rise (Fig. 5-16). By term, these levels are 10 to 5000 times of those in nonpregnant women, depending on the ovarian cycle stage.

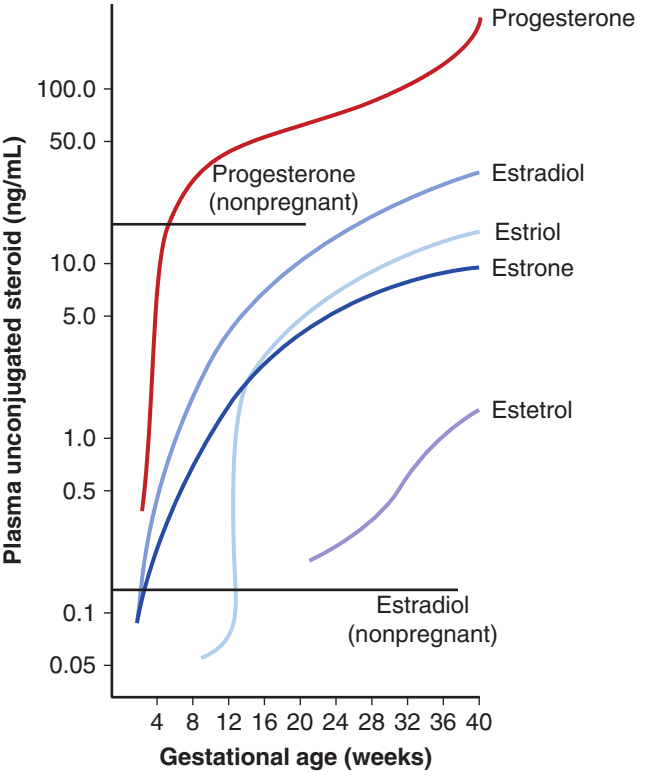


FIGURE 5-16 Plasma levels of progesterone, estradiol, estrone, estetrol, and estriol in women during the course of gestation. (Modified and redrawn with permission from Mesiano S: The endocrinology of human pregnancy and fetoplacental neuroendocrine development. In Strauss JF, Barbieri RL (eds) Yen and Jaffe's Reproductive Endocrinology: Physiology, Pathophysiology, and Clinical Management, 6th ed. Philadephia, PA: Saunders; 2009.)

The daily production rate of progesterone in late, normal, singleton pregnancies approximates 250 mg. In multifetal pregnancies, the daily production rate may exceed 600 mg. Progesterone is synthesized from cholesterol in a two-step enzymatic reaction. First, cholesterol is converted to pregnenolone within the mitochondria in a reaction catalyzed by cytochrome P450 cholesterol side-chain cleavage enzyme. Pregnenolone leaves the mitochondria and is converted to progesterone in the endoplasmic reticulum by 3β-hydroxysteroid dehydrogenase. Progesterone is released immediately by diffusion.

Although the placenta produces a prodigious amount of progesterone, the syncytiotrophoblast has a limited capacity for cholesterol biosynthesis. The rate-limiting enzyme in its biosynthesis is 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase. Because of this, the placenta must rely on an exogenous source, that is, maternal cholesterol, for progesterone formation. The trophoblast preferentially uses LDL cholesterol for progesterone biosynthesis (Simpson, 1979, 1980). This mechanism differs from placental production of estrogens, which relies principally on fetal adrenal precursors.

Although fetal well-being and placental estrogen production show a relationship, this is not the case for placental progesterone. Thus, placental endocrine function, including progesterone biosynthesis and formation of protein hormones such as hCG, may persist for weeks after fetal demise.

The metabolic clearance rate of progesterone in pregnant women is similar to that found in men and nonpregnant women. One metabolite is 5α-dihydroprogesterone (5α-DHP), and levels disproportionately rise due to synthesis in syncytiotrophoblast from both placenta-produced progesterone and fetus-derived precursor (Dombroski, 1997). Thus, the concentration ratio of 5α-DHP to progesterone is elevated in pregnancy, although the mechanisms for this are incompletely defined. Progesterone also is converted to the potent mineralocorticoid deoxycorticosterone in pregnant women and in the fetus. The concentration of deoxycorticosterone is strikingly higher in both maternal and fetal compartments (see Table 5-1). The extraadrenal formation of deoxycorticosterone from circulating progesterone accounts for most of its production in pregnancy (Casey, 1982a,b).

■ Placental Estrogen Production

During the first 2 to 4 weeks or pregnancy, rising hCG levels maintain production of estradiol in the corpus luteum. Ovarian production of both progesterone and estrogens drops significantly by the 7th week of pregnancy. At this time, there is a luteal–placental transition. Subsequently, more than half of estrogen entering maternal circulation is produced in the placenta, and it produces a continually increasing magnitude of estrogen (MacDonald, 1965a; Siiteri, 1963, 1966). Near term, normal human pregnancy is a hyperestrogenic state, and syncytiotrophoblast is producing estrogen in amounts equivalent to that produced in one day by the ovaries of no fewer than 1000 ovulatory women. This hyperestrogenic state terminates abruptly after delivery of the placenta.

Biosynthesis

In human trophoblast, neither cholesterol nor in turn progesterone can serve as precursor for estrogen biosynthesis. This is because *steroid 17α-hydroxylase/17,20-lyase (CYP17A1)* is not expressed in the human placenta. This essential enzyme converts 17-OH progesterone (a C_{21} steroid) to androstenedione, which is a C_{19} steroid and an estrogen precursor. Consequently, conversion of C_{21} steroids to C_{19} steroids is not possible.

However, dehydroepiandrosterone (DHEA) and its sulfate (DHEA-S) are also C_{19} steroids and are produced by maternal and fetal adrenal glands. These two steroids can serve as estrogen precursors in the placenta (Fig. 5-17). Ryan (1959a) found that the placenta had an exceptionally high capacity to convert appropriate C_{19} steroids to estrone and estradiol. The conversion of DHEA-S to estradiol requires placental expression of four key enzymes that are located principally in syncytiotrophoblast (Bonenfant, 2000; Salido, 1990). First, the placenta expresses high levels of steroid sulfatase (STS), which converts the conjugated DHEA-S to DHEA. DHEA is then acted upon by 3β-hydroxysteroid dehydrogenase type 1 (3βHSD) to produce androstenedione. Cytochrome P450 aromatase (CYP19) then converts androstenedione to estrone, which is then converted to estradiol by 17β-hydroxysteroid dehydrogenase type 1 (17βHSD1).

DHEA-S is the major precursor of estrogens in pregnancy (Baulieu, 1963; Siiteri, 1963). However, maternal adrenal glands do not produce sufficient amounts of DHEA-S to account for more than a fraction of total placental estrogen biosynthesis. The fetal adrenal glands are quantitatively the most important source of placental estrogen precursors in human pregnancy. Thus, estrogen production during pregnancy reflects the unique interactions among fetal adrenal glands, fetal liver, placenta, and maternal adrenal glands.

Directional Secretion

Of estradiol and estriol formed in syncytiotrophoblast, >90 percent enters maternal plasma (Gurpide, 1966). Of placental progesterone production, ≥85 percent enters maternal plasma, and little maternal progesterone crosses the placenta to the fetus (Gurpide, 1972).

This directional secretion stems from the architecture of hemochorioendothelial placentation. Steroids produced in the syncytiotrophoblast are secreted directly into maternal blood. To reach the fetus, they must first traverse the cytotrophoblast layer and then enter the stroma of the villous core and then fetal capillaries. From either of these spaces, steroids can reenter the

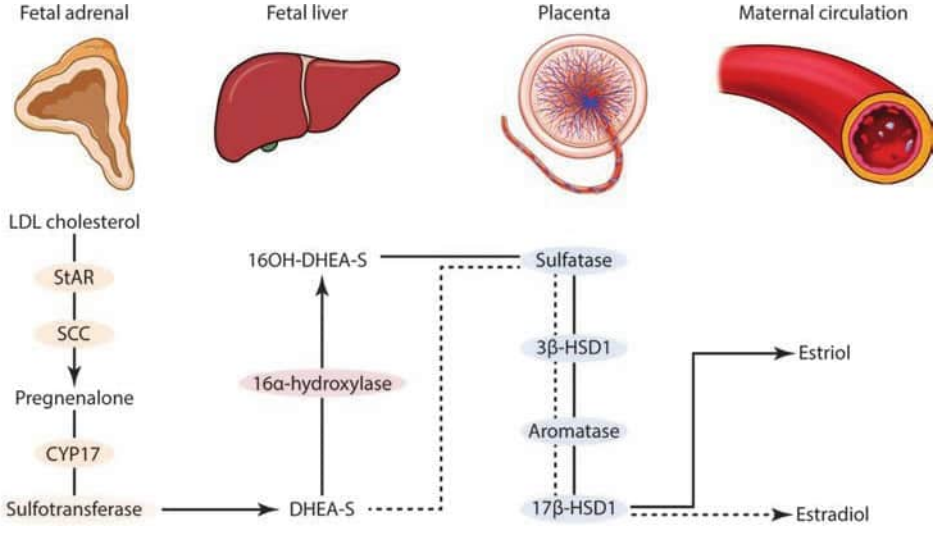


FIGURE 5-17 Schematic presentation of estrogen biosynthesis in the human placenta. Dehydroepiandrosterone sulfate (DHEA-S) is secreted in prodigious amounts by the fetal adrenal glands, and a portion is converted to 16α-hydroxydehydroepiandrosterone sulfate (16OH-DHEA-S) in the fetal liver. DHEA-S and 16OH-DHEA-S are converted in the placenta to the estrogens 17β-estradiol (E_2) and estriol (E_3). These estrogens then enter the maternal circulation. Near term, half of E_2 is derived from fetal adrenal DHEA-S and half from maternal DHEA-S. On the other hand, 90 percent of E_3 in the placenta arises from fetal 16OH-DHEA-S and only 10 percent from all other sources. 3βHSD1 = 3β-hydroxysteroid dehydrogenase type 1; 17βHSD1 = 17β-hydroxysteroid dehydrogenase type 1; CYP17 = steroid 17α-hydroxylase/17,20-lyase; LDL = low-density lipoprotein; SCC = cholesterol side-chain cleavage enzyme; StAR = steroidogenic acute regulatory protein.

syncytium. The net result of this hemochorial arrangement is that entry of steroids into the maternal circulation is substantially greater than that into fetal blood.

FETAL ADRENAL GLAND–PLACENTAL INTERACTIONS

As noted, the fetal adrenal gland is a vital source of steroid precursors for placental estrogen synthesis. This fetal gland is remarkable both morphologically and functionally. At term, its mass exceeds that in adults (Chap. 7, p. 134). More than 85 percent of the fetal gland is composed of a unique fetal zone, which has a great capacity for steroid biosynthesis. Its daily steroid production near term is 100 to 200 mg/d, which exceeds the adult steroid secretion of 30 to 40 mg/d. The unique fetal zone subsequently regresses in the first year of life.

In addition to responding to ACTH from the fetal brain, fetal adrenal gland growth is influenced by factors secreted by the placenta. This is exemplified by the continued adrenal gland growth throughout gestation and by its rapid involution immediately after birth and placenta delivery.

Placental Estriol Synthesis

Estradiol is the primary placental estrogen product at term. In addition, significant levels of *estriol* and *estetrol* are found in the maternal circulation, particularly late in gestation (see Fig. 5-16). These hydroxylated forms of estrogen derive from the placenta using substrates formed by the combined efforts of the fetal adrenal gland and fetal liver enzymes (see Fig. 5-17). For this, high levels of hepatic 16α-hydroxylase act on adrenal-derived steroids (MacDonald, 1965b; Ryan, 1959b). Thus, the disproportionate rise in estriol formation during pregnancy is accounted for by placental synthesis from plasma-borne 16-OH-DHEA-S. Near term, the fetus produces 90 percent of placental estriol and estetrol precursors in normal human pregnancy. Thus, in the past, levels of these steroids were used as an indicator of fetal well-being.

Fetal Adrenal Steroid Precursor

Cholesterol is the precursor for fetal adrenal steroidogenesis. Here, the steroid biosynthesis rate is so great that its steroidogenesis alone is equivalent to a fourth of the total daily LDL cholesterol turnover in adults. Fetal adrenal glands synthesize cholesterol from acetate, and all enzymes involved in this biosynthesis are elevated compared with those of the adult adrenal gland (Rainey, 2001). Thus, the de novo cholesterol synthesis rate by fetal adrenal tissue is extremely high. Even so, it is insufficient to account for the steroids produced by fetal adrenal glands. Therefore, cholesterol must be assimilated from the fetal circulation and mainly from LDL produced in the fetal liver (Carr, 1980, 1984; Simpson, 1979).

Fetal Conditions Affecting Estrogen Production

Several fetal disorders alter the availability of substrate for placental steroid synthesis and thus highlight the interdependence of fetal development and placental function. *Fetal demise* is followed by a striking reduction in maternal urinary estrogen levels. Similarly, after ligation of the umbilical cord with the fetus and placenta left in situ, placental estrogen production declines markedly (Cassmer, 1959). However, as previously discussed, placental progesterone production is maintained. These observations indicate that an important source of precursors for placental estrogen—but not for progesterone—biosynthesis derive from the fetus.

Anencephalic fetuses have markedly atrophic adrenal glands due to absent hypothalamic and pituitary structures that would otherwise release ACTH for adrenal stimulation. In the absence of the adrenal cortical fetal zone development, placental formation of estrogen is severely limited because of diminished availability of C_{19} steroid precursors. Indeed, urinary estrogen levels in women pregnant with an anencephalic fetus approximate only 10 percent of those found in normal pregnancy (Frandsen, 1961). With an anencephalic fetus, almost all estrogens produced arise from placental use of maternal plasma DHEA-S.

Fetal adrenal cortical hypoplasia occurs in perhaps 1 in 12,500 births (McCabe, 2001). Estrogen production in these pregnancies is also limited, which suggests the absence of C_{19} precursors.

Fetal–placental sulfatase deficiency is associated with very low estrogen levels in otherwise normal pregnancies (France, 1969). Namely, sulfatase deficiency precludes the hydrolysis of C_{19} steroid sulfates, the first enzymatic step in the placental use of these circulating prehormones for estrogen biosynthesis. This deficiency is an X-linked disorder, and thus all affected fetuses are male. Its estimated frequency is 1 case in 2000 to 5000 births and is associated with delayed labor onset. It also is associated with development of ichthyosis in affected males later in life (Bradshaw, 1986).

Fetal–placental aromatase deficiency is a rare autosomal recessive disorder in which individuals cannot synthesize endogenous estrogens (Grumbach, 2011; Simpson, 2000). Fetal adrenal DHEA-S is converted in the placenta to androstenedione, but in cases of placental aromatase deficiency, androstenedione cannot be converted to estradiol. Rather, androgen metabolites of DHEA produced in the placenta, including androstenedione and some testosterone, are secreted into the maternal or fetal circulation, or both. This can virilize the mother and the female fetus (Belgorosky, 2009; Harada, 1992).

Trisomy 21—Down syndrome—screening searches for abnormal levels of hCG, alpha-fetoprotein, and other analytes (Chap. 17, p. 338). Of these, serum unconjugated estriol levels can be low in women with Down syndrome fetuses (Benn, 2002). This likely stems from inadequate formation of C_{19} steroids in the adrenal glands of these trisomic fetuses.

Fetal erythroblastosis in some cases of severe fetal D-antigen alloimmunization can lead to elevated maternal plasma estrogen levels. A suspected cause is the greater placental mass from hypertrophy, which can be seen with such fetal hemolytic anemia (Chap. 18, p. 360).

Complete hydatidiform mole and *gestational trophoblastic neoplasias* lack a fetus and also a fetal adrenal source of C_{19} steroid precursors for trophoblast estrogen biosynthesis. Placental estrogen formation is consequently limited to the use of C_{19}

steroids from the maternal plasma, and thus estradiol is principally produced (MacDonald, 1964, 1966).

Maternal Conditions Affecting Estrogen Production

Maternal conditions can likewise affect placental estrogen production. *Glucocorticoid treatment* can inhibit ACTH secretion from the maternal and fetal pituitary glands. This diminishes maternal and fetal adrenal secretion of the placental estrogen precursor DHEA-S and leads to a striking reduction in placental estrogen formation.

With *Addison disease,* pregnant women show lower estrogen levels, principally estrone and estradiol levels (Baulieu, 1956). However, the fetal adrenal gland contribution to estriol synthesis, particularly in later pregnancy, is quantitatively much more important than that of the maternal adrenal gland.

Maternal *androgen-producing tumors* can present the placenta with elevated androgen levels. Fortunately, placenta is extraordinarily efficient in the aromatization of C_{19} steroids. For example, virtually all androstenedione entering the intervillous space is taken up by syncytiotrophoblast and converted to estradiol (Edman, 1981). None of the C_{19} steroid enters the fetus, and a female fetus is rarely virilized by a maternal androgen-secreting tumor. Indeed, virilized female fetuses of women with an androgen-producing tumor may be cases in which a nonaromatizable C_{19} steroid androgen is produced by the tumor—for example, 5α-dihydrotestosterone. Alternatively, tumor-derived testosterone could be produced very early in pregnancy in amounts that exceed the placental aromatase capacity at that time.

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CHAPTER 6

Placental Abnormalities

During pregnancy, the placenta provides the indispensable interface between mother and fetus (Chap. 5, p. 86). However, in part due to inaccessibility throughout gestation, the placenta's anatomy, physiology, and molecular structure still remain some of the most understudied and intriguing topics in obstetrics. Furthermore, the parallels between placental formation and cancer afford opportunities to understand tumor biology and pathogenesis (Costanzo, 2018; Guttmacher, 2014).

Visual placental inspection by the obstetrician is recommended, but routine pathological examination is not mandatory. Indeed, specific conditions that merit submission for detailed inspection are still debated. For example, the College of American Pathologists recommends placental examination for an extensive list of indications, however many providers are not aware (Langston, 1997; Odibo, 2016). Moreover, data are insufficient to support all of these. At minimum, the placenta and cord should be inspected in the delivery room. The decision to request pathological examination should be based on clinical and placental findings (Table 6-1) (Redline, 2008; Roberts, 2008).

NORMAL PLACENTA

At term, the typical placenta weighs 470 g, is round to oval with a 22-cm diameter, and has a central thickness of 2.5 cm (Benirschke, 2012). It is composed of a placental disc, extraplacental membranes, and three-vessel umbilical cord. The disc surface that lies against the uterine wall is the *basal plate*, which is divided by clefts into portions—termed cotyledons. The fetal surface is the *chorionic plate*. Here, the umbilical cord inserts, typically in the center. Large fetal vessels that originate from the cord vessels then spread and branch across the chorionic plate before entering stem villi of the placenta parenchyma. In tracing these, fetal arteries almost invariably cross over veins. The chorionic plate and its vessels are covered by thin amnion, which can be easily peeled away from a postdelivery specimen.

During prenatal sonographic examinations, multiple societies, including the American Institute of Ultrasound in Medicine (2018), recommend identifying and recording placental location and its relationship to the internal cervical os. As seen sonographically, the normal placenta is homogenous and 2 to 4 cm thick, lies against the myometrium, and indents into the amnionic sac. The retroplacental space is a hypoechoic area that separates the myometrium from the basal plate and measures less than 1 to 2 cm. The umbilical cord is also imaged, its fetal and placental insertion sites examined, and its vessels counted.

Many placental lesions can be identified grossly or sonographically, but other abnormalities require histopathological examination for clarification. A detailed description of these is beyond the scope of this chapter, and interested readers are referred to textbooks by Benirschke (2012), Fox (2007), and Faye-Petersen (2006) and their colleagues. Moreover, the placenta accreta spectrum, placenta previa, and gestational

TABLE 6-1. Some Indications for Placental Pathological Examination[a]

Maternal Indications
Abruption
Antepartum infection with fetal risks
Anti-CDE alloimmunization
Cesarean hysterectomy
Oligohydramnios or hydramnios
Peripartum fever or infection
Preterm (<32 wks) delivery
Postterm (>42 wks) delivery
Severe trauma
Suspected placental injury
Systemic disorders with known placental effects
Thick meconium
Unexplained late pregnancy bleeding
Unexplained or recurrent pregnancy complications
Fetal and Neonatal Indications
Admission to an acute care nursery
Birth weight <10th or >95th percentile
Fetal anemia
Fetal or neonatal compromise
Neonatal seizures
Hydrops fetalis
Infection or sepsis
Major anomalies or abnormal karyotype
Multifetal gestation
Stillbirth or neonatal death
Vanishing twin beyond the first trimester
Placental Indications
Gross lesions
Markedly abnormal placental shape or size
Markedly adhered placenta
Term cord >32 cm or <100 cm
Umbilical cord lesions
Velamentous cord insertion

[a]Indications are organized alphabetically.

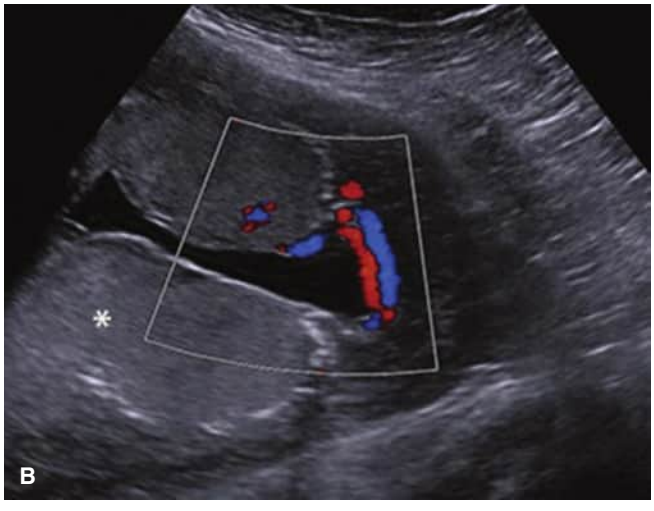
trophoblastic disease are presented in detail in Chapters 41 and 20, respectively.

SHAPE AND SIZE VARIANTS

Of variants, placentas may infrequently form as separate, nearly equally sized discs. This *bilobate placenta* may also be called bipartite placenta or placenta duplex. In these, the cord inserts between the two placental lobes—either into a connecting chorionic bridge or into intervening membranes. A placenta containing three or more equivalently sized lobes is rare and termed *multilobate*. Unlike this equal distribution, one or more disparately smaller accessory lobes—*succenturiate lobes*—may develop in the membranes at a distance from the main placenta (Fig. 6-1). These lobes have vessels that course through the membranes. Of clinical importance, if these vessels overlie the cervix to create a vasa previa, dangerous fetal hemorrhage can follow vessel laceration (p. 115). An accessory lobe can also be retained in the uterus after delivery to cause postpartum uterine atony and hemorrhage or later endometritis.

Rarely, the placental surface area varies from the norm. With *placenta membranacea*, villi cover all or nearly all the uterine cavity. This may occasionally give rise to serious hemorrhage because of associated placenta previa or accreta (Pereira, 2013). A *ring-shaped placenta* may be a variant of placenta membranacea. This placenta is annular, and a partial or complete ring of placental tissue is present. These abnormalities appear to be associated with a greater likelihood of antepartum and postpartum bleeding and fetal-growth restriction (Faye-Petersen, 2006; Steemers, 1995). With *placenta fenestrata*, the central portion of a placental disc is missing. In some cases, there is

A



B

FIGURE 6-1 Succenturiate lobe. **A.** Vessels extend from the main placental disc to supply the small round succenturiate lobe located to the left. (Reproduced with permission from Dr. Rachel Gardner.) **B.** Sonographic imaging with color Doppler shows the main placental disc implanted posteriorly (*asterisk*). The succenturiate lobe is located on the anterior uterine wall across the amnionic cavity. Vessels are identified as the long red and blue crossing tubular structures that travel within the membranes to connect these two portions of placenta.

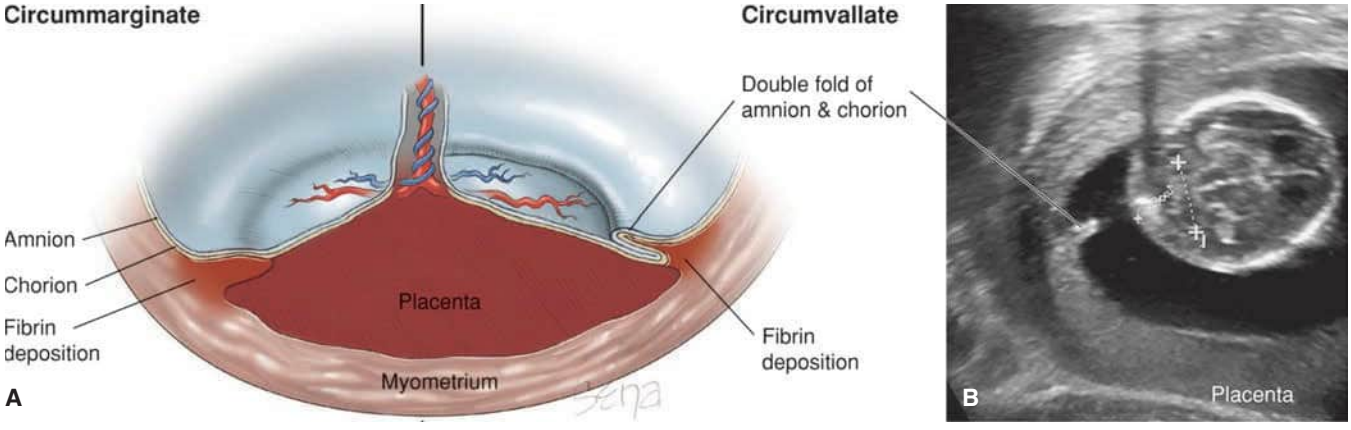


FIGURE 6-2 A. In this illustration, circummarginate (*left*) and circumvallate (*right*) varieties of extrachorial placentation are shown. A circummarginate placenta is covered by a single layer of amniochorion. **B.** This transabdominal grayscale sonographic image shows a circumvallate placenta. The double fold of amnion and chorion creates a broad, opaque white ring and ridge on the fetal surface.

an actual hole in the placenta. More often, only villous tissue is missing, and the chorionic plate remains intact.

During pregnancy, the normal placenta increases its thickness at a rate that approximates 1 mm per week. Although not measured as a component of routine sonographic evaluation, this thickness typically does not exceed 40 mm (Hoddick, 1985). *Placentomegaly* defines those thicker than 40 mm and commonly results from striking villous enlargement. Underlying maternal etiologies are diabetes mellitus or severe anemia, whereas fetal sources include hydrops, anemia, syphilis, toxoplasmosis, or infection caused by parvovirus or cytomegalovirus. In these conditions, the placenta is homogeneously thickened. In other cases placentas are thick but inhomogeneous. Partial mole is a classic example. The thickened placenta contains edematous villi, which appear as multiple, small, anechoic placental cysts (Chap. 13, p. 239). Cystic vesicles also are seen with *placental mesenchymal dysplasia*. In this rare condition, vesicles correspond to enlarged stem villi. However, unlike molar pregnancy, trophoblast proliferation is not excessive, and chromosomal complements are diploid (Woo, 2011).

Rather than villous enlargement, inhomogeneous placentomegaly often may result from collections of blood or fibrin, which impart heterogeneity to the placenta. Examples of this are discussed later and include massive perivillous fibrin deposition, intervillous or subchorionic thromboses, and large retroplacental hematomas (p. 110).

EXTRACHORIAL PLACENTATION

The chorionic plate normally extends to the periphery of the placental disc and has a diameter similar to that of the basal plate. With extrachorial placentation, however, the chorionic plate fails to extend to this periphery and leads to a chorionic plate that is smaller than the basal plate (Fig. 6-2). Circummarginate and circumvallate placentas are the two types. In a *circummarginate placenta*, fibrin and old hemorrhage lie between the placental disc and the overlying sheer amniochorion. In contrast, with a *circumvallate placenta*, the chorionic plate periphery is a thickened, opaque, gray-white circular ridge composed of a double fold of chorion and amnion.

Sonographically, the circumvallate fold can be seen as a thick, linear band of echoes extending from one placental edge to the other. On cross section, however, it appears as two "shelves," with each lying above an opposing placental margin (see Fig. 6-2). This anatomy can help differentiate this shelf from other bands (Table 6-2).

In small observational studies of circumvallate placenta diagnosed postpartum, it was associated with increased risk for antepartum bleeding, abruption, fetal demise, and preterm birth (Suzuki, 2008; Taniguchi, 2014). In a prospective sonographic investigation of 17 cases, however, Shen and associates (2007a) found most circumvallate placentas to be transient. Persistent cases were benign. In general, most otherwise uncomplicated pregnancies with either type of extrachorial placentation have normal outcomes, and no increased surveillance is usually required.

CIRCULATORY DISTURBANCES

Functionally, placental perfusion disorders can be grouped into: (1) those in which maternal blood flow to or within the intervillous space is disrupted, and (2) those with disturbed fetal blood flow through the villi. These lesions are frequently identified in the normal, mature placenta. Although they can limit maximal placental blood flow, functional reserve within the placental prevents harm in most cases. Indeed, some estimate that up to 30 percent of placental villi can be lost without untoward fetal effects (Fox, 2007). If extensive, however, these lesions can profoundly limit fetal growth.

Lesions that disrupt perfusion are frequently seen grossly or sonographically, whereas smaller lesions are seen only histologically. With sonography, many of these, such as subchorionic fibrin deposition, perivillous fibrin deposition, and intervillous thrombosis, appear as focal sonolucencies within the placenta. Greater magnetic resonance (MR) imaging use in pregnancy has permitted detection and further characterization of these lesions (Bockoven, 2020; Capuani, 2017). Importantly, in the absence of maternal or fetal complications, small isolated placental sonolucencies are considered incidental findings.

TABLE 6-2. Sonographic Bands During Pregnancy

Condition	Sonographic Findings
Normal early chorioamnionic separation	Crescent-shaped amnion mirrors the chorion's curve; distinct from the fetus; fuses after 16 weeks' gestation
Subchorionic hematoma	Echogenic blood lies between the myometrium and chorioamnion, which appears as a thin band crossing the cavity. Hemorrhage and band resolve over time
Uterine synechiae (Amnionic sheet)	2.5- to 4.0-mm-thick, broad-based band crosses the cavity. Appears shelflike on cross section
Circumvallate placenta	Broad-based band extends from one placental edge to the other, just above the placental surface. Appears shelflike on cross section
Amnionic band	Thin strands cross and appear to tether fetal parts
Pseudoamnionic band syndrome	Thin strands tether fetal parts and form after fetoscopic surgeries or amniocenteses that are complicated by membrane laceration
Uterine septum	Chorioamnionic sac of an early pregnancy fills one horn of a septate or partial bicornuate uterus. Thick band of echoes, which may be wedge-shaped, extend from uterine fundus in midline
Membranes from vanishing twin	Depending on chorionicity either a thin amnion or thicker chorioamnion spans the cavity
Placental vessels supported by membranes: velamentous insertion, succenturiate lobe	With grayscale imaging, vessels appear as bands. Color Doppler will clarify (see Figs. 6-1 and 6-6)

Modified from Dashe, 2017; Lafitte, 2017.

■ Maternal Blood Flow Disruption

Subchorionic Fibrin Deposition

These collections are caused by slowing of maternal blood flow within the intervillous space. In the upper portion of this space near the chorionic plate, blood stasis is prominent and leads to subsequent fibrin deposition. In viewing the placental fetal surface, subchorionic lesions are seen as white or yellow, firm, round, elevated plaques just beneath the chorionic plate.

Perivillous Fibrin Deposition

Stasis of maternal blood flow around an individual villus also results in fibrin deposition and can lead to diminished villous oxygenation and necrosis of syncytiotrophoblast (Fig. 6-3). These small yellow-white placental nodules are grossly visible within the parenchyma of a sectioned placenta. Within limits, these reflect normal placental aging. Deposition that affects >25 percent of villi is associated with fetal-growth restriction and adverse neonatal outcomes (Devisme, 2017; Spinillo, 2019).

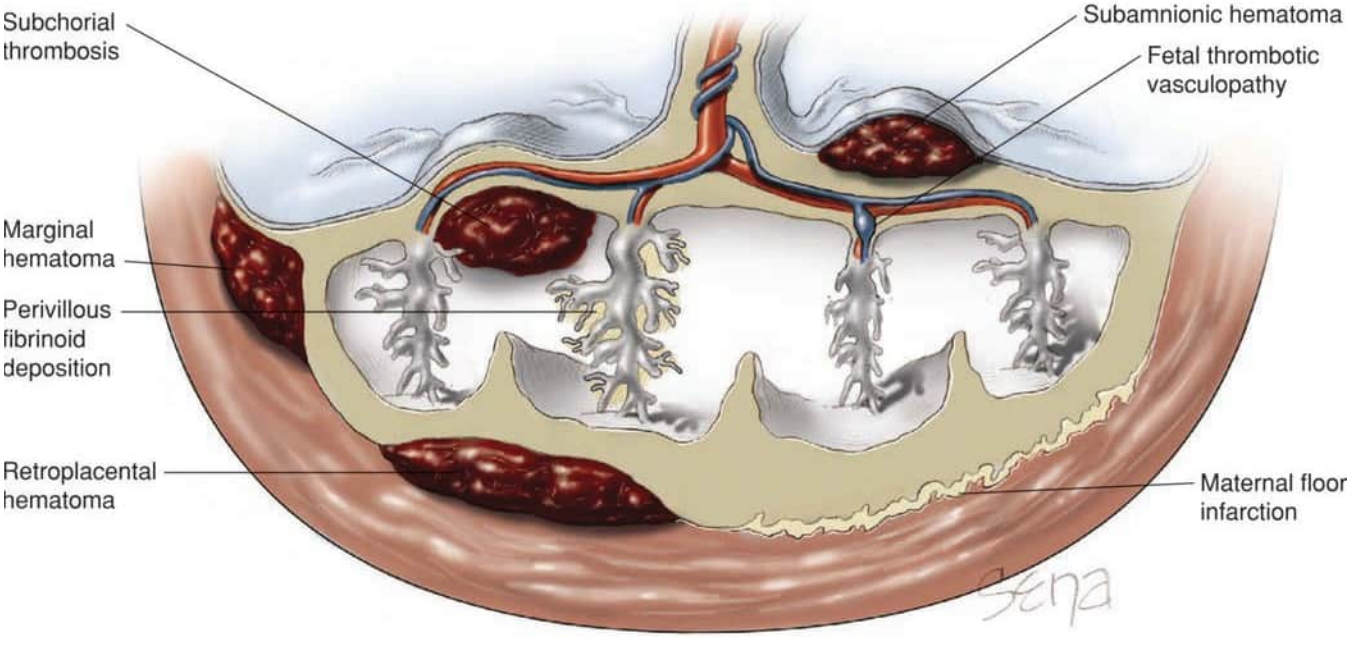


FIGURE 6-3 Potential sites of maternally and fetally related placental circulatory disturbances.

Maternal Floor Infarction. This extreme variant of perivillous fibrin deposition is a dense fibrinoid layer within the placental basal plate and is erroneously termed an infarction. *Maternal floor infarction* has a thick, yellow or white, firm corrugated surface that impedes normal maternal blood flow into the intervillous space. In specific cases that extend up and beyond the basal plate to entrap villi and obliterate the intervillous space, the term *massive perivillous fibrin deposition* is used. The etiopathogenesis is unclear, but maternal auto- or alloimmunity appears contributory (Faye-Peterson, 2018; Romero, 2013). Antiphospholipid antibody syndrome and angiogenic factors involved with preeclampsia also have been implicated (Sebire, 2002; Whitten, 2013).

These lesions are not reliably imaged with prenatal sonography, but they may create a thicker basal plate. Affected pregnancies are associated with miscarriage, fetal-growth restriction, preterm delivery, and stillbirth (Andres, 1990; Mandsager, 1994). Importantly, these adverse outcomes can recur in subsequent pregnancies.

Intervillous Thrombus

This is a collection of coagulated maternal blood normally found in the intervillous space mixed with fetal blood from a break in a villus. Grossly, these round or oval collections vary in size up to several centimeters. They appear red if recent or white-yellow if older, and they develop at any placental depth. Intervillous thrombi are common and typically not associated with adverse fetal sequelae. These reflect potential communication between maternal and fetal circulations, and thus large lesions are one cause of elevated maternal serum alpha-fetoprotein (MSAFP) levels (Table 17-5, p. 338). (Salafia, 1988).

Infarction

Chorionic villi themselves receive oxygen solely from maternal circulation and specifically from blood supplied into the intervillous space. Any uteroplacental disease that diminishes or obstructs this supply can result in infarction of an individual villus. These are common lesions in mature placentas and are benign in limited numbers. If numerous, however, placental insufficiency can develop. When they are thick, centrally located, and randomly distributed, they may be associated with preeclampsia or lupus anticoagulant.

Hematoma

The maternal–placental–fetal unit can develop several hematoma types. As depicted in Figure 6-3, these include: (1) *retroplacental hematoma*—formed between the placenta and its adjacent decidua; (2) *marginal hematoma*—formed between the chorion and decidua at the placental periphery—known clinically as *subchorionic hemorrhage*; (3) *subamnionic hematoma*—derived of fetal vessel origin and found beneath the amnion but above the chorionic plate, and (4) *subchorial thrombus* along the roof of the intervillous space and beneath the chorionic plate. With this last type, *massive subchorionic hematomas* are also known as *Breus moles.*

Sonographically, hematomas evolve with time and appear hyperechoic to isoechoic in the first week after hemorrhage, hypoechoic at 1 to 2 weeks, and finally, anechoic after 2 weeks. Most subchorionic hematomas visible sonographically are fairly small and of no clinical consequence (Naert, 2019). However, extensive retroplacental, marginal, and subchorial collections are associated with higher rates of miscarriage, stillbirth, placental abruption, and preterm delivery (Tuuli, 2011). In essence, placental abruption is a large, clinically significant retroplacental hematoma.

■ Fetal Blood Flow Disruption

Fetal Vascular Malperfusion

Placental lesions that arise from fetal circulatory disturbances are also depicted in Figure 6-3. Normally, deoxygenated fetal blood flows from the two umbilical arteries into arteries within the chorionic plate. These surface arteries divide and send branches out across the placental surface. These eventually supply individual stem villi. Remember that fetal blood is oxygenated within each villus by passive diffusion of oxygen from maternal blood contained within the intervillous space. Thus, with fetal vessel thrombosis, portions of the villus distal to the obstruction become nonfunctional. Normally, thrombi in limited numbers are found in mature placentas. If many villi are affected, which can be seen with preeclampsia, the fetus may suffer growth restriction, stillbirth, or nonreassuring fetal heart rate patterns (Chisholm, 2015; Lepais, 2014; Saleemuddin, 2010).

Villous Vascular Lesions

Villous capillaries show a spectrum of histological lesions. *Chorangiosis* describes an increased number of capillaries within terminal villi. Its definition requires ≥10 capillaries to be present in ≥10 villi in ≥10 fields viewed through a 10× lens (Altshuler, 1984). Clinically, long-standing hypoperfusion or hypoxia is thought to be causative (Stanek, 2016). *Focal chorangiosis* is increased capillary vascularity in a significant portion of the placenta but not diffusely. In one small study, lower Apgar scores and fetal vascular malperfusion were associated outcomes (Sung, 2019). Prenatal detection of chorangiosis has been reported (Inubashiri, 2017). *Chorangiomatosis* describes increased capillary number in stem villi, but terminal villi are spared. This finding has been linked with fetal-growth restriction and anomalies (Bagby, 2011). Despite these associations, the clinical significance of both vascular conditions remains unclear. *Chorioangiomas* are described subsequently.

Subamnionic Hematoma

As noted earlier, these hematomas lie between the chorionic plate and amnion. They most often are acute iatrogenic events of no clinical consequence during third-stage labor when cord traction ruptures a vessel near the cord insertion.

Large, chronic antepartum lesions may cause fetomaternal hemorrhage or fetal-growth restriction (Deans, 1998). They also may be confused with other placental masses such as chorioangioma. In most cases, color Doppler interrogation will show absent internal blood flow within a hematoma and permit differentiation (Sepulveda, 2000).

PLACENTAL CALCIFICATION

Calcium salts can be deposited throughout the placenta but are most common on the basal plate. Calcification accrues

with advancing gestation, and greater degrees are associated with smoking and higher maternal serum calcium levels (Bedir Findik, 2015). These hyperechoic deposits can easily be seen sonographically, and a grading scale from 0 to 3 reflects increasing calcification with increasing numerical grade (Grannum, 1979). Following this scheme, a grade 0 placenta is homogeneous, lacks calcification, and displays a smooth, flat chorionic plate. A grade 1 placenta has scattered echogenicities and subtle chorionic plate undulations. Grade 2 shows echogenic stippling at the basal plate. Large, echogenic comma shapes originate from an indented chorionic plate, but their curve falls short of the basal plate. Last, a grade 3 placenta has echogenic indentations extending from the chorionic plate to the basal plate, which create discrete components that resemble cotyledons. Basal plate densities also increase.

This grading scale poorly predicts neonatal outcome near term (McKenna, 2005; Mirza, 2018). However, data from two small studies link grade 3 placenta prior to 32 weeks with stillbirth and some other adverse pregnancy outcomes (Chen, 2011, 2015; Mirza, 2018).

PLACENTAL TUMORS

Chorioangioma

These benign tumors have components similar to the blood vessels and stroma of the chorionic villus. Also called chorangiomas, these placental tumors have an incidence that approximates 1 percent (Guschmann, 2003). In some cases, fetal-to-maternal hemorrhage across tumor capillaries leads to elevated levels of MSAFP. This typically prompts sonographic evaluation to exclude a neural-tube defect, which also shows high MSAFP levels. Sonographically, chorangiomas appear as a well-circumscribed, rounded, predominantly hypoechoic lesion lying near the chorionic plate and protruding into the amnionic cavity (Fig. 6-4). Documenting increased blood flow by color Doppler helps to distinguish these lesions from other placental masses such as hematoma, partial hydatidiform mole, teratoma, metastases, and leiomyoma (Prapas, 2000). Although rare, *chorangiocarcinoma* tumors mirror chorioangiomas clinically (Huang, 2015).

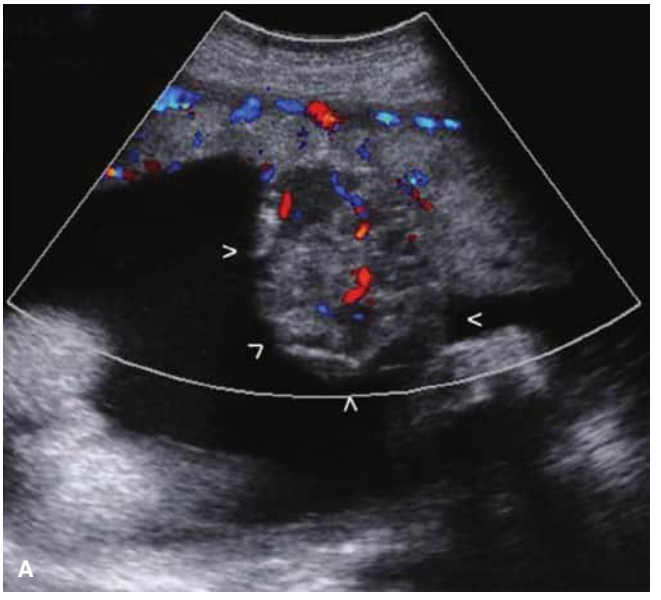
Small chorioangiomas are usually asymptomatic. Large tumors, typically those measuring >4 cm, can create significant arteriovenous shunting within the placenta to cause high-output heart failure, hydrops, and fetal death (Al Wattar, 2014). Compression or shearing of fetal erythrocytes within tumor vessels can lead to hemolysis and microangiopathic anemia (Bauer, 1978). Hydramnios, preterm delivery, and fetal-growth restriction are other sequelae (Dong, 2020). Large tumor size and fetal hydrops are the primary determinants and signal a potential adverse perinatal outcome (Buca, 2020).

Grayscale and color Doppler interrogation of the placenta and amnionic fluid volume are used to identify these tumors. Diagnostic tools that can affirm associated fetomaternal hemorrhage include MSAFP level and Kleihauer-Betke stain (Chap. 18, p. 358). With fetal concern, echocardiography assesses cardiac function, whereas middle cerebral artery interrogation is used to identify fetal anemia.

Several fetal therapies interfere with the vascular supply to the tumor and reverse fetal heart failure. At specialized perinatal centers, endoscopic laser ablation of feeder vessels to the tumor is most frequently used and is associated with favorable fetal outcomes (Hosseinzadeh, 2015). Discussed in Chapter 16, fetal transfusion can treat serious anemia, amnioreduction can temporize hydramnios, and digoxin therapy can assist fetal heart failure.

Metastatic Tumors

Maternal malignant tumors rarely metastasize to the placenta. Of those that do, melanomas, leukemias and lymphomas,



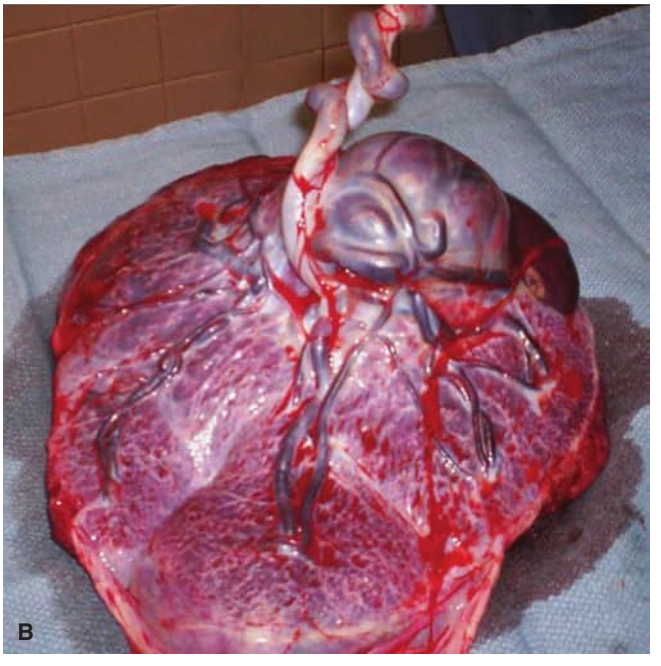


FIGURE 6-4 Placental chorioangioma. **A.** Color Doppler imaging displays blood flow through a large chorioangioma with its border outlined by white arrows. **B.** Grossly, the chorioangioma is a round, well-circumcised mass protruding from the fetal surface.

and breast cancer are the most common (Al-Adnani, 2007). Tumor cells usually are confined within the intervillous space. As a result, metastasis to the fetus is uncommon but is most often seen with melanoma (Alexander, 2003).

Similarly, cases in which fetal malignancy metastasizes to the placenta are rare (Reif, 2014). These are predominantly fetal neuroectodermal tumors, and only one case in the literature describes transplantation of tumor to the maternal uterus (Nath, 1995).

AMNIOCHORION

Chorioamnionitis

Normal genital-tract flora can colonize and infect the membranes, umbilical cord, and eventually the fetus. Bacteria most commonly ascend after prolonged membrane rupture and during labor to cause infection. Organisms initially infect the chorion and adjacent decidua in the area overlying the internal os. Subsequently, progression leads to full-thickness involvement of the membranes—chorioamnionitis. Organisms often then spread along the chorioamnionic surface to colonize and replicate in amnionic fluid. Inflammation of the chorionic plate and of the umbilical cord—*funisitis*—may follow (Kim, 2015; Redline, 2012).

Most commonly, chorioamnionitis is microscopic or occult and caused by a wide variety of microorganisms. This is frequently cited as a possible explanation for many otherwise unexplained cases of ruptured membranes, preterm labor, or both (Chap. 45, p. 789). In some cases, gross infection is characterized by visible membrane clouding and is sometimes accompanied by a foul odor that depends on bacterial species.

Other Membrane Abnormalities

Amnion nodosum is a condition characterized by numerous small, light-tan nodules affixed to the amnion that overlies the chorionic plate. These may be scraped off the fetal surface and contain deposits of fetal squames and fibrin that reflect prolonged and severe oligohydramnios (Adeniran, 2007).

Two notable bands can be formed by the fetal membranes. First, *amnionic band sequence* is an anatomical disruption sequence in which amnion bands tether, constrict, or amputate fetal parts. Bands may form spontaneously or follow fetal surgery procedures (see Table 6-2) (Lafitte, 2017). Amnionic bands commonly cause limb-reduction defects, facial clefts, or encephalocele (Barzilay, 2015; Guzmán-Huerta, 2013). Umbilical cord compromise is another sequela (Barros, 2014). Severe defects of the spine or ventral wall that accompany amnionic bands suggest a *limb-body wall complex*, described in Chapter 15 (p. 297).

Sonography often first identifies the sequelae of this sequence rather than the bands themselves. As with any fetal anomaly, targeted sonography is indicated. Identification of a limb-reduction defect, an encephalocele in an atypical location, or an extremity with edema or positional deformity should prompt careful evaluation for amnionic bands.

Management depends on the degree of anatomic deformity (Society of Maternal–Fetal Medicine, 2019). Fetoscopic laser interruption of the band may be suitable in highly selected antepartum cases (Gueneuc, 2019; Javadian, 2013).

Second, an *amnionic sheet* in contrast is formed by normal amniochorion draped over a preexisting uterine synechia. Generally, these sheets pose little fetal risk, although slightly higher rates of preterm membrane rupture and placental abruption have been described (Nelson, 2010; Tuuli, 2012).

UMBILICAL CORD

Length

Most umbilical cords at delivery measure 40 to 70 cm long, and very few measure <30 cm or >100 cm. Cord length is influenced positively by both maternal parity and body mass index (Linde, 2018). In retrospective studies, short cords have been linked with congenital malformations and intrapartum distress (Krakowiak, 2004; Linde, 2018; Yamamoto, 2016). Excessively long cords are linked with cord entanglement or prolapse and with fetal anomalies (Olaya-C, 2015; Rayburn, 1981).

Because antenatal determination of cord length is technically limited, cord diameter has been evaluated as a predictive marker for fetal outcomes. Some have linked lean cords with poor fetal growth and large-diameter cords with macrosomia (Proctor, 2013). However, the clinical utility of this parameter is still unclear (Cromi, 2007; Raio, 2003).

Coiling

Cord coiling characteristics are not currently part of standard sonographic evaluation. Usually the umbilical vessels spiral through the cord in a sinistral, that is, left-twisting direction (Fletcher, 1993; Lacro, 1987). The number of complete coils per centimeter of cord length is termed the *umbilical coiling index—UCI* (Strong, 1994). A normal, antepartum, sonographically derived UCI is 0.4, and this contrasts with a normal, postpartum, physically measured value of 0.2 (Sebire, 2007). UCIs <10th percentile are considered *hypocoiled,* and those >90th percentile are *hypercoiled*.

Clinically, the significance of coiling extremes is controversial. Some studies evaluating large, unselected cohorts find no associations between UCI values and poor neonatal outcome (Jessop, 2014; Pathak, 2010). In others, extremes are linked with various adverse outcomes but most consistently with intrapartum fetal heart rate abnormalities, preterm labor, or fetal-growth restriction (Chitra, 2012; de Laat, 2006; Pergialiotis, 2019).

Vessel Number

Counting cord vessel number is a standard component of anatomical evaluation during fetal sonographic examination and immediately after delivery (Fig. 6-5). Embryos initially have two umbilical veins. In the first trimester, the right vein typically atrophies to leave one large vein to accompany the two, thick-walled umbilical arteries. Four-vessel cords are rare and often associated with congenital anomalies (Puvabanditsin,

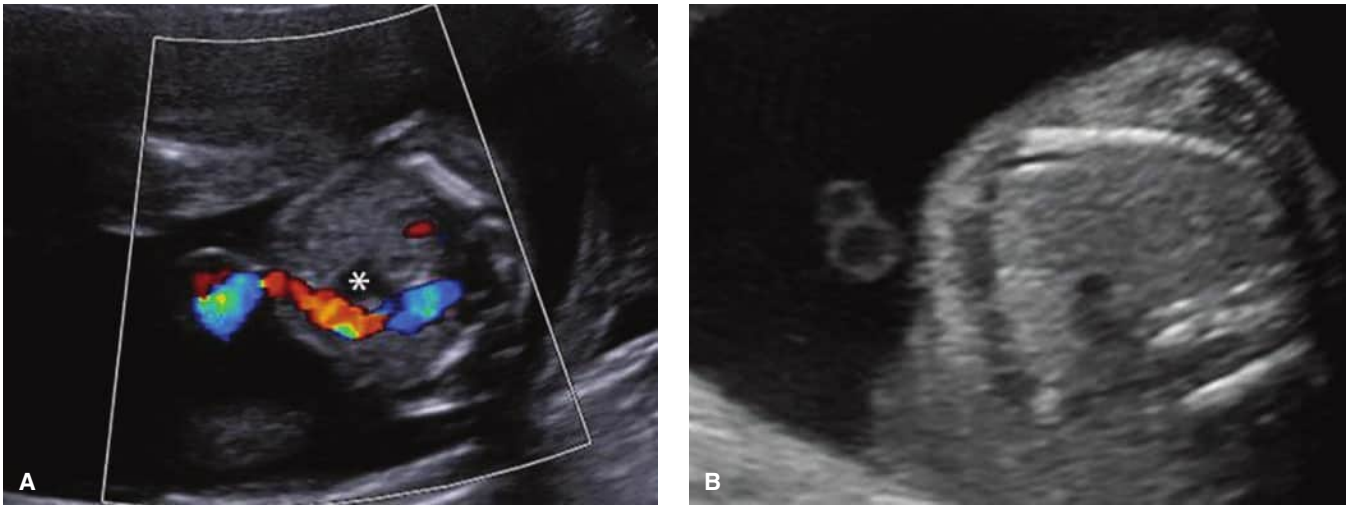


FIGURE 6-5 Two umbilical arteries are typically documented sonographically in the second trimester. They encircle the fetal bladder (*asterisk*) as extensions of the superior vesical arteries. **A.** In this color Doppler sonographic image, a single umbilical artery, shown in red, runs along the bladder wall before joining the umbilical vein (blue) in the cord. Remember with color Doppler that color signifies only blood flow direction relative to the transducer. **B.** A cross section of a floating cord segment shows the two vessels of the cord. The smaller circle is the single umbilical artery and the larger circle, the umbilical vein.

2011). If it is an isolated finding, however, prognosis can be good (Avnet, 2011).

The most common aberration is that of a single umbilical artery (SUA). Its cited incidence is 0.63 percent in liveborn neonates, 1.92 percent in perinatal deaths, and 3 percent in twins (Heifetz, 1984). Fetuses with major malformations frequently have an SUA. Thus, its identification often prompts consideration for targeted sonography and possibly fetal echocardiography. The most frequent anomalies are cardiovascular and genitourinary (Hua, 2010; Murphy-Kaulbeck, 2010). In an anomalous fetus, an SUA greatly increases the aneuploidy risk, and amniocentesis is recommended for karyotype assessment (Dagklis, 2010).

If targeted sonography finds otherwise normal anatomy, an isolated SUA in an otherwise low-risk pregnancy does not significantly raise the fetal aneuploidy risk. However, as an isolated finding, it has been associated with fetal-growth restriction and perinatal death in some but not all studies (Chetty-John, 2010; Ebbing, 2019; Voskamp, 2013). Thus, clinical monitoring of growth is reasonable, but the value of sonographic surveillance is unclear.

In contrast, a fused umbilical artery with a shared lumen is rare. It arises from failure of the two arteries to split during embryological development. The common lumen may extend through the entire cord, but, if partial, it is typically found near the placental insertion site (Yamada, 2005). In one report, these malformations were associated with a higher incidence of marginal or velamentous cord insertion but not of congenital fetal anomalies (Fujikura, 2003).

Found in most placentas, the *Hyrtl anastomosis* is a connection between the two umbilical arteries, and it lies near the cord's insertion into the placenta. This anastomosis acts physiologically to equalize pressures between the arteries (Gordon, 2007). The resulting redistribution of pressure gradients and blood flow improves placental perfusion, especially during uterine contractions or during compression of one umbilical artery. Fetuses with an SUA lack this safety valve (Raio, 1999, 2001).

Remnants and Cysts

Several structures are housed in the umbilical cord during fetal development, and their remnants may be seen when the mature cord is inspected transversely. Indeed, in grossly sectioned cords, remnants of the allantoic duct, vitelline duct, and embryonic vessels are found in 25 to 50 percent (Grottling, 2019; Jauniaux, 1989). These are not associated with congenital malformations or perinatal complications.

Cysts occasionally are found along the course of the cord. They are designated according to their origin. *True cysts* are epithelium-lined remnants of the allantoic or vitelline ducts and tend to be located closer to the fetal insertion site. In contrast, the more common *pseudocysts* form from local degeneration of Wharton jelly and occur anywhere along the cord. Both have a similar sonographic appearance. Single umbilical cord cysts identified in the first trimester tend to resolve completely, however, multiple cysts may portend miscarriage or aneuploidy (Ghezzi, 2003; Hannaford, 2013). Cysts persisting beyond this time are associated with a risk for structural defects and chromosomal anomalies (Bonilla, 2010; Zangen, 2010).

Insertion

The cord normally inserts centrally into the placental disc, but eccentric, marginal, or velamentous insertions are variants. Of these, eccentric insertions in general pose no identifiable fetal risk. Marginal insertion is a common variant—sometimes referred to as a *battledore placenta*—in which the cord anchors at the placental margin. In one population-based study, the rate was 6 percent in singleton gestations and 11 percent in twins (Ebbing, 2013). This common insertion variant rarely causes problems, but it and velamentous insertion occasionally result in the cord being pulled off during delivery of the placenta (Ebbing, 2015; Luo, 2013). In monochorionic twins, marginal insertion may be associated with weight discordance (Kent, 2011).

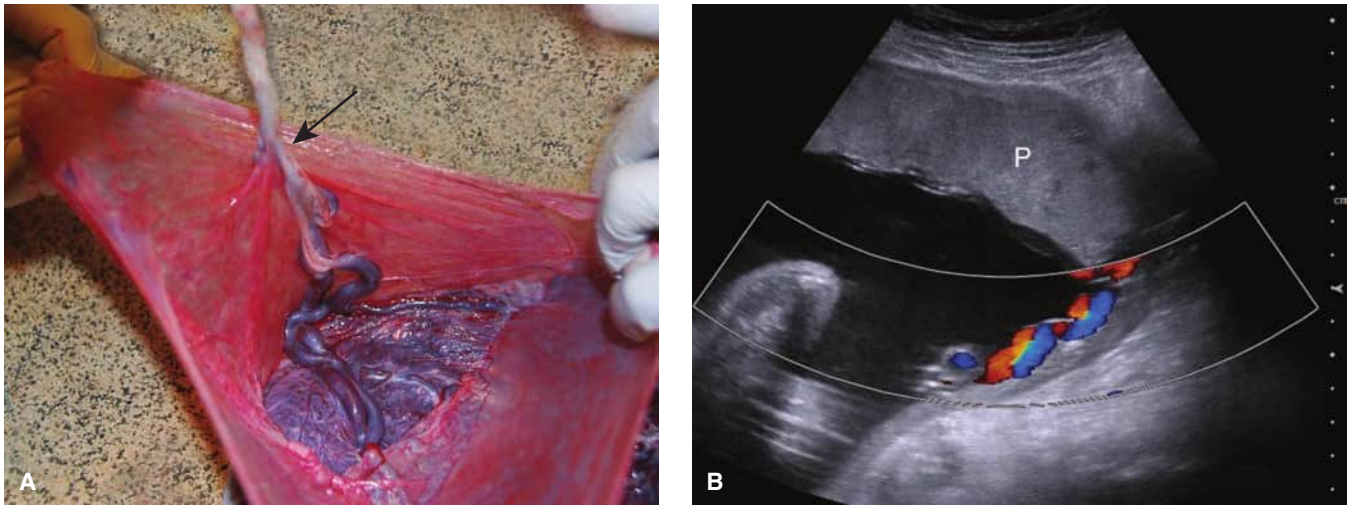


FIGURE 6-6 Velamentous cord insertion. **A.** The umbilical cord inserts into the membranes (*arrow*). From here, the cord vessels branch and are supported only by membrane until they reach the placental disc. **B.** When viewed sonographically and using color Doppler, the cord vessels appear to lie against the myometrium as they travel to insert into the margin of the placental disc (*P*).

With velamentous insertion, the umbilical vessels characteristically travel within the membranes before reaching the placental margin (Fig. 6-6). The incidence of velamentous insertion approximates 1 percent but is 6 percent with twins (Ebbing, 2013). It is more commonly seen with placenta previa (Papinniemi, 2007; Räisänen, 2012). Antenatal diagnosis is possible sonographically, and cord vessels are seen traveling along the uterine wall before entering the placental disc. Clinically, vessels are vulnerable to compression, which may lead to fetal hypoperfusion and acidemia. Higher associated rates of low Apgar scores, stillbirth, preterm delivery, and small for gestational age have been noted (de Los Reyes, 2018; Ebbing, 2017; Esakoff, 2015; Vahanian, 2015). Accordingly, monitoring of fetal growth is reasonable either clinically or sonographically (Vintzileos, 2015).

Last, with the rare furcate insertion, umbilical vessels lose their protective Wharton jelly shortly before they insert. As a result, they are covered only by an amnion sheath and prone to compression, twisting, and thrombosis.

Vasa Previa

With this condition, vessels travel within the membranes and overlie the cervical os. There, they can be torn with cervical dilation or membrane rupture, and laceration can lead to rapid fetal exsanguination. Over the cervix, vessels can also be compressed by a presenting fetal part (Matsuzaki, 2019). Vasa previa may be more common than previously estimated, and rates are 1 case in 338 to 365 pregnancies (Hasegawa, 2012; Klahr, 2019). Vasa previa is classified as type 1, in which vessels are part of a velamentous cord insertion, and type 2, in which involved vessels span between portions of a bilobate or a succenturiate placenta (Catanzarite, 2001). Two other risks are conception with in vitro fertilization and second-trimester placenta previa, with or without later migration (Baulies, 2007; Schachter, 2003).

Compared with intrapartum diagnosis, antepartum diagnosis greatly improves the perinatal survival rate, which ranges from 97 to 100 percent (Oyelese, 2004; Swank, 2016; Zhang, 2021). Thus, vasa previa is ideally identified early, although this is not always possible. Effective screening for vasa previa begins during scheduled midtrimester sonographic examination. In suspicious cases, transvaginal sonography is added and shows cord vessels inserting into the membranes and vessels running above the cervical internal os (Fig. 6-7). Routine color Doppler interrogation of the placental cord insertion site, particularly in cases of placenta previa or low-lying placenta, may aid its detection. With this, the vessel waveform reflects the fetal heart rate. In one systematic review, the median prenatal detection rate was 93 percent (Ruiter, 2015).

Once vasa previa is identified, subsequent imaging is reasonable because up to 39 percent of cases ultimately resolve (Erfani, 2019; Klahr, 2019). Bed rest apparently has no added advantage. Antenatal corticosteroids can be provided as indicated or given prophylactically at 28 to 32 weeks' gestation to cover possible urgent preterm delivery. Antenatal hospitalization may be considered at 30 to 34 weeks to permit surveillance and expedited delivery for labor, bleeding, or rupture of membranes. Data supporting this are limited, and admission may best serve women with risk factors that portend early delivery (Society for Maternal-Fetal Medicine, 2015). A few cases of antepartum fetoscopic surgery with vessel laser ablation are described (Hosseinzadeh, 2015; Johnston, 2014). However, current practice is early scheduled cesarean delivery. The American College of Obstetricians and Gynecologists (2021) recommends cesarean delivery at 34 to 36 weeks' gestation.

At delivery, the fetus is expeditiously delivered after the hysterotomy incision in case a vessel is lacerated during uterine entry. Delayed cord clamping is not encouraged.

In all pregnancies, otherwise unexplained vaginal bleeding either antepartum or intrapartum should prompt consideration of vasa previa and a lacerated fetal vessel. In many cases, bleeding is rapidly fatal, and neonatal salvage is not possible. With less hemorrhage, however, it may be possible to distinguish fetal versus maternal bleeding. Various tests can be used, and

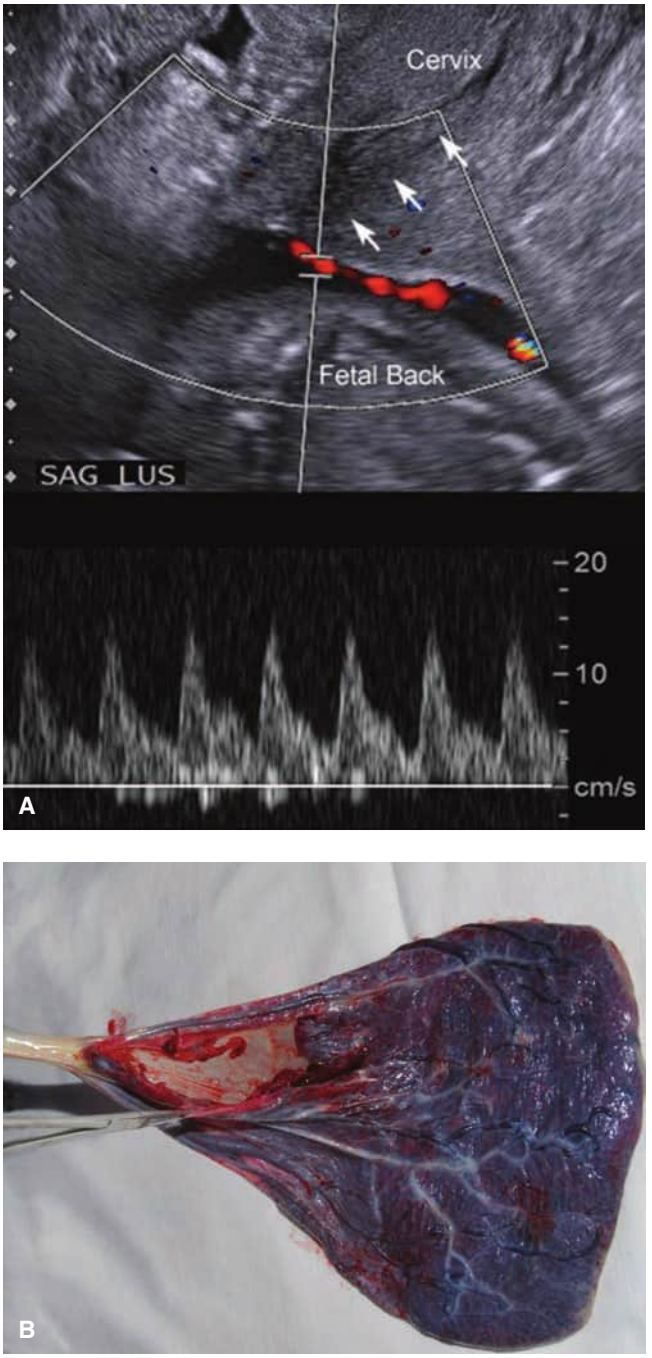


FIGURE 6-7 Vasa previa. **A.** Using color Doppler, an umbilical vessel (*red linear structure*) is seen overlying the internal os and cervical canal (*arrows*). At the bottom, the Doppler waveform seen with this vasa previa has the typical appearance of an umbilical artery. **B.** The amniotomy site (*held open by hemostat*), which was created at the time of cesarean hysterotomy, illustrates how fetal vessels may be lacerated and why fetal delivery should be prompt (Reproduced with permission from Dr. Julie Lo.)

each relies on the increased resistance of fetal hemoglobin to denaturing by alkaline or acid reagents (Odunsi, 1996).

Knots, Strictures, and Loops

Various mechanical abnormalities in the cord can impede blood flow and sometimes cause fetal harm. Of these, *true knots* are found in approximately 1 percent of births. These form from fetal movement, and associated risks include hydramnios and diabetes mellitus (Hershkovitz, 2001; Räisänen, 2013). Knots are especially common and dangerous in monoamnionic twins, which are discussed in Chapter 48 (p. 845). In singleton fetuses, the stillbirth risk is increased four- to tenfold compared with those without knots (Airas, 2002; Sørnes, 2000).

Knots can be found incidentally during antepartum sonography, and a "hanging noose" sign is suggestive (Ramon y Cajal, 2006). Three-dimensional and color Doppler aid diagnostic accuracy (Hasbun, 2007). With these knots, optimal fetal surveillance is unclear but may include umbilical artery Doppler velocimetry, nonstress testing, or subjective fetal movement monitoring (Rodriguez, 2012). Allowing vaginal delivery is suitable, and intrapartum fetal heart rate tracings do not differ from unaffected pregnancies (Carter, 2018). In these cases, cesarean delivery rates are not increased and cord blood acid-base values are usually normal (Airas, 2002; Maher, 1996).

In contrast, *false knots* form from focal redundancy and folding of an umbilical cord vessel rather than knotting. These lack clinical significance.

A cord stricture is a focal narrowing of the diameter that usually develops near the fetal cord insertion site (Peng, 2006). Pathological features typically include absent Wharton jelly at the narrowed segment and obliteration of cord vessels (Sun, 1995). In most instances, the fetus is stillborn (French, 2005). Even less common is a cord stricture caused by an amnionic band.

Cord loops are frequently encountered and are caused by coiling around various fetal parts during movement. A cord around the neck—a *nuchal cord*—is common, and vaginal delivery is suitable. One loop is reported in 20 to 34 percent of deliveries; two loops in 2.5 to 5 percent; and three loops in 0.2 to 0.5 percent (Kan, 1957; Sørnes, 1995; Spellacy, 1966). During labor, up to 20 percent of fetuses with a nuchal cord have moderate to severe variable heart rate decelerations, and these are associated with a lower umbilical artery pH (Hankins, 1987). Decelerations are not relieved by amnioinfusion (Spong, 1996). Cords wrapped around the body can have similar effects (Kobayashi, 2015). Despite their frequency, nuchal cords are not associated with greater rates of adverse perinatal outcome (Henry, 2013; Masad, 2019).

Last, in a *funic presentation,* the umbilical cord is the presenting part. These are uncommon and most often are associated with fetal malpresentation (Kinugasa, 2007). A funic presentation in some cases is identified with placental sonography and color flow Doppler (Ezra, 2003). Overt or occult cord prolapse can complicate labor. Thus, once identified at term, cesarean delivery is typically recommended.

Vascular

Cord hematomas are rare and generally follow rupture of an umbilical vessel, usually the vein, and hemorrhage into the Wharton jelly. Hematomas have been associated with abnormal cord length, umbilical vessel aneurysm, trauma, entanglement, umbilical vessel venipuncture, and funisitis (Gualandri, 2008). Most are identified postpartum, but hematomas are recognized

sonographically as hypoechoic masses that lack blood flow (Chou, 2003). Sequelae include stillbirth or intrapartum abnormal fetal heart rate pattern (Abraham, 2015; Barbati, 2009; Sepulveda, 2005; Towers, 2009). However, case reports have described normal outcomes (Sanchex-Codez, 2018).

Umbilical cord vessel thromboses are rare in utero events and seldom diagnosed antepartum. Approximately 70 percent are venous, 20 percent are venous and arterial, and 10 percent are arterial thromboses (Heifetz, 1988). These all have high associated rates of stillbirth, fetal-growth restriction, and intrapartum fetal distress (Minakami, 2001; Sato, 2006; Shilling, 2014). If these are identified antepartum as hypoechoic masses without blood flow, data from case reports support consideration of prompt delivery of viable-aged fetuses (Kanenishi, 2013).

An *umbilical vein varix* can complicate either the intraamnionic or fetal intraabdominal portion of the umbilical vein. Sonographically and complemented by color Doppler, rare intraamnionic varices show cystic dilation of the umbilical vein that is contiguous with a normal-caliber portion. Of complications, an intraamnionic varix may compress an adjacent umbilical artery or can rupture or thrombose. A systematic review of 250 cases found that approximately one fifth is associated with other anomalies. Isolated cases had reassuring outcomes but typically required antenatal surveillance (di Pasquo, 2018).

The rare *umbilical artery aneurysm* is caused by congenital thinning of the vessel wall with diminished support from Wharton jelly. Indeed, most form at or near the cord's placental insertion site, where this support is absent. These are associated with SUA, trisomy 18, amnionic fluid volume extremes, fetal-growth restriction, and stillbirth (Hill, 2010; Vyas, 2016). At least theoretically, these aneurysms could cause fetal compromise and death by compression of the umbilical vein. With aneurysms measuring >5 cm, the blood reservoir within the aneurysm may pose a risk for high-output heart failure (Matsuki, 2017). These aneurysms may appear sonographically as a cyst with a hyperechoic rim. Within the aneurysm, color flow and spectral Doppler interrogation demonstrate either low-velocity or turbulent nonpulsatile flow (Olog, 2011; Shen, 2007b). Although not codified, management may include fetal karyotyping, antenatal fetal surveillance, and early delivery to prevent stillbirth (Doehrman, 2014). Some recommend delivery by cesarean to avoid aneurysm rupture.

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CHAPTER 7

Embryogenesis and Fetal Development

Contemporary obstetrics incorporates physiology and pathophysiology of the fetus, and its development and environment. As a result, the fetus is considered a patient and is given the same meticulous care provided for the mother. Section 6 is dedicated to the fetal patient, however, virtually every aspect of obstetrics can affect the developing fetus.

GESTATIONAL AGE

Several terms define pregnancy duration and thus fetal age (Fig. 7-1). *Gestational age* or *menstrual age* is the time elapsed since the first day of the last menstrual period (LMP), a time that actually precedes conception. This starting time, which is usually approximately 2 weeks before ovulation and fertilization and nearly 3 weeks before blastocyst implantation, has traditionally been used. Embryologists describe embryofetal development in *ovulation age*, or the time in days or weeks from ovulation. Another term is *postconceptional age,* which is nearly identical to ovulation age.

Until recently, clinicians customarily calculated menstrual age, and with this, term pregnancy averages 280 days or 40 weeks between the first day of the LMP and birth. This corresponds to 9 and 1/3 calendar months. However, menstrual cycle length variability among women renders many of these calculations inaccurate. This realization, combined with the frequent use of first-trimester sonography, has led to more accurate gestational age determination (Duryea, 2015). Much of this change stems from the accuracy of early sonographic measurement. As a result, the American College of Obstetricians and Gynecologists, the American Institute of Ultrasound in Medicine, and the Society for Maternal-Fetal Medicine (2019) together recommend the following:

1. First-trimester sonography is the most accurate method to establish or reaffirm gestational age.
2. In conceptions achieved with in vitro fertilization (IVF), the embryo age and egg transfer date are used.
3. If available, the gestational ages calculated from the LMP and from first-trimester sonography are compared, and the estimated date of confinement (EDC) is recorded and discussed with the patient.
4. The best obstetrical estimate of gestational age at delivery is recorded on the birth certificate.

The embryofetal crown-rump length in the first trimester is accurate ± 5 to 7 days. Thus, if sonographic gestational

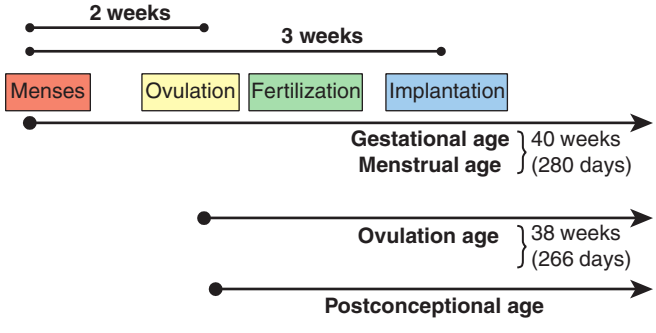

FIGURE 7-1 Terminology used to describe pregnancy duration.

age differs by more than 5 days prior to 9 weeks' gestation, or by more than 7 days later in the first trimester, the EDC is changed. These and discrepant values in the second and third trimester are discussed further in Chapter 14 (p. 248).

Naegele Rule

An EDC based on the LMP can be quickly estimated as follows: add 7 days to the first day of the LMP and subtract 3 months. For example, if the first day of the LMP was October 5, the due date is 10–05 minus 3 (months) plus 7 (days) = 7–12, or July 12 of the following year. This calculation has been termed the *Naegele rule*. The period of gestation can also be divided into three units of approximately 14 weeks each. These three *trimesters* are important obstetrical milestones.

In addition to estimating the EDC with either Naegele rule or "pregnancy wheels," calculator tools in the electronic medical record and smartphone applications can provide a calculated EDC and gestational age. For example, the American College of Obstetricians and Gynecologists (2020) has developed a calculator application that incorporates sonographic criteria and the LMP or embryo transfer date (Chap. 14, p. 248).

EMBRYONIC DEVELOPMENT

The complexity of embryofetal development is immense. Figure 7-2 shows a developmental sequence of various organ systems. New information regarding organ development continues to accrue. For example, imaging techniques help to unravel the contributions of gene regulation and tissue interaction to eventual three-dimensional organ morphology (Anderson, 2016). Others have described the sequence of gene activation that underlies cardiac development (p. 126).

Zygote and Blastocyst Development

During the first 2 weeks after ovulation and then fertilization, the zygote—or preembryo—progresses to the blastocyst stage. The blastocyst implants 6 or 7 days following fertilization. The 58-cell blastocyst differentiates into five cells—*the inner cell mass*, which develops into the embryo. The remaining 53 cells form placental trophoblast. Details of implantation and early development of the blastocyst and placenta are described in Chapter 5 (p. 86).

Embryonic Period

The conceptus is termed an embryo at the beginning of the third week after ovulation and fertilization. Primitive chorionic villi form, and this coincides with the expected day of menses. The embryonic period, during which time organogenesis takes place, lasts 6 weeks. It begins the third week from the LMP and continues through the eighth week. The embryonic disc is well defined, and most pregnancy tests that measure human

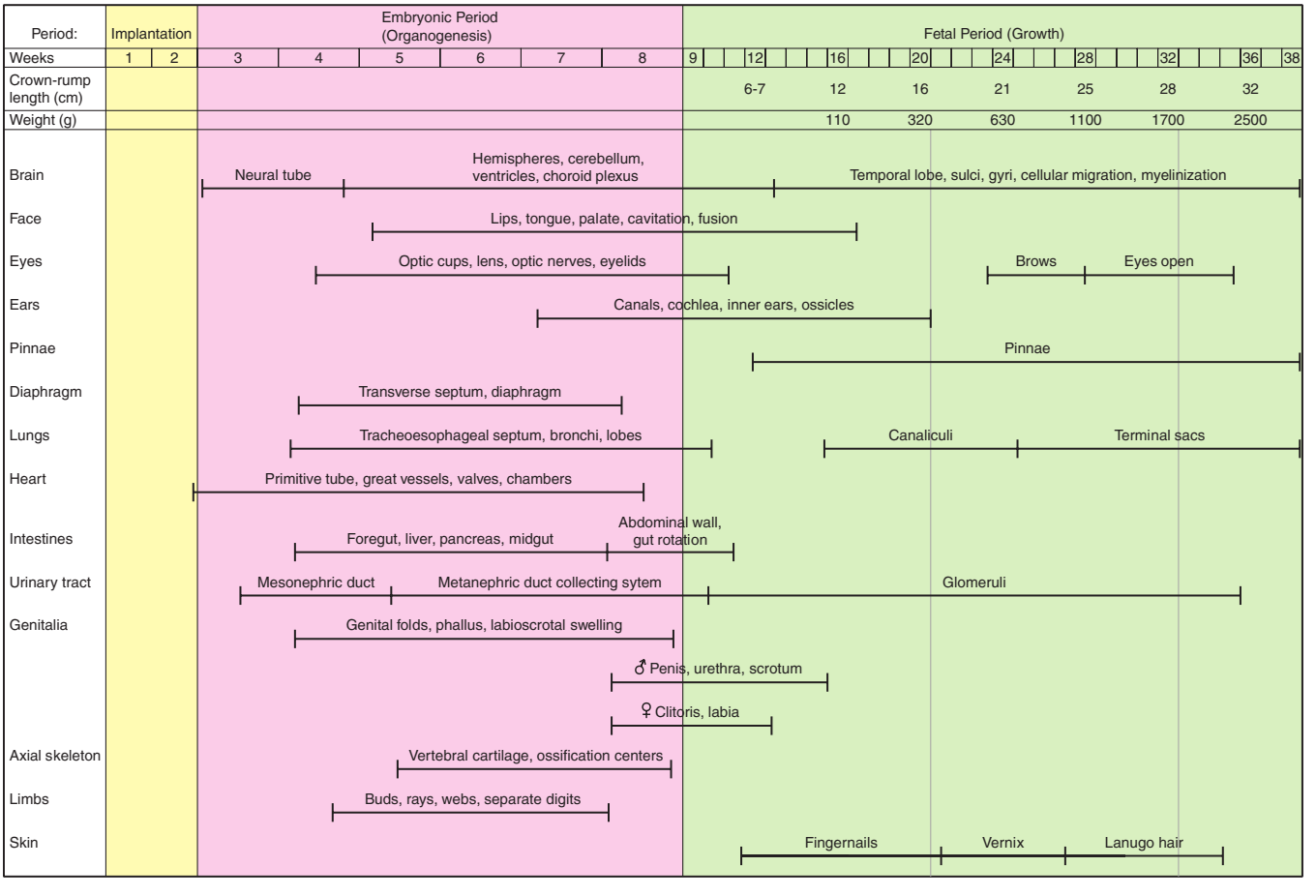

FIGURE 7-2 Embryofetal development according to gestational age determined by the first day of the last menses. Times are approximate.

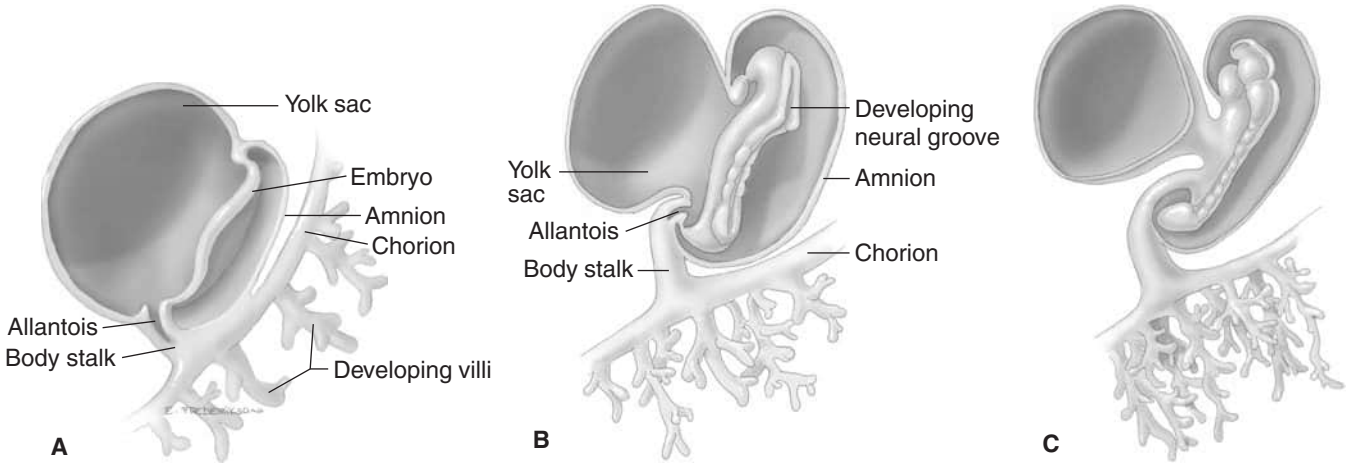

FIGURE 7-3 Early human embryos. Ovulation ages: **A.** 19 days (presomite). **B.** 21 days (7 somites). **C.** 22 days (17 somites). (After drawings and models in the Carnegie Institute.)

chorionic gonadotropin (hCG) become positive by this time. As shown in Figure 7-3, the body stalk is now differentiated. There are villous cores in which angioblastic chorionic mesoderm can be distinguished and a true intervillous space that contains maternal blood.

During the third week, fetal blood vessels in the chorionic villi appear. In the fourth week, a cardiovascular system has formed (Fig. 7-4) (Moore, 2008). Thereby, a true circulation is established both within the embryo and between the embryo and the chorionic villi. Partitioning of the primitive heart begins. Also in the fourth week, the neural plate forms, and it subsequently folds to form the neural tube. By the end of the fifth menstrual week, the chorionic sac measures approximately 1 cm in diameter. The embryo is 3 mm long and can be

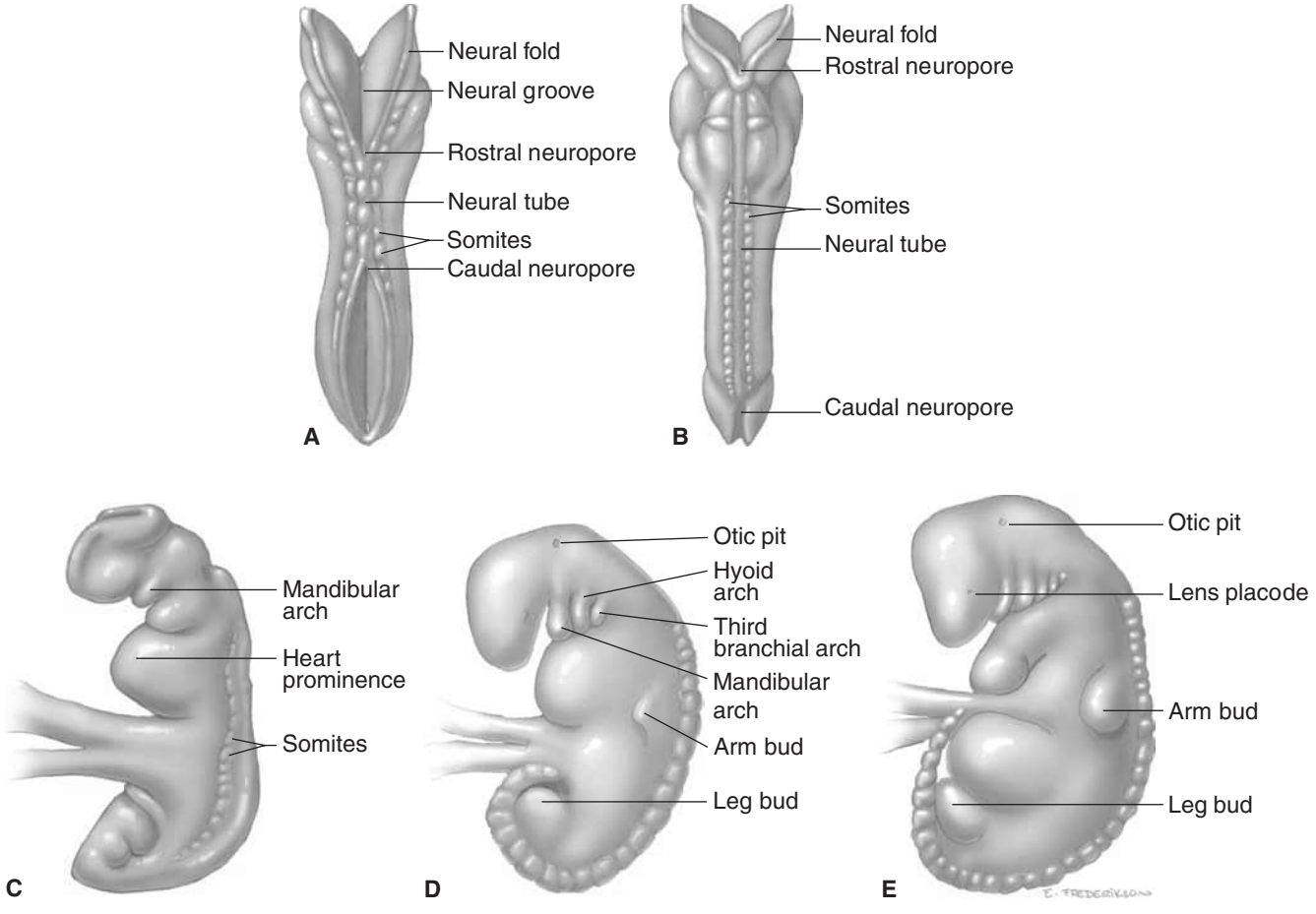

FIGURE 7-4 Three- to four-week-old embryos. **A, B.** Dorsal views of embryos during 22 to 23 days of development showing 8 and 12 somites, respectively. **C–E.** Lateral views of embryos during 24 to 28 days, showing 16, 27, and 33 somites, respectively.

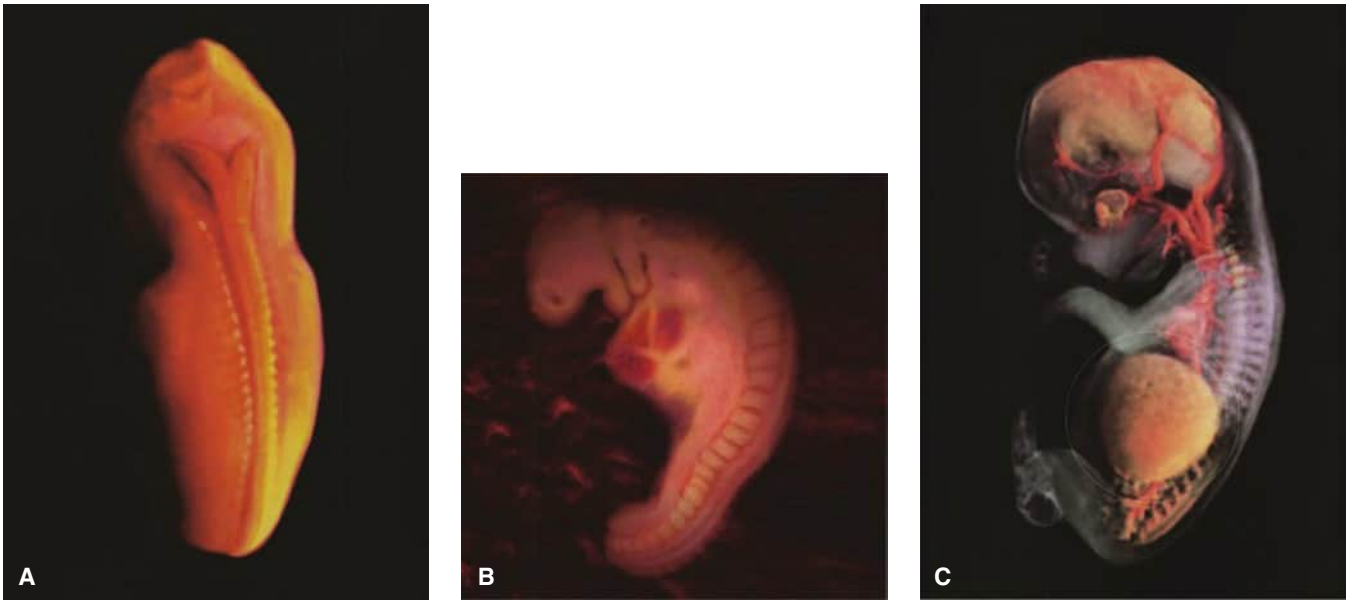

FIGURE 7-5 Embryo photographs. **A.** Dorsal view of an embryo at 24 to 26 days and corresponding to Figure 7-4C. **B.** Lateral view of an embryo at 28 days and corresponding to Figure 7-4D. **C.** Lateral view of embryofetus at 56 days, which marks the end of the embryonic period and the beginning of the fetal period. The liver is within the white, halo circle. (From Werth B, Tsiaras A: From Conception to Birth: A Life Unfolds. New York, Doubleday, 2002.)

measured sonographically. Arm and leg buds have developed, and the amnion is beginning to ensheathe the body stalk, which thereafter becomes the umbilical cord. At the end of the sixth week, the embryo is approximately 9 mm long, and the neural tube has closed (Fig. 7-5). Cardiac motion is almost always discernable sonographically (Fig. 7-6).

The cranial end of the neural tube closes by 38 days from the LMP, and the caudal end closes by 40 days. Thus, the neural tube has closed by the end of the sixth week. And by the end of the eighth week, the crown-rump length approximates 22 mm. Fingers and toes are present, and the arms bend at the elbows. The upper lip is complete, and the external ears form definitive elevations on either side of the head. Three-dimensional images and videos of human embryos from the Multi-Dimensional Human Embryo project can be seen at: embryo.soad.umich.edu/.

FETAL DEVELOPMENT AND PHYSIOLOGY

Fetal Period Epochs

The transition from embryonic to fetal periods occurs at 7 weeks after fertilization, corresponding to 9 weeks after the LMP. At this time, the fetus approximates 24 mm in length, most organ systems have developed, and the fetus enters a period of growth and maturation. These phases are outlined in Figure 7-2.

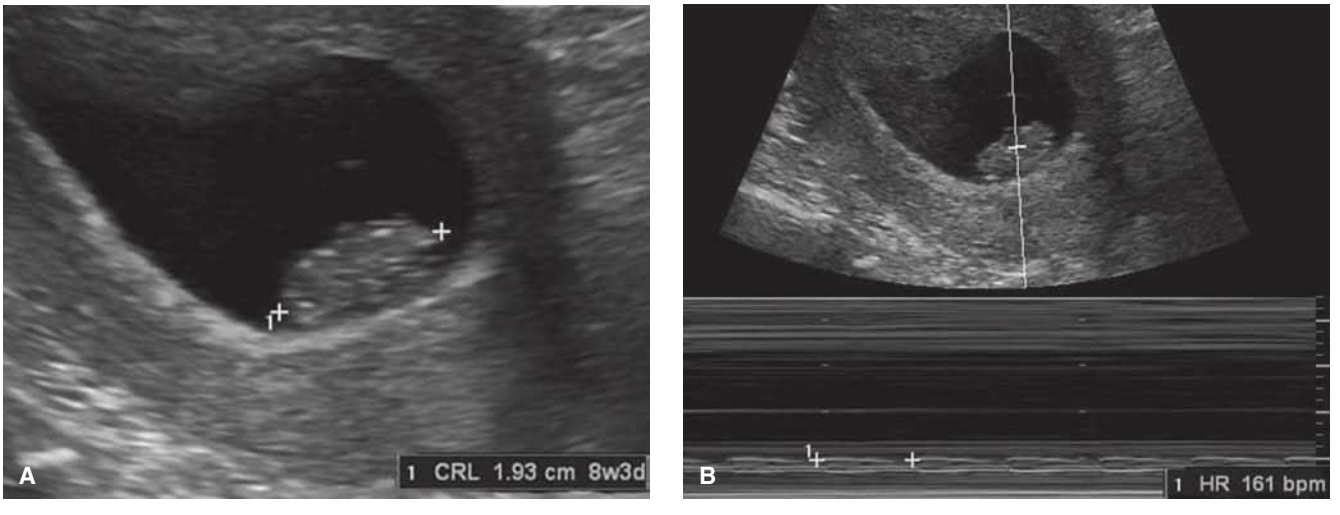

FIGURE 7-6 **A.** This image of an 8-week, 3-day embryo depicts measurement of the crown-rump length, which is 1.93 cm at this gestational age. **B.** Despite the early gestational age, M-mode imaging readily demonstrates embryonic cardiac activity. The heart rate in this image is 161 beats per minute.

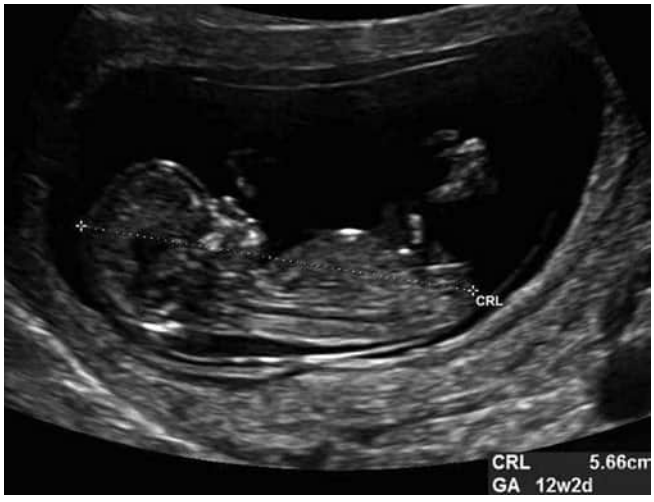

FIGURE 7-7 This image of a 12-week, 2-day embryo depicts measurement of the crown-rump length. The fetal profile, cranium, and a hand and foot also are visible in this image.

12 Gestational Weeks

The uterus usually is just palpable above the symphysis pubis. Fetal growth is rapid, and the fetal crown-rump length is 5 to 6 cm (Fig. 7-7). Centers of ossification have appeared in most fetal bones, and the fingers and toes have become differentiated. Skin and nails develop, and scattered rudiments of hair appear. The external genitalia are beginning to show definitive signs of male or female gender. The fetus begins to make spontaneous movements.

16 Gestational Weeks

Fetal growth slows at this time. The crown-rump length is 12 cm, and the fetal weight approximates 150 g. Clinically, the sonographic crown-rump length is not measured beyond 13 weeks, which corresponds to approximately 8.4 cm. Instead, biparietal diameter, head circumference, abdominal circumference, and femur length are measured. Fetal weight in the second and third trimesters is estimated from a combination of these measurements (Chap. 14, p. 248).

Eye movements begin at 16 to 18 weeks, coinciding with midbrain maturation. By 18 weeks in the female fetus, the uterus is formed and vaginal canalization begins. By 20 weeks in the male, testicles start to descend.

20 Gestational Weeks

This is the midpoint of pregnancy as estimated from the LMP. The fetus now weighs somewhat more than 300 g, and weight increases substantially in a linear manner. From this point onward, the fetus moves approximately every minute and is active 10 to 30 percent of the day (DiPietro, 2005). Brown fat forms, and the fetal skin becomes less transparent. Downy lanugo covers its entire body, and some scalp hair can be seen. Cochlear function develops between 22 and 25 weeks, and this maturation continues for 6 months after delivery.

24 Gestational Weeks

The fetus now weighs almost 700 g. The skin is characteristically wrinkled, and fat deposition begins. The head is still comparatively large, and eyebrows and eyelashes are usually recognizable. By 24 weeks, the secretory type II pneumocytes have initiated surfactant secretion (Chap. 32, p. 587). The canalicular period of lung development, during which the bronchi and bronchioles enlarge and alveolar ducts develop, is nearly completed. Despite this, a fetus born at this time will attempt to breathe, but many will die because the terminal sacs, required for gas exchange, have not yet formed. Although dependent on racial and ethnic factors, and as discussed in Chapter 45 (p. 785), the overall survival rate at 24 weeks barely exceeds 50 percent (Janevic, 2018). By 26 weeks, the eyes open. Nociceptors are present over all the body, and the neural pain system is developed (Kadic, 2012). The fetal liver and spleen are important early sites for hemopoiesis (Fanni, 2018).

28 Gestational Weeks

The crown-rump length approximates 25 cm, and the fetus weighs about 1100 g. The thin skin is red and covered with vernix caseosa. The pupillary membrane has just disappeared from the eyes. Isolated eye blinking peaks at 28 weeks. The bone marrow now becomes the major site of hemopoiesis. The otherwise normal neonate born at this age has a 90-percent chance of survival without physical or neurological impairment.

32 and 36 Gestational Weeks

At 32 weeks, the fetus has attained a crown-rump length approximating 28 cm and a weight of about 1800 g. The skin surface is still red and wrinkled. In contrast, by 36 weeks, the fetal crown-rump length averages about 32 cm, and the weight approximates 2800 g (Duryea, 2014). Because of subcutaneous fat deposition, the body is more rotund, and the previous wrinkled facies are now fuller. Normal fetuses have a nearly 100-percent survival rate.

40 Gestational Weeks

This is considered term, and the fetus is fully developed. The average crown-rump length measures about 36 cm, and the average weight approximates 3500 g.

■ Central Nervous System Development

Brain Development

The cranial end of the neural tube closes by 38 days from the last menstrual period, and the caudal end closes by 40 days. Hence, folic acid supplementation to prevent neural-tube defects must be in place before this point to be efficacious (Chap. 9, p. 168). The walls of the neural tube form the brain and spinal cord. The lumen becomes the ventricular system of the brain and the central canal of the spinal cord. During the sixth week, the cranial end of the neural tube forms three primary vesicles. In the seventh week, five secondary vesicles develop: the telencephalon—future cerebral hemispheres; diencephalon—thalami; mesencephalon—midbrain; metencephalon—pons and cerebellum; and myelencephalon—medulla. This is, in part, controlled by *Hox* genes, and defects result in abnormal signaling that leads to neuropathic anomalies (Arendt, 2018). Meanwhile, flexures develop and fold the brain into its typical

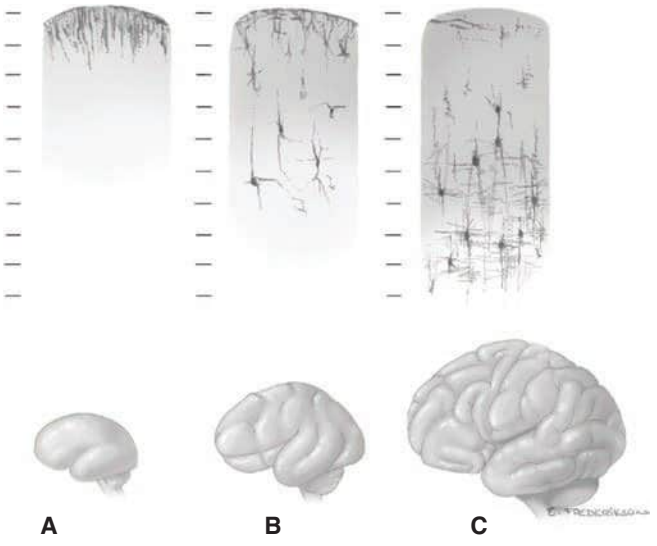

FIGURE 7-8 Neuronal proliferation and migration are complete at 20 to 24 weeks. During the second half of gestation, organizational events proceed with gyral formation and proliferation, differentiation, and migration of cellular elements. Approximate gestational ages are shown. **A.** 20 weeks. **B.** 35 weeks. **C.** 40 weeks.

configuration. The end of the embryonic period signifies completion of primary and secondary neutralization.

At 3 to 4 months' gestation, *neuronal proliferation* peaks. As expected, disorders in this cerebral development phase profoundly worsen function (Ortega, 2017; Volpe, 2018). One example is Zika virus infection (Rothan, 2019). *Neuronal migration* occurs almost simultaneously and peaks at 3 to 5 months. This process is characterized by movement of millions of neuronal cells from their ventricular and subventricular zones to areas of the brain in which they reside for life (Fig. 7-8). Upregulation of gene expression for neuronal migration has been described (Di Donato, 2017). Noninvasive methods to study fetal neurodevelopment also have been reported (Goetzl, 2016; Wang, 2015).

As gestation progresses, the fetal brain appearance steadily changes. Thus, it is possible to identify fetal age from its external appearance (Volpe, 2018). Neuronal proliferation and migration proceed along with gyral growth and maturation (see Fig. 7-8). Sequential maturation studies using magnetic resonance (MR) imaging have characterized the developing fetal brain (Dubois, 2014; Meng, 2012; Wang, 2015).

Myelination of the ventral roots of the cerebrospinal nerves and brainstem begins at approximately 6 months, but most myelination progresses after birth. This lack of myelin and incomplete skull ossification permit fetal brain structure to be seen sonographically throughout gestation.

Spinal Cord

Whereas the superior two thirds of the neural tube give rise to the brain, the inferior third forms the spinal cord. In the embryo, the spinal cord extends along the entire vertebral column length, but after that it lags behind vertebral growth. Ossification of the entire sacrum is visible sonographically by approximately 21 weeks (Chap. 15, p. 276). By 24 weeks, the spinal cord extends to S_1, at birth to L_3, and in the adult to L_1. Spinal cord myelination begins at midgestation and continues through the first year of life. Synaptic function is sufficiently developed by the eighth week to demonstrate flexion of the neck and trunk. During the third trimester, integration of nervous and muscular function proceeds rapidly (Molina, 2017).

Cardiovascular System

The embryology of the heart is highly complex. At its earliest stages of formation, the fetal heart undergoes molecular programming, and more than a hundred genes and molecular factors are integral to its morphogenesis (Kathiriya, 2015; Moore, 2020). These molecular factors include the *hypoxia-inducible factor—HIF* and *homeobox (HOX)*—family.

To summarize its embryology, the straight cardiac tube is formed by the 23rd day during an intricate morphogenetic sequence, during which each segment arises at a unique time. Between 4 and 7 weeks the heart undergoes extensive growth and morphological modification, leading to the formation of a partially septated four-chambered heart with a set of primitive valves (Sylva, 2014). The valves develop, and the aortic arch forms by vasculogenesis. Chapter 8 of Hurst's The Heart has a full description (Torres, 2017). Late in fetal life, coronary angiogenesis vascularizes the myocardium (Lu, 2021).

Fetal Circulation

This unique circulation is substantially different from that of the adult and functions until birth, when it changes dramatically. For example, fetal blood is oxygenated by the placenta and does not need to enter the pulmonary vasculature. Thus, most of the right ventricular output bypasses the lungs. In addition, the fetal heart chambers work in parallel, not in series. This effectively supplies the brain and heart, compared with the rest of the body, with more highly oxygenated blood from the dominant right ventricle.

Oxygen and nutrient materials required for fetal growth and maturation are delivered from the placenta by the single umbilical vein (Fig. 7-9). The vein then divides into the ductus venosus and the portal sinus. The ductus venosus is the major branch of the umbilical vein and traverses the liver to enter the inferior vena cava directly. Because it does not supply oxygen to the intervening tissues, it carries well-oxygenated blood directly to the heart. In contrast, the portal sinus carries blood to the hepatic veins primarily on the left side of the liver, and oxygen is extracted. The relatively deoxygenated blood from the liver then flows back into the inferior vena cava, which also receives more deoxygenated blood returning from the lower body. Blood flowing to the fetal heart from the inferior vena cava, therefore, consists of an admixture of arterial-like blood that passes directly through the ductus venosus and less well-oxygenated blood that returns from most of the veins below the level of the diaphragm. The oxygen content of blood delivered to the heart from the inferior vena cava is thus lower than that leaving the placenta.

Because the ventricles of the fetal heart work in parallel, this allows the right ventricle to account for two thirds of the total cardiac output. Well-oxygenated blood enters the left ventricle,

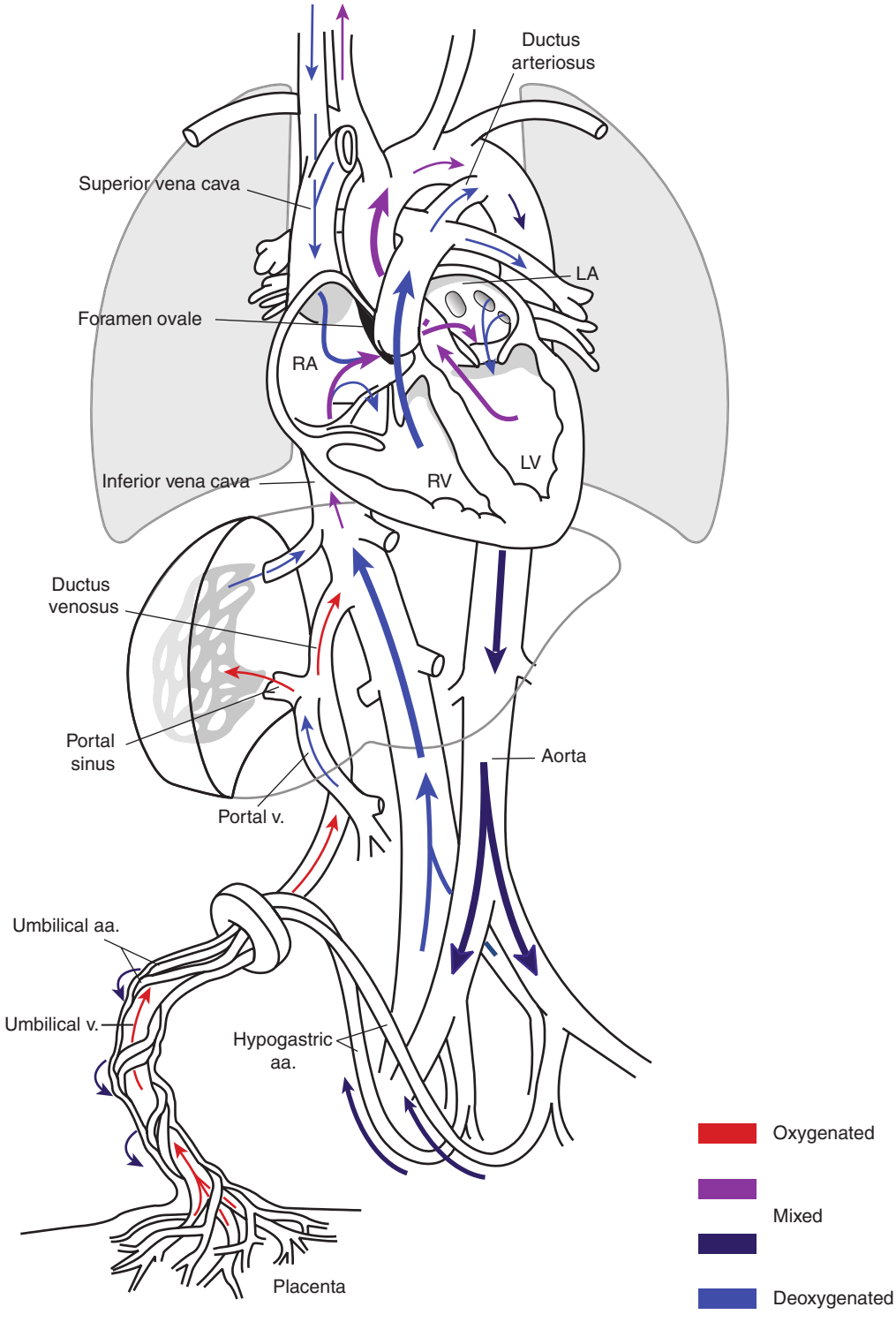

FIGURE 7-9 The intricate nature of the fetal circulation is evident. The degree of blood oxygenation in various vessels differs appreciably from that in the postnatal state. aa = arteries; LA = left atrium; LV = left ventricle; RA = right atrium; RV = right ventricle; v = vein.

which supplies the heart and brain, and less oxygenated blood enters the right ventricle, which supplies the rest of the body. Congenital cardiac defects may contribute to dysregulated brain development or placenta dysfunction (Fantasia, 2018; Lauridsen, 2017).

These two separate circulations are maintained by right-atrium anatomy, which effectively directs entering blood to either the left atrium or the right ventricle, depending on its oxygen content. This separation of blood according to its oxygen content is aided by the pattern of blood flow in the inferior vena cava. The well-oxygenated blood tends to course along the dorsomedial aspect of the inferior vena cava and the less oxygenated blood flows along the lateral vessel wall. This aids their shunting into opposite sides of the heart. Once this blood enters the right atrium, the configuration of the upper interatrial septum—the *crista dividens*—preferentially shunts

the well-oxygenated blood from the medial side of the inferior vena cava through the foramen ovale into the left heart. Here, it is directed to the heart and brain (Dawes, 1962). After these tissues extract needed oxygen, the resulting less oxygenated blood returns to the right atrium through the superior vena cava. Blood flow velocity in the superior vena cava rises from 20 weeks until term (Stefopoulou, 2021).

The less oxygenated blood coursing along the lateral wall of the inferior vena cava enters the right atrium and is deflected through the tricuspid valve to the right ventricle. The superior vena cava courses inferiorly and anteriorly as it enters the right atrium, ensuring that less well-oxygenated blood returning from the brain and upper body also will be shunted directly to the right ventricle. Similarly, the ostium of the coronary sinus lies just superior to the tricuspid valve so that less oxygenated blood from the heart also returns to the right ventricle. As a result of this blood flow pattern, blood in the right ventricle is 15 to 20 percent less saturated with oxygen than blood in the left ventricle.

Almost 90 percent of blood exiting the right ventricle is shunted through the ductus arteriosus to the descending aorta. High pulmonary vascular resistance and comparatively lower resistance in the ductus arteriosus and the umbilical–placental vasculature ensure that only about 8 percent of right ventricular output goes to the lungs (Fineman, 2014). Thus, one third of the blood passing through the ductus arteriosus is delivered to the body. The remaining right ventricular output returns to the placenta through the two hypogastric arteries. These two arteries course from the level of the bladder along the abdominal wall to the umbilical ring and into the cord as the umbilical arteries. In the placenta, this blood picks up oxygen and other nutrients and is recirculated to the umbilical vein.

Circulatory Changes at Birth

After birth, the umbilical vessels, ductus arteriosus, foramen ovale, and ductus venosus normally constrict or collapse. With the functional closure of the ductus arteriosus and the expansion of the lungs, blood leaving the right ventricle preferentially enters the pulmonary vasculature to become oxygenated before it returns to the left heart (Hillman, 2012). Virtually instantaneously, the ventricles, which had worked in parallel in fetal life, now effectively work in series. The more distal portions of the hypogastric arteries undergo atrophy and obliteration within 3 to 4 days after birth. These become the umbilical ligaments, whereas the intraabdominal remnants of the umbilical vein form the ligamentum teres. The ductus venosus constricts by 10 to 96 hours after birth and is anatomically closed by 2 to 3 weeks. This ultimately forms the ligamentum venosum (Fineman, 2014).

Fetoplacental Blood Volume

Although precise measurements of human fetoplacental blood volume are lacking, Usher and associates (1963) reported values in term normal newborns to average 78 mL/kg when immediate cord clamping was conducted. Gruenwald (1967) found that the fetal blood volume contained in the placenta after prompt cord clamping averaged 45 mL/kg of fetal weight. Thus, fetoplacental blood volume at term is approximately 125 mL/kg of fetal weight. This is important when assessing the magnitude of fetomaternal hemorrhage, which is discussed in Chapter 18 (p. 358).

Hemopoiesis

Embryo hemopoiesis begins in the yolk sac and endothelium, followed by the liver, and then spleen and bone marrow (Canu, 2021). Transitions are intricate and involve several genes and protein complexes (Shao, 2018). Both myeloid and erythroid cells are continually produced by progenitors that derive from hemopoietic stem cells (Fanni, 2018; Heinig, 2015). The first erythrocytes released into the fetal circulation are nucleated and macrocytic. The mean cell volume is at least 180 fL in the embryo and decreases to 105 to 115 fL at term. Normal adult volume ranges from 80 to 95 fL. The erythrocytes of aneuploid fetuses generally do not undergo this maturation and maintain high mean cell volumes, which average 130 fL (Sipes, 1991). As fetal development progresses, more and more circulating erythrocytes are smaller and nonnucleated. With fetal growth, both the blood volume in the common fetoplacental circulation and hemoglobin concentration increase. As shown in Table 7-1, fetal hemoglobin concentrations rise across pregnancy. For clinical purposes, the Society for Maternal-Fetal Medicine (2015) recommends a cutoff fetal hematocrit value of 30 percent to define anemia.

Because of their large size, fetal erythrocytes have a short life span, which progressively lengthens to approximately 90 days at term (Pearson, 1966). As a consequence, red blood cell concentrations rise. Reticulocytes are initially present at high levels but decrease to 4 to 5 percent of the total at term. Fetal erythrocytes differ structurally and metabolically from those in the adult (Baron, 2012). They are more deformable, which serves

TABLE 7-1. Fetal Hemoglobin Concentrations Across Pregnancy

Weeks' Gestation	Multiples of the Median		
	1.16 (95th percentile)	1.00 (median)	0.84 (5th percentile)
	grams per deciliter		
18	12.3	10.6	8.9
20	12.9	11.1	9.3
22	13.4	11.6	9.7
24	13.9	12.0	10.1
26	14.3	12.3	10.3
28	14.6	12.6	10.6
30	14.8	12.8	10.8
32	15.2	13.1	10.9
34	15.4	13.3	11.2
36	15.6	13.5	11.3
38	15.8	13.6	11.4
40	16.0	13.8	11.6

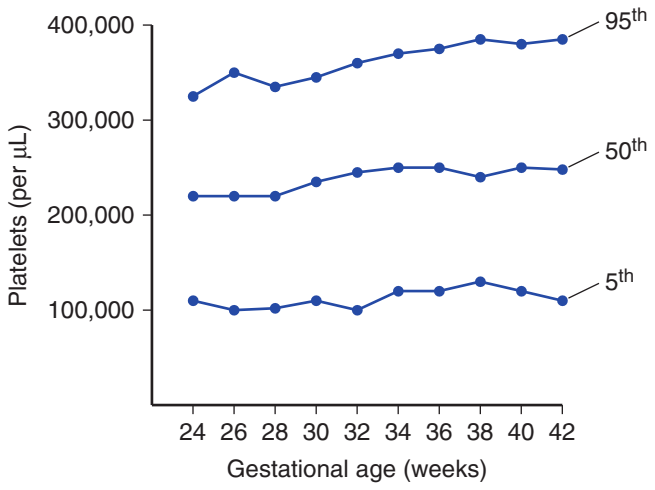

FIGURE 7-10 Platelet counts by gestational age obtained the first day of life. Mean values and 5th and 95th percentiles are shown. (Data from Christensen RD, Henry E, Antonio DV: Thrombocytosis and thrombocytopenia in the NICU: incidence, mechanisms and treatments, J Matern Fetal Neonatal Med 25 Suppl 4:15, 2012.)

to offset their higher volume and viscosity. They also contain several enzymes with appreciably different activities.

Erythropoiesis is controlled primarily by fetal erythropoietin because maternal erythropoietin does not cross the placenta. Fetal hormone production is influenced by testosterone, estrogen, prostaglandins, thyroid hormone, lipoproteins, and importantly, by fetal hypoxia (Teramo, 2018). Serum erythropoietin levels rise with fetal maturity. The fetal liver is an important source until renal production begins near term. The erythropoietin concentration in amnionic fluid correlates closely with that in umbilical venous blood obtained by cordocentesis. After birth, erythropoietin normally may not be detectable for up to 3 months.

In contrast, platelet production reaches stable levels by midpregnancy, although there is some variation across gestation (Fig. 7-10). The fetal and neonatal platelet count is subject to various agents, which are discussed in Chapter 18 (p. 359).

Fetal Hemoglobin

This tetrameric protein is composed of two copies of two different peptide chains, which determine the type of hemoglobin produced (Fig. 7-11). Normal adult hemoglobin A1 is made of α and β chains. During embryonic and fetal life, various α and β chain precursors are produced. This results in the serial production of several different embryonic hemoglobins. At least 17 genetic loci potentially regulate erythropoiesis (Tumburu, 2017). Genes for β-type chains are on chromosome 11, and those for α-type chains on chromosome 16. Each of these genes is turned on and then off during fetal life, until α and β genes, which direct the production of adult hemoglobin A1, are permanently activated.

The timing of production of each of these early hemoglobins corresponds to the site of hemoglobin production. Fetal blood is first produced in the yolk sac, where hemoglobins Gower 1, Gower 2, and Portland are made. Erythropoiesis then moves to the liver, where fetal hemoglobin F is produced. When hemopoiesis finally moves to the bone marrow, adult-type hemoglobin A1 appears in fetal red blood cells and is present in progressively greater amounts as the fetus matures (Lessard, 2018).

The final adult version of the α chain is produced exclusively by 6 weeks. After this, there are no functional alternative versions, and the gene for the zeta (ζ) globin chain is downregulated. If the gene coding the α globin chain undergoes mutation, no alternate α-type chain can be substituted to form functional hemoglobin. In contrast, at least two versions of the β chain—δ and γ—remain in production throughout fetal life and beyond. With a mutation in the gene coding the β globin chain, these two other versions of the β chain often continue to be produced, resulting in either hemoglobin A2 ($\alpha_2\delta_2$) or

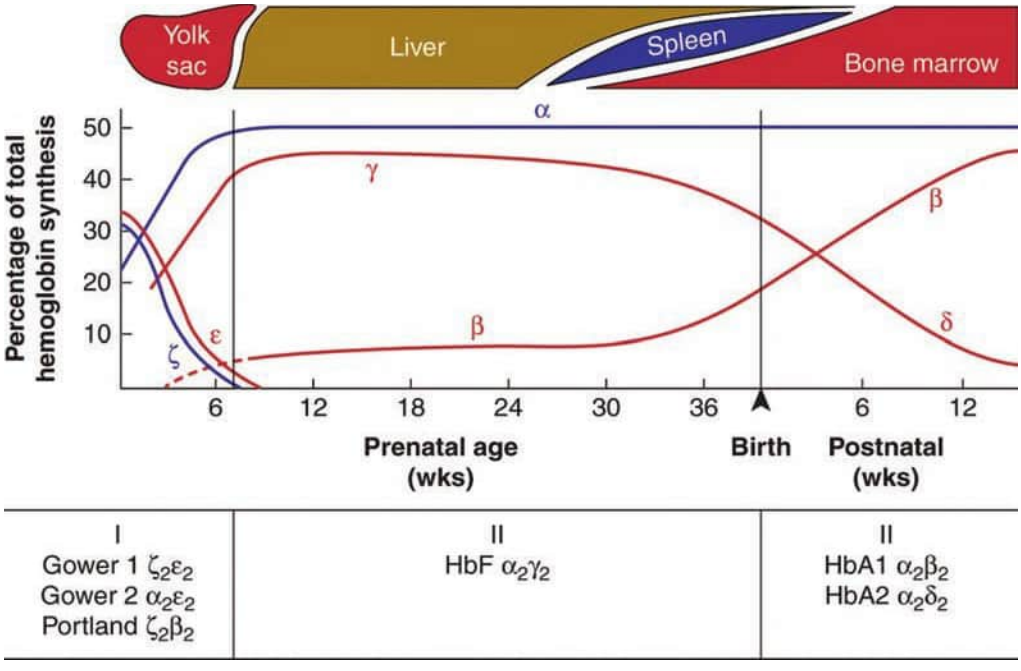

FIGURE 7-11 Hemoglobin types transition throughout pregnancy. Alpha (α) and zeta (ζ) globin chains are interchangeable. The beta (β) globin chain can be replaced by epsilon (ε), gamma (γ), or delta (δ) globin chains. In embryonic life (stage I), ζ and ε globin chain production is gradually replaced by α and γ globin chain production. Hemoglobin F is the main type in fetal life (stage II). After birth (stage III), HbA1 predominates.

hemoglobin F ($\alpha_2\gamma_2$), which substitute for the abnormal or missing hemoglobin A1.

Genes are turned off by methylation of their control region, which is discussed in Chapter 13 (p. 322). In some situations, methylation does not occur. For example, in newborns of diabetic women, hemoglobin F may persist due to hypomethylation of the γ gene (Perrine, 1988). With sickle-cell anemia, the γ gene remains unmethylated, and large quantities of fetal hemoglobin continue to be produced. As discussed in Chapter 59 (p. 1053), elevated hemoglobin F levels are associated with fewer sickle-cell disease symptoms, and pharmacological modification of these levels by hemoglobin F–inducing drugs is one treatment approach (Pasricha, 2018).

Hemoglobins A and F function differently. At any given oxygen tension and at identical pH, fetal erythrocytes that contain mostly hemoglobin F bind more oxygen than do those that contain nearly all hemoglobin A (Fig. 50-2, p. 886). This is because hemoglobin A binds 2,3-diphosphoglycerate (2,3-DPG) more avidly than does hemoglobin F. Remember that 2,3-DPG is an intraerythrocyte phosphate, and hemoglobin has a reciprocal affinity for 2,3-DPG and oxygen (Benesch, 1968). Thus, hemoglobin A's greater 2,3-DPG binding lowers its oxygen affinity compared with hemoglobin F. Moreover, during pregnancy, maternal 2,3-DPG levels are greater, and because fetal erythrocytes have lower concentrations of 2,3-DPG, fetal cells have increased oxygen affinity.

The amount of hemoglobin F in fetal erythrocytes begins to decrease in the last weeks of pregnancy. At term, approximately three fourths of total hemoglobin levels are hemoglobin F. During the first 6 to 12 months of life, the hemoglobin F proportion continues to decline and eventually reaches the low levels found in adult erythrocytes (Pasricha, 2018).

Coagulation Factors

With the exception of fibrinogen, other hemostatic proteins do not exist in embryonic forms. The fetus starts producing normal, adult-type procoagulant, fibrinolytic, and anticoagulant proteins by 12 weeks. Because they do not cross the placenta, their concentrations at birth are markedly below the levels that develop within a few weeks of life (Corrigan, 1992). In normal neonates, the levels of factors II, VII, IX, X, and XI, and of protein S, protein C, antithrombin, and plasminogen, all approximate 50 percent of adult levels. In contrast, levels of factors V, VIII, XIII, and fibrinogen are closer to adult values (Saracco, 2009). Maternal vitamin K deficiency has been associated with fetal cerebral hemorrhage (Goto, 2018). Without prophylactic treatment, the levels of vitamin K–dependent coagulation factors usually drop even further during the first few days after birth. This decline is amplified in breastfed infants and may lead to newborn hemorrhage (Chap. 33, p. 606). Schott (2018) and Konstantinidi (2019) and their colleagues have provided thromboelastographic parameters for both healthy and sick term newborns.

Fetal fibrinogen, which appears as early as 5 weeks, has the same amino acid composition as adult fibrinogen but different properties (Klagsbrun, 1988). It forms a less compressible clot, and the fibrin monomer has a lower degree of aggregation (Heimark, 1988). Although plasma fibrinogen levels at birth are less than those in nonpregnant adults, the protein is functionally more active than adult fibrinogen (Ignjatovic, 2011). Neonates have higher cord plasma levels and fibronectin-fibrinogen complexes compared with maternal levels (Lis-Kuberka, 2018).

Levels of functional fetal factor XIII (fibrin stabilizing factor) are significantly reduced compared with those in adults (Henriksson, 1974). Nielsen (1969) described low levels of plasminogen and elevated fibrinolytic activity in cord plasma compared with that of maternal plasma. Platelet counts in cord blood are in the normal range for nonpregnant adults.

Despite this relative reduction in procoagulants, the fetus appears to be protected from hemorrhage, and fetal bleeding is rare. Even after invasive fetal procedures such as cordocentesis, excessive bleeding is uncommon. Ney and coworkers (1989) have shown that amnionic fluid thromboplastins and a factor(s) in Wharton jelly combine to aid coagulation at the umbilical cord puncture site.

Various *thrombophilias* may cause thromboses and pregnancy complications in adults (Chap. 55, p. 976). If the fetus inherits one of these mutations, thrombosis and infarction can develop in the placenta or fetal organs. This is usually seen with homozygous inheritance. One example is homozygous protein C mutation, which causes *purpura fulminans*.

Plasma Proteins

Liver enzymes and other plasma proteins are produced by the fetus, and these levels do not correlate with maternal levels (Weiner, 1992). Concentrations of plasma proteins, which include albumin, lactic dehydrogenase, aspartate and alanine aminotransferases, and γ-glutamyl transpeptidase, all rise. Conversely, prealbumin levels decline with gestational age (Fryer, 1993). At birth, mean total plasma protein and albumin concentrations in fetal blood are similar to maternal levels. This is important because albumin binds unconjugated bilirubin to prevent *kernicterus* in the newborn (Chap. 33, p. 606).

■ Respiratory System

Lung maturation and biochemical indices of functional fetal lung maturity are important predictors of early neonatal outcome. Morphological or functional immaturity at birth leads to the development of the *respiratory distress syndrome* (Chap. 34, p. 615). A sufficient amount of surface-active materials—collectively referred to as *surfactant*—in the amnionic fluid is evidence of fetal lung maturity (Warburton, 2017). As Liggins (1994) emphasized, however, the structural and morphological maturation of fetal lung also is extraordinarily important to proper lung function.

Anatomical Maturation

Like the branching of a tree, lung development proceeds along an established timetable. As with other organ systems, gene activation and deactivation control these functions (Miller, 2019). The lung primordium is an outgrowth from foregut endoderm at approximately 20 days' gestation. The lung bud arises at 25 days and within this framework, four essential lung

development stages are described by Moore (2020). First, the *pseudoglandular stage* entails growth of the intrasegmental bronchial tree between the 5th and 17th weeks. The microvasculature begins to develop, and the lung looks microscopically like a gland. Second, during the *canalicular stage*, from 16 to 25 weeks, the bronchial cartilage plates extend peripherally. Each terminal bronchiole gives rise to several respiratory bronchioles, and each of these in turn divides into multiple saccular ducts. Third, the *terminal sac stage* begins after 25 weeks. During this stage, primordial alveoli give rise to primitive pulmonary alveoli, that is, the terminal sacs. Simultaneously, an extracellular matrix develops from proximal to distal lung segments until term. The fourth *alveolar stage* begins during the late fetal period and continues well into childhood. An extensive capillary network is built, the lymphatic system forms, and type II pneumocytes begin to produce surfactant. At birth, only approximately 15 percent of the adult number of alveoli is present. Thus, the lung continues to grow and add more alveoli for up to 8 years.

Various insults can upset this process, and their timing determines the sequelae. During the embryonic phase, abnormalities in lung development include esophageal and tracheal atresia, tracheoesophageal fistula, and pulmonary agenesis. Another example is fetal renal agenesis in which amnionic fluid is absent at the beginning of lung growth, and major defects occur in all four developmental stages. Similarly, the fetus with membrane rupture and subsequent oligohydramnios before 20 weeks usually exhibits nearly normal bronchial branching and cartilage development but has immature alveoli. In contrast, membrane rupture after 24 weeks may have minimal long-term effect on pulmonary structure. Last, vitamin D is thought to be important for several aspects of lung development (Hart, 2015; Ustun, 2020).

Pulmonary Surfactant

After the first breath, the terminal sacs must remain expanded despite the pressure imparted by the tissue-to-air interface, and surfactant keeps them from collapsing. Surfactant is formed in type II pneumocytes that line the alveoli. These cells are characterized by multivesicular bodies that produce the lamellar bodies in which surfactant is assembled. During late fetal life, at a time when the alveolus is characterized by a water-to-tissue interface, the intact lamellar bodies are secreted from the lung and swept into the amnionic fluid during respiratory-like movements that are termed fetal breathing. At birth, with the first breath, an air-to-tissue interface is established in the lung alveolus. Surfactant uncoils from the lamellar bodies and spreads to line the alveolus to prevent alveolar collapse during expiration. Thus, the fetal lungs' capacity to produce surfactant establishes lung maturity.

Surfactant Composition. Gluck (1972) and Hallman (1976) and their coworkers approximated that 90 percent of surfactant dry weight is lipid, specifically glycerophospholipids. Proteins account for the other 10 percent. Nearly 80 percent of the glycerophospholipids are phosphatidylcholines (lecithins). The principal active component that constitutes half of surfactant is a specific lecithin, which is dipalmitoyl phosphatidylcholine (DPPC or PC). Phosphatidylglycerol (PG) accounts for another 8 to 15 percent. Its precise role is unclear because newborns without PG usually do well. The other major constituent is phosphatidylinositol (PI).

Surfactant Synthesis. Biosynthesis takes place in the type II pneumocytes. The apoproteins are produced in the endoplasmic reticulum, and the glycerophospholipids are synthesized by cooperative interactions of several cellular organelles. Phospholipid is the primary surface tension–lowering component of surfactant, whereas the apoproteins aid the forming and reforming of a surface film.

The major apoprotein is surfactant A (SP-A), which is a glycoprotein with a molecular weight of 28,000 to 35,000 Da. It is synthesized in the type II cells, and its content in amnionic fluid increases with gestational age and fetal lung maturity. *SP-A* gene expression is demonstrable by 29 weeks (Mendelson, 2005). Specifically, *SP-A1* and *SP-A2* are two separate genes on chromosome 10, and their regulation is distinctive and different (McCormick, 1994).

Corticosteroids and Fetal Lung Maturation. Since Liggins (1969) observed accelerated lung maturation in lamb fetuses given glucocorticosteroid prior to preterm delivery, many suggested that fetal cortisol stimulates lung maturation and surfactant synthesis. It is unlikely, however, that corticosteroids are the only stimulus for augmented surfactant formation. But, when these are administered at certain critical times, they may improve preterm fetal lung maturation. Antenatal betamethasone and dexamethasone for lung maturation and neonatal replacement surfactant therapy are discussed in Chapter 34 (p. 617).

Breathing

Fetal respiratory muscles develop early, and chest wall movements are detected sonographically as early as 11 weeks (Koos, 2014). Breathing is essential for normal lung growth and development. From the beginning of the fourth month, the fetus engages in respiratory movement sufficiently intense to move amnionic fluid in and out of the respiratory tract. Some extrauterine events have effects on fetal breathing, for example, maternal exercise stimulates it (Sussman, 2016).

■ Digestive System

After its embryogenic formation from the yolk sac as the primordial gut, the digestive system forms the intestines and various appendages. The foregut gives rise to the pharynx, lower respiratory system, esophagus, stomach, proximal duodenum, liver, pancreas, and biliary tree. The midgut gives rise to the distal duodenum, jejunum, ileum, cecum, appendix, and the right colon. The hindgut develops into the left colon, rectum, and the superior portion of the anal canal that empties into the cloaca (Kruepunga, 2018). Numerous malformations develop in these structures from improper rotation, fixation, and partitioning. A common example is one of the several types of intestinal atresias (Moore, 2020; Stoll, 2017).

Swallowing begins at 10 to 12 weeks, coincident with the ability of the small intestine to undergo peristalsis and

to actively transport glucose (Koldovsky, 1965). As a correlate, neonates born preterm may have swallowing difficulties because of immature gut motility (Singendonk, 2014). Much of the water in swallowed fluid is absorbed, and unabsorbed matter is propelled to the lower colon. Gitlin (1974) demonstrated that late in pregnancy, approximately 800 mg of soluble protein is ingested daily by the fetus. The stimulus for swallowing is unclear, but the fetal neural analogue of thirst, gastric emptying, and change in the amnionic fluid composition are potential factors (Boyle, 1992). The fetal taste buds may play a role because saccharin injected into amnionic fluid increases swallowing, whereas injection of a noxious chemical inhibits it (Liley, 1972).

Fetal swallowing appears to have little effect on amnionic fluid volume early in pregnancy because the volume swallowed is small compared with the total. However, term fetuses swallow between 200 and 760 mL per day—an amount comparable to that of the term neonate (Pritchard, 1966). Thus at term, amnionic fluid volume regulation can be substantially altered by fetal swallowing. For example, as discussed in Chapter 14 (p. 256), if swallowing is inhibited, hydramnios is common.

Hydrochloric acid and some digestive enzymes are present in the stomach and small intestine in minimal amounts in the early fetus. Intrinsic factor is detectable by 11 weeks, and pepsinogen by 16 weeks. The preterm neonate, depending on its gestational age, may have transient deficiencies of these enzymes. The small intestinal histological appearance is normal (Meier, 2018).

Stomach emptying appears to be stimulated primarily by volume. A dilated stomach suggests obstruction (McCormick, 2021). Movement of amnionic fluid through the gastrointestinal system may enhance growth and development of the alimentary canal. That said, other regulatory factors likely are involved. For example, anencephalic fetuses, in which swallowing is limited, often have normal amnionic fluid volume and normal-appearing gastrointestinal tract.

Meconium

Fetal bowel contents consist of various products of secretion, such as glycerophospholipids from the lung, desquamated fetal cells, lanugo, scalp hair, and vernix. It also contains undigested debris from swallowed amnionic fluid. The dark greenish-black color forms from bile pigments, especially biliverdin. Meconium can pass from normal bowel peristalsis in the mature fetus or from vagal stimulation. It can also pass when hypoxia stimulates arginine vasopressin (AVP) release from the fetal pituitary gland. AVP stimulates colonic smooth muscle to contract, resulting in intraamnionic defecation (Rosenfeld, 1985). Meconium is toxic to the respiratory system, and its inhalation can result in *meconium aspiration syndrome*.

Liver

The hepatic diverticulum is an outgrowth of the endodermal lining of the foregut. Epithelial liver cords and primordial cells differentiate into hepatic parenchyma. By 9 weeks, the liver accounts for 10 percent of fetal weight (Moore, 2020). Serum liver enzyme levels increase with gestational age. As noted, in early gestation, fetal hepatic hemopoiesis is a key source of blood and immune cells (p. 125) (Popescu, 2019).

The fetal liver has a gestational-age-related capacity to conjugate bilirubin, which forms from hemoglobin breakdown (Morioka, 2015). Because of hepatic immaturity, the preterm newborn is at particular risk for unconjugated hyperbilirubinemia (Chap. 33, p. 606). And because the life span of normal fetal macrocytic erythrocytes is shorter than that of the adult, relatively more unconjugated bilirubin is produced. Of this unconjugated form, only a small fraction is conjugated by the fetal liver, and this is excreted into the intestine and ultimately oxidized to biliverdin. Instead, most of the unconjugated bilirubin is excreted into the amnionic fluid after 12 weeks and transferred across the placenta (Bashore, 1969). Importantly, placental bilirubin transfer is bidirectional. Thus, a woman with severe hemolysis has excess unconjugated bilirubin that readily passes to the fetus and then into the amnionic fluid. Conversely, conjugated bilirubin is not exchanged to any significant degree between mother and fetus.

Most fetal cholesterol derives from hepatic synthesis, which satisfies the large demand for low-density lipoprotein (LDL) cholesterol by the fetal adrenal glands. However, an estimated 20 to 50 percent of fetal cholesterol originates from the mother, is transferred through the placenta, and released to circulating fetal apolipoproteins (Baardman, 2012; Pecks, 2014). Fetuses with growth restriction have lower cholesterol levels due to diminished fetal synthesis rather than diminished maternal supply (Pecks, 2019).

Hepatic glycogen is present in low concentration during the second trimester, but near term, levels rise rapidly and markedly to reach concentrations that are two- to threefold higher than those in the adult liver. After birth, glycogen content falls precipitously.

Pancreas

This gland arises from dorsal and ventral pancreatic buds from the endoderm of the foregut (Moore, 2020). Gene regulation of its development has been reviewed (Jennings, 2015). Insulin-containing granules can be identified by 9 to 10 weeks, and insulin is detectable in fetal plasma at 12 weeks (Adam, 1969). Between 19 and 36 weeks, Kivilevitch and associates (2017) were able to visualize the pancreas sonographically in 60 percent of fetuses.

The fetal pancreas responds to hyperglycemia by secreting insulin (Obenshain, 1970). Islets of Langerhans are enlarged in fetuses of mothers with metabolic abnormalities (Avagliano, 2019). These fetuses likely can be identified by sonographic pancreatic hyperechogenicity (Akkaya, 2018). Glucagon has been identified in the fetal pancreas at 8 weeks. Although hypoglycemia does not cause an increase in fetal glucagon levels, similar stimuli do so by 12 hours after birth (Chez, 1975).

Most pancreatic enzymes are present by 16 weeks. Trypsin, chymotrypsin, phospholipase A, and lipase are found in the 14-week fetus, and their concentrations increase with gestational age (Werlin, 1992). Amylase has been identified in amnionic fluid at 14 weeks (Davis, 1986). The exocrine function of the fetal pancreas is limited. Physiologically important

secretion occurs only after stimulation by a secretagogue such as acetylcholine, which is released locally after vagal stimulation (Werlin, 1992). Cholecystokinin normally is released only after protein ingestion and thus ordinarily is not found in the fetus.

Urinary System

Renal development involves interaction between pluripotential stem cells, undifferentiated mesenchymal cells, and epithelial components (Fanos, 2015). Two primitive urinary systems—the pronephros and the mesonephros—precede development of the metanephros, which forms the final kidney. The pronephros involutes by 2 weeks, and the mesonephros produces urine at 5 weeks and degenerates by 11 to 12 weeks. Failure of these two structures either to form or to regress may result in anomalous urinary system development. Between 9 and 12 weeks, the ureteric bud and the nephrogenic blastema interact to produce the metanephros. Glomeruli develop and filtration begins by week 9 (Moore, 2020). The kidney and ureter develop from intermediate mesoderm. The bladder and urethra develop from the urogenital sinus. The bladder also develops in part from the allantois. Urogenital embryology is a focus of Chapter 3.

By week 14, the loop of Henle is functional and reabsorption occurs (Smith, 1992). New nephrons continue to be formed until 36 weeks (Lindström, 2018). In preterm neonates, their formation continues after birth. Although the fetal kidneys produce urine, their ability to concentrate and modify the pH is limited even in the mature fetus. Fetal urine is hypotonic with respect to fetal plasma and has low electrolyte concentrations.

Renal vascular resistance is high, and the filtration fraction is low compared with adult values (Smith, 1992). Fetal renal blood flow and thus urine production are controlled or influenced by the renin-angiotensin system, the sympathetic nervous system, prostaglandins, kallikrein, and atrial natriuretic peptide. The glomerular filtration rate increases with gestational age from less than 0.1 mL/min at 12 weeks to 0.3 mL/min at 20 weeks. In later gestation, the rate remains constant when corrected for fetal weight (Smith, 1992). Hemorrhage or hypoxia generally decreases renal blood flow, glomerular filtration rate, and urine output.

Urine usually is found in the bladder even in small fetuses. The fetal kidneys start producing urine at 12 weeks. By 18 weeks, they are producing 7 to 14 mL/d, and at term, this increases to 650 mL/d (Wladimiroff, 1974). Maternally administered furosemide augments fetal urine formation, whereas uteroplacental insufficiency, fetal-growth restriction, and other fetal disorders can lower it. Obstruction of the urethra, bladder, ureters, or renal pelves can damage renal parenchyma and distort fetal anatomy (Müller Brochut, 2014). Pathological correlates and prenatal therapy of urinary tract obstruction are discussed in Chapter 19 (p. 376).

Kidneys are not essential for survival in utero but influence control of amnionic fluid composition and volume. Thus, abnormalities that cause chronic fetal anuria are usually accompanied by oligohydramnios and pulmonary hypoplasia (Cotton, 2017).

Endocrine Gland Development

The fetal endocrine system is functional for some time before the central nervous system reaches maturity (Mulchahey, 1987).

Pituitary Gland

The anterior pituitary gland develops from oral ectoderm—the *Rathke pouch*—whereas the posterior pituitary gland derives from neuroectoderm. Embryonic development involves a complex and highly spatiotemporally regulated network of signaling molecules and transcription factors (Bancalari, 2012; Montenegro, 2019).

Anterior and Intermediate Lobes. The adenohypophysis, or anterior pituitary, differentiates into five cell types that secrete six protein hormones. Of these types, lactotropes produce prolactin (PRL), somatotropes produce growth hormone (GH), corticotropes produce adrenocorticotropic hormone (ACTH), thyrotropes produce thyroid-stimulating hormone (TSH), and gonadotropes produce luteinizing hormone (LH) and follicle-stimulating hormone (FSH).

ACTH is first detected in the fetal pituitary gland at 7 weeks, and GH and LH have been identified by 13 weeks. By the end of the 17th week, the fetal pituitary gland synthesizes and stores all pituitary hormones. Moreover, the fetal pituitary is responsive to tropic hormones and is capable of secreting these early in gestation (Grumbach, 1974). The fetal pituitary secretes β-endorphin, and cord blood levels of β-endorphin and β-lipotropin rise with fetal arterial partial pressure of carbon dioxide ($Paco_2$) (Browning, 1983).

The intermediate lobe in the fetal pituitary gland is well developed. The cells of this structure begin to disappear before term and are absent from the adult pituitary.

Neurohypophysis. The posterior pituitary gland or neurohypophysis is well developed by 10 to 12 weeks, and oxytocin and arginine vasopressin are demonstrable. Both hormones probably function in the fetus to conserve water by actions directed largely at the lung and placenta rather than kidney. Vasopressin levels in umbilical cord plasma are strikingly higher than maternal levels (Chard, 1971).

Thyroid Gland

The thyroid primordium arises from the endoderm of the primordial pharynx (Moore, 2020). The thyroid migrates to its final position, and the obliterated thyroglossal duct connects to the foramen cecum of the tongue.

The pituitary–thyroid system is functional by the end of the first trimester. By 10 to 12 weeks, the thyroid gland is able to synthesize hormones, and thyrotropin, thyroxine, and thyroid-binding globulin (TBG) have been detected in fetal serum as early as 11 weeks (Bernal, 2007). Thyroid follicles have formed and colloid is present. The placenta actively concentrates iodine on the fetal side, and by 12 weeks and throughout pregnancy, the fetal thyroid concentrates iodine more avidly than does the maternal thyroid. Thus, maternal administration of either radioiodine or appreciable amounts of ordinary iodine is hazardous after this time (Chap. 66, p. 1174). Normal fetal levels of free thyroxine (T_4), free triiodothyronine (T_3), and TBG rise

steadily throughout gestation (Ballabio, 1989). Compared with adult levels, by 36 weeks, fetal serum concentrations of TSH are higher, total and free T_3 concentrations are lower, and T_4 is similar. This suggests that the fetal pituitary may not become sensitive to feedback until late pregnancy.

Fetal thyroid hormone plays a role in the normal development of virtually all fetal tissues, especially the brain (Andersen, 2018; Jansen, 2019). Congenital hypothyroidism is a heterogenous disorder for which several candidate genes have been identified (Moore, 2020). With hypothyroidism, it was previously believed that normal fetal growth and development provided evidence that T_4 was not essential for fetal growth. It is now known, however, that growth proceeds normally because small quantities of maternal T_4 prevent antenatal cretinism in fetuses with thyroid agenesis (Forhead, 2014; Vulsma, 1989). As discussed in Chapter 61 (p. 1098), the fetus with congenital hypothyroidism typically does not develop stigmata of cretinism until after birth (Abduljabbar, 2012). Because administration of thyroid hormone will prevent this, by state law, all newborns are tested for high serum levels of TSH (Chap. 32, p. 594).

The placenta prevents substantial passage of maternal thyroid hormones to the fetus by rapidly deiodinating maternal T_4 and T_3 to form reverse T_3, a relatively inactive thyroid hormone. Several antithyroid antibodies cross the placenta when present in high concentrations (Pelag, 2002). Those include the long-acting thyroid stimulators (LATS), LATS-protector (LATS-P), and thyroid-stimulating immunoglobulin (TSI). Congenital hyperthyroidism develops when maternal thyroid-stimulating antibody crosses the placenta to stimulate the fetal gland to secrete thyroxine (Donnelley, 2015). These fetuses develop large goiters as shown in Figure 61-3 (p. 1092). They also display tachycardia, hepatosplenomegaly, hematological abnormalities, craniosynostosis, and growth restriction. As children, they have perceptual motor difficulties, hyperactivity, and reduced growth (Johns, 2018).

Immediately after birth, thyroid function and metabolism undergo major change. Cooling to room temperature evokes a sudden and marked increase in TSH secretion. This in turn causes a progressive increase in serum T_4 levels that are maximal 24 to 36 hours after birth. There are nearly simultaneous elevations of serum T_3 levels.

Adrenal Glands

These glands develop from two separate tissues. The medulla derives from neural crest ectoderm, whereas the fetal and adult cortex arise from intermediate mesoderm. The gland grows rapidly through cell proliferation and angiogenesis, cellular migration, hypertrophy, and apoptosis (Ishimoto, 2011). Expression of the *Kiss1R* gene, alone or in concert with corticotropin-releasing hormone, stimulates fetal adrenal growth (Katugampola, 2017). Fetal glands are enormous in relation to body size and are 10 to 20 times larger than adult glands (Karsli, 2019; Moore, 2020). The bulk is made up of the inner or fetal zone of the adrenal cortex and involutes rapidly after birth. This zone is scant to absent in rare instances in which the fetal pituitary gland is congenitally absent. The function of the fetal adrenal glands is discussed in Chapter 5 (p. 102).

Immunological System

Infections in utero have provided an opportunity to examine mechanisms of the fetal immune response (Chap. 67, p. 1182). Evidence of immunological competence has been reported as early as 13 weeks (Stabile, 1988). In cord blood at or near term, the average level for most components approximates half that of the adult values.

B cells differentiate from pluripotent hemopoietic stem cells that migrate to the liver (Berthault, 2017; Melchers, 2015). Despite this, in the absence of a direct antigenic stimulus such as infection, fetal plasma immunoglobulins consist almost totally of transferred maternal immunoglobulin G (IgG). Thus, antibodies in the newborn most often reflect maternal immunological experiences (American College of Obstetricians and Gynecologists, 2019). The interaction between maternal and fetal T cells is described in Chapter 5 (p. 93).

Immunoglobulin G

Maternal IgG transport correlates with placental Fc receptor expression (Lozano, 2018). Fetal transport begins at approximately 16 weeks and increases thereafter. Because the bulk of IgG is acquired during the last 4 weeks, preterm neonates are poorly endowed with protective maternal antibodies. Newborns begin to slowly produce IgG, and adult values are not attained until age 3 years. In certain situations, the transfer of IgG antibodies from mother to fetus can be harmful rather than protective. The classic example is hemolytic disease of the fetus and newborn resulting from Rh-antigen alloimmunization (Chap. 18, p. 353).

Immunoglobulins M and A

In the adult, production of immunoglobulin M (IgM) in response to an antigenic stimulus is superseded in a week or so predominantly by IgG production. Similarly, very little IgM is produced by normal fetuses not exposed to infection, but with infection, the IgM response predominates and remains so for weeks to months in the newborn. And, because IgM is not transported from the mother, any IgM in the fetus or newborn is that which it produced. Thus, specific IgM levels in umbilical cord blood may be elevated in those with congenital infection. According to the American College of Obstetricians and Gynecologists (2019), elevated IgM levels are usually found in newborns with congenital infection such as rubella, cytomegalovirus infection, or toxoplasmosis. In infants, adult levels of IgM are normally attained by age 9 months.

Immunoglobulin A (IgA) ingested in colostrum provides mucosal protection against enteric infections. There is only a small amount of fetal secretory IgA found in amnionic fluid (Quan, 1999).

Lymphocytes and Monocytes

The immune system develops early, and B lymphocytes are derived from primordial stem cells and appear in fetal liver by 9 weeks and in blood and spleen by 12 weeks (Moore, 2020). T lymphocytes begin to leave the thymus at approximately 14 weeks. Despite this, the newborn responds poorly to immunization, and especially poorly to bacterial capsular

polysaccharides. This immature response may stem from a deficient response of newborn B cells to polyclonal activators or from a lack of T cells that proliferate in response to specific stimuli (Hayward, 1983). In the newborn, monocytes are able to process and present antigen when tested with maternal antigen-specific T cells. DNA methylation patterns are developmentally regulated during monocyte-macrophage differentiation and contribute to the antiinflammatory phenotype in macrophages (Kim, 2012).

■ Musculoskeletal System

The origin of most muscles and bones is mesodermal. MYOD is a member of the family of myogenic regulatory factors that activates transcription of muscle-specific genes (Moore, 2020). The limb buds appear by the fourth week. Most skeletal muscle derives from myogenic precursor cells in the somites. The skeleton arises from condensed mesenchyme—embryonic connective tissue—which eventually forms hyaline cartilage models of the bones. Osteoclasts arise from erythro-myeloid progenitors (Jacome-Galarza, 2019). By the end of the embryonic period, ossification centers have developed, and bones harden by endochondral ossification.

ENERGY AND NUTRITION

Because of the small amount of yolk in the human ovum, growth of the embryofetus is dependent on maternal nutrients during the first 2 months. During the first few days after implantation, blastocyst nutrition comes from the interstitial fluid of the endometrium and the surrounding maternal tissue.

Maternal adaptations to store and transfer nutrients to the fetus are discussed in Chapter 4 and summarized here. Three major maternal storage depots are the liver, muscle, and adipose tissue. These maternal depots and the storage hormone insulin are intimately involved in the metabolism of the nutrients absorbed from the gut. Maternal insulin secretion is sustained by increased serum levels of glucose and amino acids. The net effect is maternal storage of glucose as glycogen primarily in liver and muscle, retention of some amino acids as protein, and storage of the excess as fat (Abeysekera, 2016). Storage of maternal fat peaks in the second trimester and then declines as fetal energy demands rise in the third trimester (Pipe, 1979). Interestingly, the placenta appears to act as a nutrient sensor, altering transport based on the maternal supply and environmental stimuli (Jansson, 2006b, Wesolowski, 2017).

During times of fasting, glucose is released from glycogen, but maternal glycogen stores cannot provide an adequate amount of glucose to meet requirements for maternal energy and fetal growth. Augmentation is provided by cleavage of triacylglycerols, stored in adipose tissue, which results in free fatty acids and activation of lipolysis.

■ Glucose and Fetal Growth

Although dependent on the mother for nutrition, the fetus also actively participates in providing its own nutrition. At midpregnancy, fetal serum glucose concentration is independent of maternal levels and may exceed them. Glucose is the major nutrient for fetal growth and energy. Logically, mechanisms exist to minimize maternal glucose use so that the limited maternal supply is available to the fetus. As one example, human placental lactogen (hPL) is a hormone normally abundant in the mother but not the fetus and has an insulin antagonist effect. It blocks the peripheral uptake and use of glucose, while instead promoting mobilization and use of free fatty acids by maternal tissues (Chap. 5, p. 98). This hormone is also diabetogenic as discussed in Chapter 60 (p. 1068). Last, intrinsic epigenetic changes play a role (Hansen, 2017). For example, nonalcoholic fatty liver disease (NAFLD) is associated with fetal macrosomia (Lee, 2019).

Glucose Transport

The transfer of D-glucose across cell membranes is accomplished by a carrier-mediated, stereospecific, nonconcentrating process of facilitated diffusion. There are 14 glucose transport proteins (GLUTs) encoded by the *SLC2A* gene family and characterized by tissue-specific distribution (Joshi, 2021). Several of these are expressed by trophoblast (Stanirowski, 2017). GLUT-1, GLUT-3, and GLUT-4 primarily aid glucose uptake by the placenta and are located in the plasma membrane of the syncytiotrophoblast microvilli (Acosta, 2015; James-Allan, 2019). DNA methylation regulates expression of placental *GLUT* genes, with epigenetic modification across gestation (Novakovic, 2013). Methylation increases as pregnancy advances and is induced by almost all growth factors.

In addition to its transport role, the placenta uses glucose for its metabolic functions. Fetal and placental glucose consumption are inversely related. Thus, placental glucose use is a key modulator of maternal-fetal transfer (Michelsen, 2019).

Lactate is a product of glucose metabolism and transported across the placenta also by facilitated diffusion. By way of cotransport with hydrogen ions, lactate is probably transported as lactic acid.

Fetal Macrosomia

The precise biomolecular events in the pathophysiology of fetal macrosomia are not defined. Nonetheless, fetal hyperinsulinemia is clearly one driving force (Luo, 2012). As discussed with fetal-growth disorders in Chapter 47 (p. 824), insulin-like growth factor and leptin and other adipokines are important regulators of placental development and function (Gao, 2012). Maternal obesity begets fetal macrosomia. In addition, theories suggest that maternal obesity affects fetal cardiomyocyte growth that may result in fetal cardiomyopathy or even congenital heart disease (Roberts, 2015).

■ Leptin

This polypeptide hormone was originally identified as a product of adipocytes and a regulator of energy homeostasis by curbing appetite. It also contributes to angiogenesis, hemopoiesis, osteogenesis, pulmonary maturation, and neuroendocrine, immune, and reproductive functions (Briffa, 2015). Leptin is produced by the mother, fetus, and placenta. It is expressed in syncytiotrophoblast and fetal vascular endothelial cells. Of

placental production, 5 percent enters the fetal circulation, whereas 95 percent is transferred to the mother (Hauguel-de Mouzon, 2006).

Leptin concentrations peak in amnionic fluid at midpregnancy (Scott-Finley, 2015). Fetal serum leptin levels begin increasing at approximately 34 weeks and are correlated with fetal weight. This hormone is involved in the development and maturation of the heart, brain, kidneys, and pancreas, and its levels are decreased with fetal-growth restriction (Briffa, 2015; Yalinbas, 2019). Abnormal levels are associated with fetal-growth disorders, gestational diabetes, and preeclampsia, but not maternal obesity (Allbrand, 2018; Gurugubelli, 2018). Postpartum, leptin levels decline in both the newborn and mother. Perinatal leptin is associated with the development of metabolic syndromes later in life (Briffa, 2015).

Free Fatty Acids and Triglycerides

The term newborn has a large proportion of fat, which averages 15 percent of body weight (Kimura, 1991). Thus, late in pregnancy, a substantial part of the substrate transferred to the human fetus is stored as fat. Although maternal obesity raises placental fatty acid uptake and fetal fat deposition, it does not appear to affect fetal organ growth (Dubé, 2012). Neutral fat in the form of triglycerides does not cross the placenta, but glycerol does. Despite this, evidence supports that abnormal maternal concentrations of triglycerides—both low and high levels—are associated with major congenital anomalies (Nederlof, 2015).

There is preferential placental-fetal transfer of long-chain polyunsaturated fatty acids (Fonseca, 2018). Lipoprotein lipase is present on the maternal but not on the fetal side of the placenta. This arrangement favors hydrolysis of triacylglycerols in the maternal intervillous space yet preserves these neutral lipids in fetal blood. Fatty acids transferred to the fetus can be converted to triglycerides in the fetal liver.

The placental uptake and use of LDL is an alternative mechanism for fetal assimilation of essential fatty acids and amino acids (Chap. 5, p. 100). LDL binds to specific receptors in the coated-pit regions of the syncytiotrophoblast microvilli. The large LDL particle, measuring about 250,000 Da, is taken up by a process of receptor-mediated endocytosis. The apoprotein and cholesterol esters of LDL are hydrolyzed by lysosomal enzymes in the syncytium to yield: (1) cholesterol for progesterone synthesis; (2) free amino acids, including essential amino acids; and (3) essential fatty acids, primarily linoleic acid. Interestingly, maternal cholesterol is obligatory for steroid hormone synthesis, but increasing levels are associated with fetal aortic atherogenesis (de Nigris, 2018).

Amino Acids

The placenta concentrates many amino acids in the syncytiotrophoblast, which are then transferred to the fetal side by diffusion. In cordocentesis blood samples, the amino acid concentration in umbilical cord plasma is greater than in maternal venous or arterial plasma. DNA methylation serves to regulate transporter gene expression (Simner, 2017). Transport system activity is influenced by gestational age and environmental factors. These include heat stress, hypoxia, under- and overnutrition, and hormones such as glucocorticoids, growth hormone, and leptin (Briffa, 2015). Trophoblastic mammalian target of rapamycin complex 1 (mTORC1) regulates placental amino acid transporters and modulates transfer across the placenta (Jansson, 2012). In vivo studies suggest an upregulation of transport for certain amino acids and a greater delivery rate of these to the fetuses of women with gestational diabetes associated with fetal overgrowth (Jansson, 2006a).

Proteins

Placental transfer of larger proteins is limited, but there are exceptions. As discussed, IgG crosses the placenta in large amounts via endocytosis and trophoblast Fc receptors. IgG transfer depends on maternal levels of total IgG, gestational age, placental integrity, IgG subclass, and antigenic potential (Palmeira, 2012). Conversely, the larger immunoglobulins—IgA and IgM—of maternal origin are effectively excluded from the fetus.

Ions and Trace Metals

Calcium and phosphorus are actively transported from mother to fetus. Calcium is transferred for fetal skeletal mineralization (Olausson, 2012). A calcium-binding protein is produced in placenta. Parathyroid hormone–related protein (PTH-rP), as the name implies, acts as a surrogate PTH in many systems (Chap. 5, p. 99). PTH is not found in fetal plasma, but PTH-rP is present, suggesting that PTH-rP is the fetal parathormone (Martin, 2016). The expression of PTH-rP in cytotrophoblasts is modulated by the extracellular concentration of Ca^{2+} (Hellman, 1992). It seems possible that PTH-rP synthesized in decidua, placenta, and other fetal tissues is important in fetal Ca^{2+} transfer and homeostasis.

Another example is the unidirectional transfer of iron. Typically, maternal plasma iron concentration is much lower than that in her fetus. Even with severe maternal iron-deficiency anemia, the fetal hemoglobin mass is normal.

Iodine transport is clearly attributable to a carrier-mediated, energy-requiring active process. And, as discussed in Chapter 61 (p. 1097), the placenta concentrates iodine (Velasco, 2018). The concentrations of zinc in the fetal plasma also are greater than those in maternal plasma. Conversely, copper levels in fetal plasma are less than those in maternal plasma. This fact is of particular interest because important copper-requiring enzymes are necessary for fetal development.

Placental Sequestration of Heavy Metals

The heavy metal–binding protein metallothionein-1 is expressed in human syncytiotrophoblast. This protein binds and sequesters a host of heavy metals, including zinc, copper, lead, and cadmium. Despite this, fetal exposure is variable (Caserta, 2013). For example, lead enters the fetal environment at a level 90 percent of maternal concentrations. In contrast, placental transfer of cadmium is limited (Kopp, 2012).

The most common source of environmental cadmium is cigarette smoke.

Metallothionein also binds and sequesters copper in placental tissue. This accounts for the low copper levels in cord blood (Iyengar, 2001). It is possible that cadmium provokes metallothionein synthesis in the amnion. This may cause copper sequestration, a pseudocopper deficiency, and in turn, diminished amnion tensile strength.

Vitamins

The concentration of vitamin A (retinol) is greater in fetal than in maternal plasma and is bound to retinol-binding protein and to prealbumin. Retinol-binding protein is transferred from the maternal compartment across the syncytiotrophoblast. The transport of vitamin C—ascorbic acid—from mother to fetus is accomplished by an energy-dependent, carrier-mediated process. As a result, the concentration of ascorbic acid is two to four times higher in fetal plasma than in maternal plasma (Morriss, 1994). Levels of principal vitamin D metabolites, including 1,25-dihydroxycholecalciferol, are greater in maternal plasma than in fetal plasma. The 1β-hydroxylation of 25-hydroxyvitamin D_3 is known to take place in placenta and in decidua.

PLACENTAL ROLE IN EMBRYOFETAL DEVELOPMENT

The placenta is the organ of transfer between mother and fetus. Within this bidirectional maternal-fetal interface, maternal oxygen and nutrients transfer to the fetus, whereas CO_2 and metabolic wastes are directed back to the mother. Fetal blood, which is contained in the fetal capillaries of the chorionic villi, has no direct contact with maternal blood, which remains in the intervillous space. Instead, bidirectional transfer depends on processes that allow or aid the transport through the syncytiotrophoblast that lines chorionic villi (Michelsen, 2017).

With this system, breaks in the chorionic villi permit escape of fetal/placental cells and other blood-borne material into the maternal circulation. This leakage is the mechanism by which some D-negative women become sensitized by the erythrocytes of their D-positive fetus (Chap. 18, p. 353). The escape of fetal cells can also lead to fetal microchimerism from entrance of allogeneic fetal cells, including trophoblast, into maternal blood and other organs (Rijnink, 2015). Volumes are estimated to range from 1 to 6 cells/mL at midpregnancy. Some fetal cells become "immortal" in that they persist in the maternal circulation and organs following pregnancy. As discussed in Chapter 61 (p. 1109), the clinical corollary is that some maternal autoimmune diseases such as Hashimoto thyroiditis may be provoked by such microchimerism.

Last, cell-free DNA (cfDNA) is released from syncytiotrophoblast during normal physiological cell turnover. After 10 weeks, 10 to 15 percent of all cfDNA in maternal plasma is trophoblastic DNA (Norton, 2015; Shaffer, 2018). This phenomenon underlies one maternal-serum screening method for fetal aneuploidy, which is discussed in Chapters 16 and 17 (pp. 327 and 335).

The Intervillous Space

Maternal blood within the intervillous space is the primary source of maternal–fetal transfer. Blood from the maternal spiral arteries directly bathes the trophoblast layer that surrounds the villi. Substances transferred from mother to fetus first enter the intervillous space and are then transported to the syncytiotrophoblast. As such, the chorionic villi and intervillous space function together as the fetal lung, gastrointestinal tract, and kidney.

Circulation within the intervillous space is described in Chapter 5 (p. 92). Intervillous and uteroplacental blood flow increases throughout pregnancy, and at term, the residual volume of the intervillous space approximates 140 mL. Moreover, uteroplacental blood flow near term ranges from 700 to 900 mL/min, and most of this blood apparently goes to the intervillous space (Pates, 2010).

Placental Transfer

In the terminal villi, substances that pass from maternal to fetal blood must first traverse the syncytiotrophoblast, the attenuated cytotrophoblast layer, the thinned villous stroma, and finally, the fetal capillary wall. Although this histological barrier separates maternal and fetal circulations, it is not a simple physical barrier. First, throughout pregnancy, syncytiotrophoblast actively or passively permits, facilitates, and adjusts the amount and rate of substance transfer to the fetus. As discussed in Chapter 5 (p. 92), the maternal-facing syncytiotrophoblast surface is characterized by a complex microvillus structure. The fetal-facing basal cell membrane is the site of transfer to the intravillous space. Finally, the villous capillaries are an additional site for transport from the intravillous space into fetal blood, or vice versa. In determining the effectiveness of the human placenta as an organ of transfer, several variables are important and shown in Table 7-2. Epigenetic placental changes brought about by methylation of genes engaged in nutrient transfer also play a role (Kerr, 2018).

Mechanisms of Transfer

Most substances with a molecular mass <500 Da pass readily through placental tissue by simple diffusion. These include

TABLE 7-2. Variables of Maternal-Fetal Substance Transfer

Maternal plasma concentration
Maternal carrier-protein binding
Maternal blood flow rate through the intervillous space
Trophoblast surface area size available for exchange
Physical trophoblast properties to permit simple diffusion
Trophoblast biochemical machinery for active transport
Substance metabolism by the placenta during transfer
Fetal intervillous capillary surface area size for exchange
Fetal blood concentration of the substance
Fetal carrier-protein binding
Villous capillary blood flow rate
DNA methylation of transporter genes

oxygen, CO_2, water, most electrolytes, and anesthetic gases (Carter, 2009). Some low-molecular-weight compounds undergo transfer facilitated by syncytiotrophoblast. These are usually those that have low concentrations in maternal plasma but are essential for normal fetal development.

Insulin, steroid hormones, and thyroid hormones cross the placenta, but very slowly. The hormones synthesized in situ in the syncytiotrophoblast enter both the maternal and fetal circulations, but not equally (Chap. 5, p. 86). Examples are hCG and hPL concentrations, which are much lower in fetal plasma than in maternal plasma. High-molecular-weight substances usually do not traverse the placenta, but there are important exceptions. As discussed, one is IgG—molecular weight 160,000 Da—which is transferred by way of a specific trophoblast receptor–mediated mechanism (Stach, 2014).

Although simple diffusion is an important method of placental transfer, the trophoblast and chorionic villus unit demonstrate enormous selectivity in transfer. As discussed, important in this regard is DNA methylation of transporter genes (Kerr, 2018; Simner, 2017). The net results are different metabolite concentrations on the two sides of the villus.

Transfer of Oxygen and Carbon Dioxide

Placental oxygen transfer is blood flow limited. Using estimated uteroplacental blood flow, Longo (1991) calculated oxygen delivery to be approximately 8 mL O_2/min/kg of fetal weight. Because of the continuous passage of oxygen from maternal blood in the intervillous space to the fetus, its oxygen saturation resembles that in maternal capillaries. The average oxygen saturation of intervillous blood is estimated to be 65 to 75 percent, with a partial pressure (Pao_2) of 30 to 35 mm Hg. The oxygen saturation of umbilical vein blood is similar but has a somewhat lower oxygen partial pressure (Ramsay, 1996). As noted earlier, fetal hemoglobin has a higher oxygen affinity than adult hemoglobin.

The placenta is highly permeable to CO_2, which traverses the chorionic villus by diffusion more rapidly than oxygen. Near term, the partial pressure of carbon dioxide ($Paco_2$) in the umbilical arteries averages 50 mm Hg, which is approximately 5 mm Hg higher than in the maternal intervillous blood. Fetal blood has less affinity for CO_2 than does maternal blood, thereby favoring CO_2 transfer from fetus to mother. Also, mild maternal hyperventilation results in a fall in $Paco_2$ levels, favoring a transfer of CO_2 from the fetal compartment to maternal blood.

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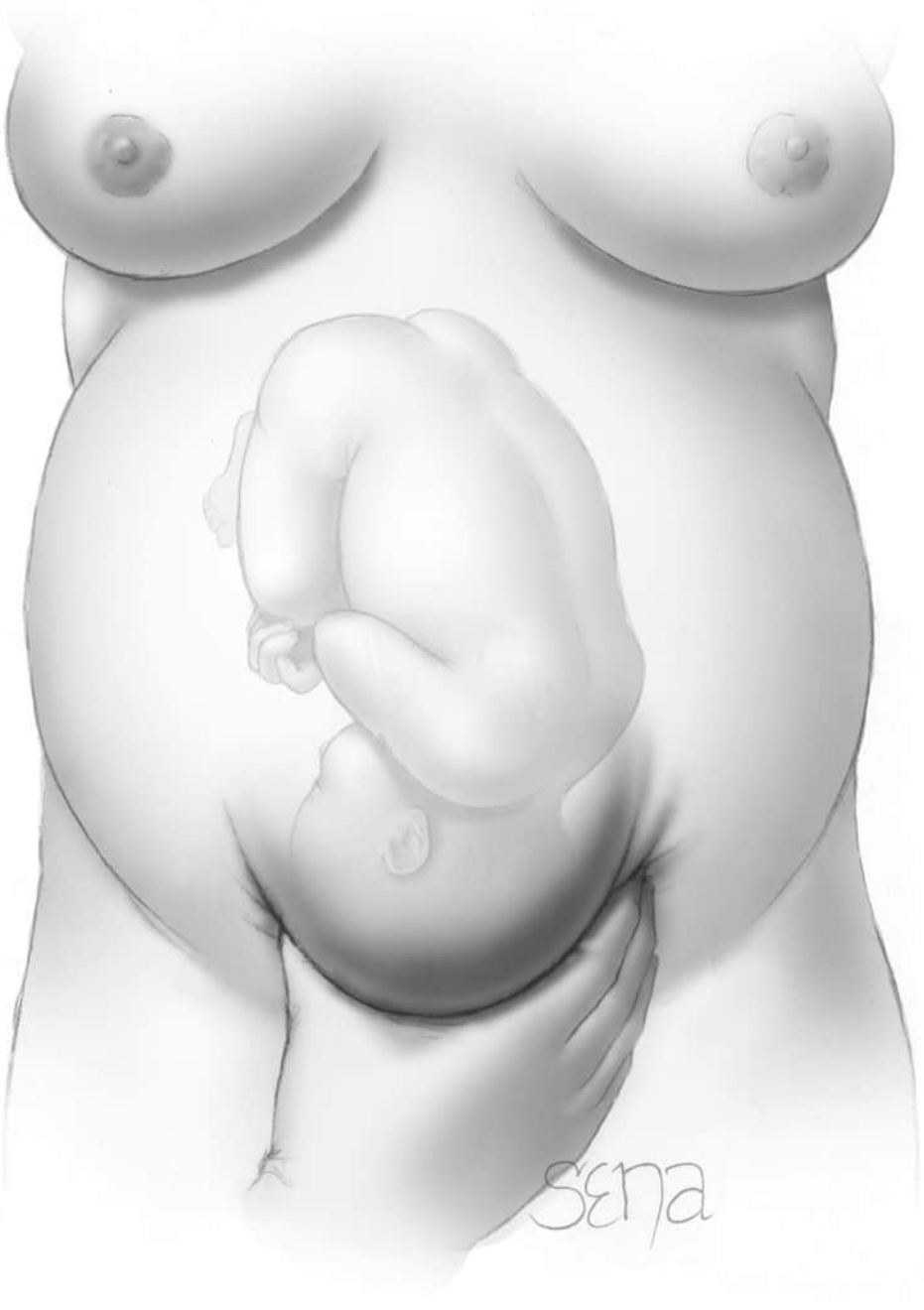
SECTION 4

PRECONCEPTIONAL AND PRENATAL CARE



CHAPTER 8

Teratology, Teratogens, and Fetotoxic Agents

Birth defects are common. Of all newborns, 2 to 3 percent have a major congenital abnormality detectable at birth (Cragan, 2009; Dolk, 2010). Some medications undoubtedly pose significant risk to the developing embryo or fetus (Table 8-1). However, 80 percent of birth defects do not have an obvious etiology, and of those with an identified cause, nearly 95 percent of cases have chromosomal or genetic origins (Feldkamp, 2017). The U.S. Food and Drug Administration (FDA) (2018) estimates that <1 percent of all birth defects are caused by medications (Fig. 8-1).

That said, significant concern surrounds medication use in pregnancy. This is because many pregnant women are prescribed medications and because safety data are often lacking. Investigators from the National Birth Defects Prevention Study found that women take an average of two to three medications per pregnancy and that 70 percent use medication in the first trimester (Mitchell, 2011). A population-based review from Canada found that 65 percent of women fill ≥1 prescription during pregnancy (Leong, 2019). Between 2010 and 2019, the FDA approved 290 new drugs, and only 11 percent had human data related to pregnancy (Byrne, 2020).

TERATOLOGY

The study of birth defects and their etiology is termed teratology, derived from the Greek *teratos,* meaning monster. A *teratogen* may be broadly defined as any agent that acts during embryonic or fetal

TABLE 8-1. Selected Teratogenic and Fetotoxic Agents

Acitretin	Methotrexate
Alcohol	Mycophenolate
Angiotensin-converting enzyme inhibitors	Nitrofurantoin
Angiotensin-receptor blockers	Non-steroidal anti-inflammatory drugs
Bexarotene	Paroxetine
Carbamazepine	Phenobarbital
Cocaine	Phenytoin
Corticosteroids	Radioactive iodine
Cyclophosphamide	Ribavirin
Endothelin-receptor antagonists[a]	Sulfonamides
Fluconazole	Tamoxifen
Isotretinoin	Tetracyclines
Lead	Thalidomide and analogues[b]
Leflunomide	Tobacco
Lithium	Toluene
Marijuana	Topiramate
Mercury	Trastuzumab
Methamphetamine	Valproic acid
Methimazole	Warfarin

[a]Includes ambrisentan, bosentan, and macitentan.
[b]Includes lenalidomide and pomalidomide.

development to produce a permanent alteration of form or function. Thus, a teratogen may be a medication or other chemical substance, a physical or environmental factor such as heat or radiation, a maternal metabolite as in diabetes or phenylketonuria, or an infection such as cytomegalovirus.

Strictly defined, a teratogen causes structural abnormalities. A *hadegen*—after the god Hades—is an agent that interferes with normal maturation and function of an organ. A *trophogen* is an agent that alters growth. Substances in the latter two groups typically affect development in the fetal period or postnatally and are thus fetotoxins rather than teratogens.

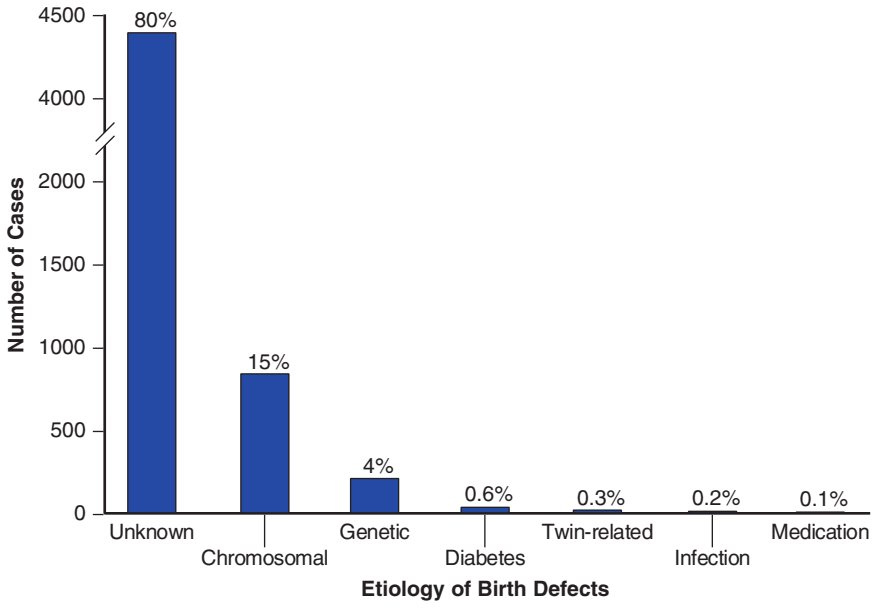


FIGURE 8-1 Etiology of birth defects. Known and unknown causes of 5504 birth defects from a population-based review of 270,878 births.

Criteria for Determining Teratogenicity

The guidelines shown in Table 8-2 were proposed by Shepard (1994) as a framework for discussion and have proved useful for nearly 30 years. Although each individual criterion is not required to establish teratogenicity, the following tenets should be considered (Shepard, 2002a):

- The abnormality has been completely characterized. This is preferably done by a geneticist or dysmorphologist because different genetic and environmental factors may produce similar defects. It is easiest to prove causation when a rare exposure produces a rare anomaly, when at least three cases with the same exposure have been identified, and when the defect is severe.
- The agent must cross the placenta. Although almost all drugs cross the placenta, transport must be of sufficient quantity to directly influence embryonic or fetal development or to alter maternal or placental metabolism to exert an indirect effect. Placental transfer depends on maternal metabolism; on specific characteristics of the drug, such as protein binding and storage, molecular size, electrical charge, and lipid solubility; and on placental metabolism, such as by the cytochrome P_{450} enzyme system. In early pregnancy, the placenta also has a relatively thick membrane that slows diffusion.
- Exposure must occur during a critical developmental period.
  - The *preimplantation period* is the 2 weeks between fertilization and implantation and is known as the "all or none" period. As the zygote undergoes cleavage, an insult damaging a large number of cells typically causes embryonic death. However, if only a few cells are injured, compensation may be possible and allow normal development.
  - The *embryonic period* extends from the second through the eighth week postconception. It encompasses organogenesis and is thus the most crucial period with regard to structural malformations. Critical developmental periods for each organ system are illustrated in Figure 7-2 (p. 122).
  - The *fetal period*, which is beyond 8 weeks postconception, is characterized by continued maturation and functional development. During this time, certain organs remain vulnerable.
- A biologically plausible association is supportive. Because birth defects and medication exposures are both common, they may be temporally but not causally related.
- Epidemiological findings must be consistent. Because initial evaluation of teratogen exposure is often retrospective, it may be hampered by recall bias, inadequate reporting, and

TABLE 8-2. Criteria for Determining Teratogenicity

Essential Criteria:

1. Careful delineation of clinical cases, particularly if there is a specific defect or syndrome
2. Proof that exposure occurred at a critical time during development (see Fig. 7-2, p. 122)
3. Consistent findings by at least two epidemiological studies with:
   a. exclusion of bias,
   b. adjustment for confounding variables,
   c. adequate sample size (power),
   d. prospective ascertainment if possible, and
   e. relative risk (RR) of 3.0 or greater, some recommend RR of 6.0 or greater

   or

   For a rare environmental exposure associated with a rare defect, at least three reported cases. This is easiest if the defect is severe.

Ancillary Criteria:

4. The association is biologically plausible
5. Teratogenicity in experimental animals is important but not essential
6. The agent acts in an unaltered form in an experimental model

incomplete assessment of the exposed population. Potential confounding factors include varying dosages, concomitant drug therapy, and comorbid maternal disease(s). Familial and environmental variables also can influence development of birth defects. Thus, an important criterion for teratogenicity is that two or more high-quality epidemiological studies report similar findings. Last, a relative risk of *3.0 or greater* is generally considered necessary to support the hypothesis, whereas a lesser risk is interpreted with caution (Khoury, 1992).

- The suspected teratogen causes a defect in animal studies. This criterion is not obligatory, and for litigation purposes, establishment of a causal relationship between an exposure and an outcome in humans requires human data (Teratology Society Public Affairs Committee, 2005).

Failure to employ these tenets and criteria has contributed to erroneous conclusions regarding the safety of some widely used drugs. The poster child for this is the medicolegal fiasco surrounding Bendectin. This antiemetic was a combination of doxylamine and pyridoxine, with or without dicyclomine. More than 30 million women used this drug worldwide, and it was safe and effective for nausea and vomiting in early pregnancy. The 3-percent congenital anomaly rate among exposed fetuses was not different from the background rate (McKeigue, 1994). Despite considerable evidence that this combination of an antihistamine and a B-vitamin is not teratogenic, Bendectin was the target of numerous lawsuits, and the financial burden of defending these forced its withdrawal from the marketplace in 1983. Consequently, hospitalization rates for hyperemesis doubled (Koren, 1998). Ironically, the combination of doxylamine and pyridoxine was subsequently remarketed under the brand name Diclegis and was approved by the FDA in 2013.

Studies in Pregnant Women

The study of medication safety—or teratogenicity—in pregnant women is fraught with complications. First, animal studies are necessary but insufficient. For example, thalidomide was considered harmless in several animal species but resulted in phocomelia in thousands of children born across Europe in the late 1950s and early 1960s. Second, medications are rarely approved by the FDA for a pregnancy-related indication. Despite the Common Rule's removal of pregnant women as a vulnerable population, pregnant women are routinely excluded from research (Health and Human Services, 2017; Spong, 2018). Last, drug concentration and thus embryo-fetal exposure are affected by pregnancy physiology. This includes changes in volume of distribution, cardiac output, gastrointestinal absorption, hepatic metabolism, and renal clearance. In the absence of research trials, counseling is based on case reports or series, case-control studies, cohort studies, and pregnancy registry data.

Case Reports and Series

Many major teratogens were first described by clinicians who observed a rare defect occurring after a rare exposure. This has been termed the "astute clinician model" (Carey, 2009). Congenital rubella syndrome was identified in this way by Gregg (1941), an Australian ophthalmologist whose observations challenged the view that the uterine environment was impervious to noxious agents. Other teratogens identified through case series include thalidomide and alcohol (Jones, 1973; Lenz, 1962). Shepard (2002a) recommended that establishment of teratogenicity in this way requires proven exposure at a critical time in development and at least three such cases. Unfortunately, teratogens are less likely to be identified if the exposure is uncommon, if the defects are relatively nonspecific, or if abnormalities develop in only a small proportion of exposed fetuses. A major limitation of case series is their lack of a control group.

Case-control Studies

These studies begin with groups of affected infants (cases) and unaffected controls and are structured to allow retrospective assessment of prenatal exposure to particular substances. Case-control studies are an efficient way to study rare outcomes (Alwan, 2015). These permit investigators to evaluate associations and generate useful hypotheses. However, case-control studies have inherent potential for *recall bias.* Namely, parents of an affected infant are often more likely to recall exposure than those whose child is not ill. Confounding by indication is another concern, that is, the indication for the medication may be the cause of the birth defect. And importantly, birth defect registries have statistical power to detect small differences that may not be clinically meaningful. Grimes and Schulz (2012) have cautioned that unless odds ratios in case-control studies are above three- to fourfold, the observed associations may not be correct.

The National Birth Defects Prevention Study. Funded by Congress and coordinated by the National Center on Birth Defects and Developmental Disabilities, the National Birth Defects Prevention Study (NBDPS) took place between 1997 and 2013 across ten states with active birth defects surveillance programs. It is an excellent example of a population-based case-control study. The study involved approximately 32,000 cases and nearly 12,000 controls. Live births, stillbirths, and terminated pregnancies were included. Clinical geneticists reviewed each potential case, and standardized telephone interviews were conducted with women whose pregnancies were affected or unaffected to obtain information regarding medication exposure and risk factors (Mitchell, 2011; Reefhuis, 2015).

The NBDPS identified novel—although often small—associations between individual birth defects and several classes of medications. These include antibiotics, antidepressants, antiemetics, antihypertensives, asthma medications, nonsteroidal antiinflammatory drugs (NSAIDs), and opioids (Ailes, 2016; Broussard, 2011; Fisher, 2018; Hernandez, 2012; Lin, 2012; Munsie, 2011). Pregestational diabetes was significantly associated with 46 of 50 different abnormalities studied (Tinker, 2020). The NBDPS also found associations between birth defects and exposures such as secondhand smoke, pesticides, and nitrogen oxide, which is a marker of traffic-related air pollution (Hoyt, 2016; Rocheleau, 2015; Stingone, 2017).

The NBDPS had several key limitations related to study design. First, interviews were conducted 6 weeks to 2 years following delivery, which raised the likelihood of recall bias. For example, 25 percent of women could not remember which

antibiotic they had taken (Ailes, 2016). Additionally, only two thirds of women agreed to participate, and there were differences in ethnicity and socioeconomic status between cases and controls. These factors may have contributed to selection bias (Reefhuis, 2015). Further, medical records were not reviewed to verify dosage, and this precluded assessment of dose-response relationships. Last, a major limitation was that because the NBDPS included only a small number of cases of each birth defect and analyzed them for many different maternal exposures, it was not possible to adjust for multiple comparisons. As a result, some of the observed associations were likely due to chance (Alwan, 2015). As one example, the study of antibiotics and birth defects included 43 comparisons and identified four significant associations, but chance alone predicted that two associations would be identified (Ailes, 2016).

Importantly, the NBDPS was able to identify statistically significant odds ratios for which the absolute risk was quite low. Such findings have the potential to complicate counseling and prenatal management. In many instances, the risk identified by the NBDPS was as low as 1 case per 1000 exposed pregnancies.

Cohort Studies

These studies begin with cohorts of pregnant women who are exposed or unexposed to a particular medication. The percentage of infants or children affected with birth defects is examined in each cohort. Because individual birth defects are rare, cohort studies require a *very* large sample size. Medicaid datasets and private insurance claims databases are commonly used for cohort studies of teratogenicity in the United States (Ehrenstein, 2010). Inability to adjust for confounding variables—such as the indication for which the medication was needed—is an important limitation of this study design.

Pregnancy Registries

Potentially harmful agents may be monitored by clinicians who prospectively enroll exposed pregnancies in a registry. The FDA (2021) maintains an active webpage of Pregnancy Exposure Registries. As of 2021, this included registries for 115 individual medications and for medication groups used to treat asthma, attention deficit hyperactivity disorder, autoimmune diseases, cancer, diabetes, epilepsy, hepatitis B and C, human immunodeficiency virus infection, hypercholesterolemia, inborn errors of metabolism, inflammatory bowel disease, multiple sclerosis, narcolepsy, psychiatric illness, and transplant rejection. Similar to case series, exposure registries are hampered by lack of a control group. The prevalence of an abnormality identified through a registry requires knowledge of the baseline prevalence of that anomaly in the population. Investigators typically use a birth defect registry to assess population prevalence. One example is the Metropolitan Atlanta Congenital Defects Program, which is an active surveillance program established in 1967 for fetuses and infants with birth defects.

COUNSELING FOR MEDICATION EXPOSURE

Questions regarding medication and illicit drug use should be part of routine preconceptional and prenatal care. Misinformation is common. Individuals tend to underestimate the background risk for birth defects in the general population and exaggerate potential risks associated with medication exposure. In one population-based study of more than 270,000 births from Utah that included 5500 fetuses and infants with major birth defects, only 4 cases were attributed to medication exposure (see Fig. 8-1) (Feldkamp, 2017). And yet, Koren and colleagues (1989) reported that a fourth of women exposed to nonteratogenic drugs thought they had a 25-percent risk for fetal anomalies. Misinformation may be amplified by inaccurate reports in the lay press. Knowledgeable counseling may allay anxiety considerably and may even avert pregnancy termination.

Several sources are available to assist providers with accurate and updated risk information. With recent changes to the FDA labeling requirements, discussed next, the manufacturer's prescribing information has become increasingly helpful. We recommend using this content for initial counseling. Published research studies can be identified using PubMed, a free database tool from the National Center for Biomedical Information. Additionally, online databases such as Reprotox, TERIS, and Shepard's Online Catalog of Teratogenic Agents offer detailed reviews of medication risks. Lactmed, a database from the National Library of Medicine, specifically deals with medication use by breastfeeding women. Its entries on specific medications describe levels in breast milk and potential effects on the infant.

Ultimately, it is the responsibility of the clinician to interpret risk information. Medication dosage and route, timing of exposure during pregnancy, other medications used, and underlying medical condition(s) are considered in this analysis. Last, the risk from lack of treatment also is weighed.

Labeling Requirements

In 1979, the FDA developed a letter classification system (A, B, C, D, X) to provide therapeutic guidance for prescribing medications in pregnancy. These letter categories were intended to simplify risk-benefit data using summary statements regarding available evidence from human or animal studies of embryonic–fetal risk. Unfortunately, information regarding medication risk was often incomplete and led to an overreliance on the category definition.

To address these deficiencies, new FDA (2014, 2020b) labeling requirements were created and went into effect in 2015. The label provides a framework to aid prescribing decisions by more clearly communicating risks and benefits. Information about each medication now incorporates a detailed summary of risks, clinical considerations, and available data (Table 8-3). Registry information is included when available. For each medication, a lactation subsection is provided, and a section addressing potential risks in females and males of reproductive potential is presented. In addition to risks associated with specific medications, the label is required to include the background risk of major birth defects and miscarriage in the general population. Because of the level of detail in the new labels, the information can be indispensable for counseling.

Presenting Risk Information

Counseling should cover not only the embryonic and fetal risks from drug exposure, but also the risks and/or genetic

TABLE 8-3. Food and Drug Administration Pregnancy Labeling Requirements

Label Subsection	Categories	Selected Specific Content
8.1 Pregnancy	Pregnancy exposure registry	Presence of a registry and contact information
	Risk summary	Structural abnormalities, embryo-fetal and/or infant mortality information, functional impairments, and alterations to growth
		Human data, animal data, and pharmacology information as an integrated summary
		Incidence of adverse outcomes, including dose effects, exposure duration, and gestational age
	Clinical considerations	Disease-associated maternal and embryo-fetal risks; dose adjustments (pregnancy or postpartum); maternal, fetal or neonatal adverse reactions; effects on labor or delivery
	Data	Content from human and animal studies and their findings and limitations
8.2 Lactation	Risk summary	Presence of a drug or its metabolite(s) in human milk, effects on the breastfed child, and effects on milk production
	Clinical considerations	Summary of available data and information about minimizing exposure
	Data	Includes content from human and animal studies that inform clinical considerations
8.3 Males and females of reproductive potential	Pregnancy testing	Testing requirement or recommendation before, during, or after drug use
	Contraception	Contraception requirement or recommendation before, during, or after drug use
	Infertility	Effects on fertility, potential reversibility, mutagenesis data, and pre-implantation loss effects

From Food and Drug Administration, 2020b.

implications of the condition for which the drug is administered. Risks associated with not treating the condition also are described. Even the manner in which information is presented affects perception. For example, women given negative information—such as a 2-percent chance of a malformed newborn—are more likely to perceive an exaggerated risk than women given positive information—such as a 98-percent chance of an unaffected infant (Jasper, 2001). Instead of citing a higher odds ratio, it may be helpful to provide the *absolute risk* for a particular defect or the *attributable risk*, which is the difference between prevalence in exposed and unexposed individuals (Conover, 2011). The association between oral corticosteroid medications and cleft lip sounds far more concerning when presented as a tripling or 200-percent increase in risk than when described as an increase from 1 to 3 cases per 1000 or as a 99.7-percent likelihood of no cleft development following exposure.

With a few notable exceptions, most commonly prescribed drugs and medications can be used with relative safety during pregnancy. Many drugs discussed in this chapter are *low-risk teratogens*, which are medications that produce defects in fewer than 10 per 1000 maternal exposures (Shepard, 2002a). Because risks conferred by low-risk teratogens are so close to the population background rate of fetal anomalies, they may not be a major factor in deciding whether to discontinue treatment for an important condition (Shepard, 2002b). All women have an approximate 3-percent chance of having a fetus or newborn with a major anomaly. Although exposure to a confirmed teratogen may elevate this risk, the magnitude of the increase is usually only 1 or 2 percent or at most, doubled or tripled. The concept of risk versus benefit is often central to counseling. Some untreated diseases pose a more serious threat to both mother and fetus than medication exposure risks.

TERATOGENIC AND FETOTOXIC AGENTS

Considering the thousands of compounds available, relatively few medications and other substances are considered to be major human teratogens or to have significant fetotoxicity. The most common examples are listed in Table 8-1. With few exceptions, in every clinical situation potentially requiring therapy with a known teratogen, alternative drugs can be given with relative safety. Realizing limitations in available evidence, pregnant women should be advised to take any medication only when it is clearly needed. Detailed sonography is generally indicated if the fetus has been exposed to any major teratogen during the embryonic period.

Alcohol

Ethanol is a potent and prevalent teratogen. It is considered the leading cause of preventable developmental disabilities

worldwide (Hoyme, 2016). In the United States, alcohol use is reported by 10 percent of pregnant women (England, 2020). Nearly 10 percent of such women admit to binge drinking in the first trimester, and 1 percent report binge drinking in the second and third trimesters.

The fetal effects of alcohol abuse have been recognized since the 1800s. Lemoine (1968) and Jones (1973) and their coworkers are credited with describing the spectrum of alcohol-related fetal defects known as *fetal alcohol syndrome.* Criteria are shown in Table 8-4 (Hoyme, 2016). For every child with the syndrome, many more are born with neurobehavioral deficits from alcohol exposure. *Fetal alcohol spectrum disorder (FASD)* is an umbrella term that includes five conditions attributed to prenatal alcohol damage: (1) fetal alcohol syndrome, (2) partial fetal alcohol syndrome, (3) alcohol-related birth defects, (4) alcohol-related neurodevelopmental disorder, and (5) neurobehavioral disorder associated with prenatal alcohol exposure (Williams, 2015). The prevalence of FASD exceeds 1 percent in 76 countries, and 1 in 13 women who consume alcohol in pregnancy has a child with FASD (Lange, 2017). The birth prevalence of fetal alcohol syndrome is estimated to be as high as 1 percent in the United States (Centers for Disease Control, 2015; Guerri, 2009). Further, studies of school-aged children have identified FASD in 2 to 5 percent (May, 2009, 2014).

TABLE 8-4. Criteria for Prenatal Alcohol Exposure, Fetal Alcohol Syndrome, and Alcohol-Related Birth Defects

Documented Prenatal Alcohol Exposure—One or More Required

1. ≥6 drinks per week for ≥2 weeks
2. ≥3 drinks per occasion for ≥2 occasions
3. Risk identified with a validated screening questionnaire
4. Laboratory testing indicating alcohol intoxication or positive alcohol-exposure biomarker
5. Documentation of an alcohol-related legal or social problem

Fetal Alcohol Syndrome Diagnostic Criteria—All Required

1. Dysmorphic facial features (≥2 required)
   a. Short palpebral fissures
   b. Thin vermilion border of the upper lip
   c. Smooth philtrum
2. Prenatal and/or postnatal growth impairment, ≤10th percentile
3. Abnormal brain growth, morphogenesis, or physiology (≥1 required)
   a. Head circumference ≤10th percentile
   b. Structural brain abnormalities
   c. Recurrent nonfebrile seizures
4. Neurobehavioral impairment (defined as >1.5 SD below mean)
   a. Child <3 years: developmental delay
   b. Child ≥3 years: global cognitive impairment, or cognitive deficit in at least 1 neurobehavioral domain, or behavioral deficit in at least 1 domain

Alcohol-Related Birth Defects

Cardiac: atrial or ventricular septal defect, aberrant great vessels, conotruncal heart defects
Skeletal: radioulnar synostosis, vertebral segmentation defects, joint contractures, scoliosis
Renal: aplastic or hypoplastic kidneys, dysplastic kidneys, horseshoe kidney, ureteral duplication
Eyes: strabismus, ptosis, retinal vascular abnormalities, optic nerve hypoplasia
Ears: conductive or neurosensory hearing loss

SD = standard deviation.

Criteria

Fetal alcohol syndrome has specific criteria (see Table 8-4). These include central nervous system (CNS) abnormalities, pre- or postnatal growth impairment, and a characteristic pattern of minor facial abnormalities (Fig. 8-2). Similar criteria have been established for the other conditions that make up FASD (Hoyme, 2016). Prenatal alcohol exposure criteria also are available to assist with assessment.

Alcohol-related birth defects include cardiac and renal anomalies, orthopedic problems, and abnormalities of the eyes and ears (see Table 8-4). An association has further been reported between periconceptional alcohol use and omphalocele and gastroschisis (Richardson, 2011). There are no established sonographic criteria for prenatal diagnosis of fetal alcohol syndrome. At Parkland Hospital, we reserve detailed sonography for pregnancies that have met the exposure criteria listed in Table 8-4. Third-trimester assessment of fetal growth also should be considered.

Fetal vulnerability to alcohol is modified by genetic and environmental factors, nutritional status, coexisting maternal disease, and maternal age (Abel, 1995). Binge drinking, however, is believed to pose particularly high risk for alcohol-related birth

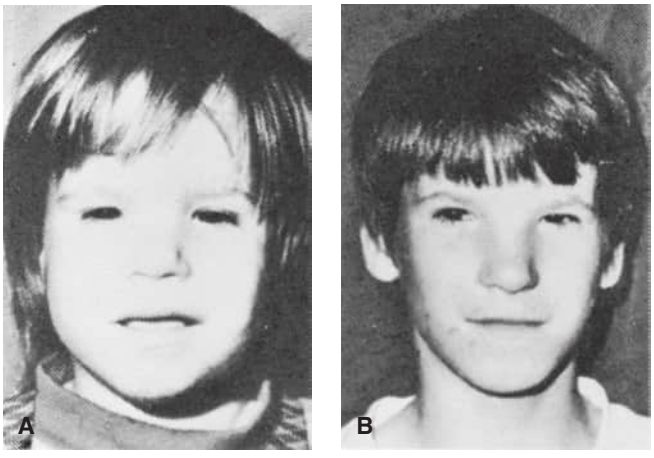


FIGURE 8-2 Fetal alcohol syndrome. **A.** At 2½ years. **B.** At 12 years. Note persistence of short palpebral fissures, epicanthal folds, flat midface, hypoplastic philtrum, and thin upper vermilion border. (Reproduced with permission from Streissguth AP, Clarren, SK, Jones KL. Natural history of fetal alcohol syndrome: a 10-year follow-up of eleven patients, Lancet. 1985 Jul 13;2(8446):85–91.)

defects and has also been linked to a greater risk for stillbirth (Centers for Disease Control, 2015; Strandberg-Larsen, 2008). The American College of Obstetricians and Gynecologists, Centers for Disease Control and Prevention (CDC), and the American Academy of Pediatrics have stressed that *no* amount of alcohol can be considered safe in pregnancy (American College of Obstetricians and Gynecologists, 2020a; Williams, 2015).

Antiepileptic Medications

Traditionally, women with epilepsy requiring treatment with medication were informed that their risk for fetal malformations was increased. More recent data suggest that the risk may not be as great as once thought, particularly for newer agents. The most frequently reported anomalies are orofacial clefts, cardiac malformations, and neural-tube defects.

Of agents in current use, valproic acid confers the highest risk (Vajda, 2016). The North American Antiepileptic Drug (NAAED) Pregnancy Registry reported that major malformations developed in 9 percent of fetuses with first-trimester valproate exposure. This included a 4-percent risk for neural-tube defects (Hernandez-Diaz, 2012). School-aged children with prior in utero exposure to valproic acid have poorer cognitive development—including significantly lower intelligence quotient (IQ) scores—than children exposed to other antiepileptic drugs (Bromley, 2014; Meador, 2009).

Regarding other specific anticonvulsants, one metaanalysis identified increased malformation rates among exposed children compared with rates among children born to women with untreated epilepsy. Rates were twofold higher among children exposed to carbamazepine or phenytoin, threefold higher among those exposed to phenobarbital, and fourfold higher among those exposed to topiramate as monotherapy (Weston, 2016). The risk for fetal malformations is approximately doubled if multiple agents are required (Vajda, 2016). Several older anticonvulsants may produce a constellation of findings similar to the *fetal hydantoin syndrome*. The syndrome is characterized by distinctive features such as hypertelorism, low nasal bridge, and midface hypoplasia; hypoplasia of the distal phalanges and nails; growth impairment; and intellectual disability.

Importantly, evidence to date suggests that these risks do not appear to hold for the newer agents levetiracetam and lamotrigine (Mølgaard-Nielsen, 2011; Weston, 2016). A review of 208 pregnancies with first-trimester lamotrigine exposure from the Israeli Teratology Information Service found no increase in the rate of major malformations and no case of oral cleft (Diav-Citrin, 2017). Similarly, the International Lamotrigine Pregnancy Registry followed more than 1500 pregnancies with first trimester exposure and observed no effect on the rate of major malformations (Cunnington, 2011). The Motherisk Program reviewed eight studies of levetiracetam and concluded that monotherapy was associated with a 2-percent major malformation rate, no different from that for the general population (Chaudhry, 2014). More recently, a review of 465 pregnancies reported to the Levetiracetam Pregnancy Registry found no evidence of teratogenicity (Scheuerle, 2019).

Providers are encouraged to enroll pregnant women treated with antiepileptic medication in the NAAED Pregnancy Registry. Management of epilepsy in pregnancy is discussed in Chapter 63 (p. 1128).

Angiotensin-converting Enzyme Inhibitors and Receptor Blocking Drugs

These medications may result in *angiotensin-converting enzyme (ACE)-inhibitor fetopathy*. Normal renal development depends on the fetal renin-angiotensin system. ACE-inhibitor medication may cause fetal hypotension and renal hypoperfusion, with subsequent ischemia and anuria (Guron, 2000; Pryde, 1993). Reduced perfusion can result in fetal-growth restriction and calvarium maldevelopment, and oligohydramnios may lead to pulmonary hypoplasia and limb contractures (Barr, 1991). Because angiotensin-receptor blockers have a similar mechanism of action, concerns regarding fetotoxicity have been generalized to include this entire medication class. A recent review of nearly 200 pregnancies from teratology information services found a 30-percent fetopathy risk with angiotensin-receptor blockers compared with a 3-percent risk with ACE-inhibitor exposure beyond 20 weeks' gestation (Weber-Schoendorfer, 2020).

Concerns about ACE-inhibitor embryotoxicity have largely been disproven. In 2006, a review of 29,000 infants from the Tennessee Medicaid database identified a two- to threefold greater risk for neonatal cardiac and CNS abnormalities among the 209 that had prenatal ACE-inhibitor exposure (Cooper, 2006). Subsequent larger studies have not corroborated these observations. In a retrospective cohort study of more than 460,000 pregnancies, risks for birth defects were not higher with ACE inhibitors than with other antihypertensive medications (Li, 2011). Similarly, a review of 1.3 million pregnancies from the Medicaid Analytic eXtract found no increased risk for any malformation with ACE-inhibitor exposure after adjusting for confounding factors such as diabetes (Bateman, 2017). Thus, women with inadvertent first-trimester exposure to these medications may be reassured. Importantly, given the many therapeutic options for treating hypertension during pregnancy, discussed in Chapter 53 (p. 949), ACE inhibitors and angiotensin receptor-blocking drugs should be avoided in pregnancy.

Antifungal Medications

From this class of drugs, fluconazole has been associated with a pattern of congenital malformations resembling the autosomal recessive *Antley-Bixler syndrome*. Abnormalities include oral clefts, abnormal facies, and cardiac, skull, long-bone, and joint abnormalities. Such findings have been reported only with chronic, first-trimester, high-dose treatment at doses of 400 to 800 mg daily.

Regarding low-dose treatment of vulvovaginal candidiasis, the Motherisk Program conducted a systematic review of pregnancies with first-trimester oral fluconazole exposure of 150 or 300 mg in total (Alsaad, 2015). The overall risk for birth defects was not greater, although a small increase in rates of cardiac malformations could not be excluded. A population-based cohort study from Denmark identified a threefold greater

risk for tetralogy of Fallot following exposure to low-dose fluconazole (Mølgaard-Nielsen, 2013). The birth prevalence of tetralogy of Fallot rose from 3 to 10 cases per 10,000. Notably, investigators did not identify increased risks for 14 other birth defects previously associated with exposure to high-dose azole antifungal agents (Mølgaard-Nielsen, 2013). A subsequent review of more than 37,000 pregnancies with first-trimester fluconazole exposure did not identify an association with cardiac abnormalities (Zhu, 2020). Based on reported risks, we do not perform detailed sonography or fetal echocardiography following low-dose fluconazole exposure.

Antiinflammatory Agents

Nonsteroidal Antiinflammatory Drugs

This drug class includes both aspirin and traditional NSAIDs such as ibuprofen and indomethacin. They exert their effects by inhibiting prostaglandin synthesis. In a report from the NBDPS, at least 20 percent of pregnant women recall first-trimester NSAID use, particularly ibuprofen and aspirin, and such exposure is not a major risk factor for birth defects (Hernandez, 2012).

When taken in late pregnancy, however, indomethacin may cause constriction of the fetal ductus arteriosus and subsequent pulmonary hypertension. Fetal ductal constriction is more likely with third trimester use that exceeds 72 hours. The drug also may decrease fetal urine production and amnionic fluid volume (Rasanen, 1995; van der Heijden, 1994; Walker, 1994). In one systematic review, indomethacin tocolysis was associated with a 1.5-fold risk for bronchopulmonary dysplasia, intraventricular hemorrhage, and necrotizing enterocolitis (Hammers, 2015a,b).

Based on a review of 35 cases of oligohydramnios or neonatal kidney problems reported to the FDA Adverse Event Reporting System database, the FDA recommends that pregnant women ≥20 weeks' gestation avoid NSAID use (Food and Drug Administration, 2020a). If NSAIDs are needed for more than 48 hours, ultrasound evaluation of amnionic fluid should be considered. Oligohydramnios usually resolves within 6 days of discontinuing NSAIDs, but there are cases in which infants have died of renal failure.

With aspirin, a low dosage of 100 mg daily or less does *not* confer a greater risk for constriction of the ductus arteriosus or for adverse infant outcomes (Grab, 2000). As with other NSAIDs, however, high-dose aspirin use should be avoided, particularly in the third trimester.

Leflunomide

This is a pyrimidine-synthesis inhibitor used to treat rheumatoid arthritis. Leflunomide is considered contraindicated in pregnancy. In rats and rabbits, leflunomide results in hydrocephalus, eye anomalies, skeletal anomalies, and embryo death when given at or below human-equivalent doses (Sanofi-Aventis, 2016). The active metabolite, teriflunomide, is detectable in plasma for up to 2 years following discontinuation of the medication. Women who become pregnant while taking leflunomide, and even those of childbearing potential who have discontinued it, are recommended to undergo an accelerated drug elimination procedure with either cholestyramine or activated charcoal (Sanofi-Aventis, 2016).

Reassuringly, studies of exposed human pregnancies have not confirmed these teratogenic effects (Berard, 2018; Chambers, 2010). In a cohort of 60 women with first-trimester leflunomide exposure who completed cholestyramine washout, the rate of birth defects was not increased (Chambers, 2010). A recent review of more than 500 exposed pregnancies found that the rate of major birth defects was 3 percent, similar to the general population (Henson, 2020). The rate of spontaneous abortion also was not increased.

Antimicrobial and Antiviral Drugs

Medications used to treat infections are among those most frequently administered during pregnancy. Over the years, experience has accrued regarding their general safety. With few exceptions, commonly used antimicrobial agents are without embryo-fetal safety concerns.

Nitrofurantoin

From NBDPS results, first-trimester nitrofurantoin exposure is linked to a twofold risk for cleft lip (Ailes, 2016). Considering that the birth prevalence of clefts approximates 1 case per 1000, the likelihood that a nitrofurantoin-exposed fetus would *not* have a cleft would thus be 998 per 1000. For other birth defects, initial associations with this antibiotic did not persist in the final NBDPS cohort (Ailes, 2016).

In one systematic review of nitrofurantoin exposure in pregnancy, results of cohort and case-control studies differed (Goldberg, 2015). Five cohort studies included 9275 exposed pregnancies and nearly 1.5 million unexposed pregnancies, and the review found no higher risk for any malformation. However, among three case-control studies that had nearly 40,000 cases matched with 130,000 controls, the rate of hypoplastic left heart syndrome was threefold greater (Goldberg, 2015). For context, this increase in risk would result in a birth prevalence of fewer than 1 case per 1000 exposed infants. Nitrofurantoin is considered contraindicated in pregnant women with known or suspected glucose-6-phosphate dehydrogenase (G6PD) deficiency because of risk for hemolytic anemia and other hematologic abnormalities. In the absence of G6PD deficiency, the There are no concerns with second- or third-trimester nitrofurantoin use, and first-trimester use is appropriate if no suitable alternatives are available.

Sulfonamides

These drugs are often combined with trimethoprim and used to treat infections during pregnancy. One indication is treatment of methicillin-resistant *Staphylococcus aureus (MRSA)* infection. The NBDPS, which included 107 pregnancies with periconceptional trimethoprim-sulfamethoxazole exposure and birth defects, identified a fivefold greater risk to have offspring with esophageal atresia or diaphragmatic hernia (Ailes, 2016). Similar to findings with nitrofurantoin exposure, this degree of increase would confer a risk of approximately 1 case per 1000 exposed infants for these selected birth defects. However, these findings have not been corroborated by other reports. One review from the Medication Exposure in Pregnancy Risk Evaluation Program included more than 7500 infants with first-trimester exposure

to trimethoprim-sulfamethoxazole (Hansen, 2016). Compared with either unexposed infants or those exposed to penicillins or cephalosporins, no higher risk for any congenital abnormality was identified. Given this reassuring data, we consider sulfonamides appropriate for first-trimester use if suitable alternatives are lacking.

Sulfonamides are considered contraindicated in pregnant women with known or suspected G6PD deficiency because of risk for hemolytic anemia and other hematologic abnormalities. Additionally, sulfonamides displace bilirubin from protein-binding sites. Thus, if given near the time of preterm delivery, these agents theoretically might worsen neonatal hyperbilirubinemia. However, a population-based review of more than 800,000 births from Denmark found no association between exposure to sulfamethoxazole in late pregnancy and neonatal jaundice (Klarskov, 2013).

Tetracyclines

These drugs are not commonly used in pregnant women. They have been associated with yellowish-brown discoloration of the deciduous teeth when used after 25 weeks' gestation. The risk for subsequent dental caries is not increased (Billings, 2004; Kutscher, 1966). Doxycycline has a reduced ability to chelate calcium orthophosphate compared with other tetracyclines and is preferred if needed. A systematic review of doxycycline-exposed pregnancies identified no higher rates of either birth defects or staining of deciduous teeth (Cross, 2016).

Ribavirin

This antiviral nucleoside analogue is a component of therapy for hepatitis C infection, discussed in Chapter 58 (p. 1038). Ribavirin causes birth defects in multiple animal species at doses significantly lower than those recommended for human use. Reported malformations include skull, palate, eye, skeleton, and gastrointestinal abnormalities. The drug has a half-life of 12 days and persists in extravascular compartments following therapy discontinuation. Treated women must use two forms of contraception and have monthly pregnancy tests while on therapy and for 6 months following drug discontinuation (Merck, 2020). Ribavirin use is also contraindicated in men whose partners are pregnant.

■ Antineoplastic Agents

Cancer management in pregnancy includes many chemotherapeutic agents generally considered to be at least potentially toxic to the embryo, fetus, or both. For the many novel polyclonal antibody therapies designated as antineoplastics, there is little information concerning safety. The National Toxicology Program (2013) conducted a review of 300 pregnancies with first-trimester exposure and identified major malformations in 14 percent. Treatment of cancer in pregnancy is discussed in Chapter 66 (p. 1163). Risks associated with selected agents for which experience in pregnancy has accrued are considered next.

Cyclophosphamide

This alkylating agent inflicts a chemical insult on developing fetal tissues and leads to cell death and heritable DNA alterations in surviving cells. Pregnancy loss rates are greater, and reported fetal abnormalities include skeletal anomalies, limb defects, cleft palate, and eye abnormalities (Enns, 1999; Kirshon, 1988). The risk for a major abnormality is estimated to be 18 percent (National Toxicology Program, 2013). Surviving infants may have growth abnormalities and developmental delays. Environmental exposure among health-care workers is associated with a higher risk for spontaneous abortion.

Methotrexate

This folic-acid antagonist is a potent teratogen. It is used for cancer chemotherapy, immunosuppression of autoimmune diseases and psoriasis, nonsurgical treatment of ectopic pregnancy, and medical abortion. It acts similarly to aminopterin, which is no longer used clinically, and can cause defects known collectively as the fetal *methotrexate-aminopterin syndrome*. Associated craniofacial abnormalities include craniosynostosis with a "clover-leaf" skull, wide nasal bridge, low-set ears, and micrognathia (Del Campo, 1999). Exposure has also been linked to central nervous system abnormalities, cardiac defects, and limb anomalies (Cumberland Pharmaceuticals, 2020). Intellectual impairment has been described. The embryo is thought to be most vulnerable at 8 to 10 weeks postconception and at dosages of at least 10 mg/week. However, this is not universally accepted (Feldkamp, 1993). Because of its distribution, methotrexate can remain in the body for prolonged periods. Thus, preconceptional exposure is not without risk.

The standard 50-mg/m^2 dose given to treat ectopic pregnancy or to induce abortion exceeds the 10-mg/week threshold dose. Reports describe cardiac anomalies, particularly conotruncal defects, in intrauterine pregnancies inadvertently treated with methotrexate for suspected ectopic pregnancy (Dawson, 2014; Hyoun, 2012).

Tamoxifen

This nonsteroidal selective estrogen-receptor modulator (SERM) is used as an adjuvant to treat breast cancer. In animal studies, tamoxifen has been associated with malformations similar to those caused by diethylstilbestrol (DES) exposure in rodents, including vaginal adenosis. One review of 167 pregnancies reported a fetal abnormality in 13 percent but emphasized that evidence was limited (Schuurman, 2019). Abnormalities have included ambiguous genitalia and craniofacial anomalies.

Trastuzumab

This is a recombinant monoclonal antibody directed to the human epidermal growth factor receptor 2 (HER2) protein. Used to treat breast and gastric cancers that express HER2 protein, this drug has not been associated with fetal malformations. However, postmarketing surveillance identified cases of oligohydramnios sequence resulting in pulmonary hypoplasia, renal failure, skeletal abnormalities, and neonatal death (Genentech, 2020). Surveillance for these complications is recommended for exposed pregnancies and for those treated at any time in the 7 months prior to conception. A trastuzumab pregnancy exposure registry and a pregnancy pharmacovigilance program have been established to monitor pregnancy outcomes. These warnings also apply to those treated with ado-trastuzumab emtansine.

Endothelin-receptor Antagonists

Bosentan, ambrisentan, and macitentan are three endothelin-receptor antagonists used to treat pulmonary arterial hypertension (Chap. 52, p. 930). The endothelin-receptor signaling pathway is important for neural-crest development. Mice deficient in endothelin receptors develop neural-crest cell defects that include craniofacial and cardiac outflow tract abnormalities (de Raaf, 2015). Each of these three agents has been found to cause similar birth defects in multiple animal species (Janssen, 2019a,b). No human data are available. Endothelin-receptor antagonists may be obtained only through restricted access programs, each of which has stringent requirements that include contraception and monthly pregnancy testing (Gilead, 2019; Janssen, 2019a,b).

Immunosuppressant Medications

Selected autoimmune diseases and their treatment are reviewed in Chapter 62 (p. 1109).

Corticosteroids

Glucocorticoids and mineralocorticoids have antiinflammatory and immunosuppressive actions. They are used to treat serious disorders such as asthma and autoimmune disease. Corticosteroids have been associated with orofacial clefts in animal studies, but the absolute risk is small. In a metaanalysis of case-control studies by the Motherisk Program, systemic corticosteroid exposure was associated with a threefold rate increase, conferring an absolute risk of 3 clefts per 1000 exposed fetuses (Park-Wyllie, 2000). A 10-year prospective cohort study by the same group, however, did not identify an increased overall risk for major malformations. Based on these findings, corticosteroids are not considered to represent a major teratogenic risk.

Potential risks associated with prednisone or methylprednisolone are considered to be lower than those with other corticosteroids. Prednisolone, the active metabolite of prednisone, is itself metabolized and rendered inactive by the placental enzyme 11β-hydroxysteroid dehydrogenase 2 (Murphy, 2007). Thus, it is thought to reach the fetus less effectively.

Mycophenolate Mofetil

This inosine monophosphate dehydrogenase inhibitor, and a related agent, mycophenolic acid, are immunosuppressants. They are used to prevent rejection in organ-transplant recipients and to treat autoimmune disease (Chap. 62, p. 1112). Mycophenolate is a potent teratogen. From the National Transplantation Pregnancy Registry, of pregnancies in which mycophenolate was not discontinued until after the first trimester, birth defects complicated 30 percent, and another 30 percent spontaneously aborted (King, 2017). One prospective review by the European Network of Teratology Information Services similarly identified a spontaneous loss rate of nearly 30 percent in exposed pregnancies. More than 20 percent of liveborn infants had major anomalies (Hoeltzenbein, 2012).

Many affected infants have a pattern of defects termed *mycophenolate embryopathy*. This includes microtia, auditory canal atresia, clefts, coloboma and other eye anomalies, short fingers with hypoplastic nails, and cardiac defects (Anderka, 2009; Merlob, 2009). A Risk Evaluation and Mitigation Strategy (REMS) has been developed for mycophenolate prescribers who treat women with reproductive potential. REMS are safety strategies mandated by the FDA to help manage known risks associated with a medicine yet still allow patients to have access to the benefits of a given drug.

Lead

Lead crosses the placenta via passive diffusion. Prenatal lead exposure is associated with fetal-growth impairment and with childhood neurodevelopmental delays. According to the CDC (2010), no level of lead exposure is considered safe in pregnancy. Although routine testing is not recommended, risk factors should be assessed in all pregnancies (American College of Obstetricians and Gynecologists, 2019a). Care and testing for at-risk pregnancies is discussed in Chapter 10 (p. 188).

Mercury

The developing nervous system is particularly susceptible to mercury. In the 1950s and early 1960s, children born near Minamata Bay, Japan were found to have congenital Minamata disease—severe neurological abnormalities from methylmercury exposure in utero (Yorifuji, 2020). Prenatal exposure causes disturbances in neuronal cell division and migration. This leads to a range of defects from microcephaly to intellectual disability, choreo-athetoid movement abnormalities, motor delays, and behavioral abnormalities (Grandjean, 2011).

The principal concern for prenatal mercury exposure is the consumption of certain species of large fish and seafood (Chap. 10, p. 188). Methylmercury cannot be eliminated by cooking. It crosses the placenta and can accumulate in the fetus. The FDA (2019) advises that pregnant women and breastfeeding mothers avoid consumption of king mackerel, marlin, orange roughy, shark, swordfish, tilefish, and bigeye tuna.

Psychiatric Medications

Treatment of psychiatric illness in pregnancy, including a discussion of the risks and benefits of various psychiatric medications, is described in Chapter 64 (p. 1142).

Antipsychotic Medications

No antipsychotic medications are considered teratogenic. Exposed neonates can manifest abnormal extrapyramidal muscle movements and withdrawal symptoms that include agitation, abnormally enhanced or diminished muscle tone, tremor, agitation, somnolence, respiratory abnormalities, and feeding difficulty. Such findings are nonspecific and transient. An FDA (2017) alert cited all medications in this class. Included are older medications like haloperidol and chlorpromazine and newer medications such as aripiprazole, olanzapine, quetiapine, and risperidone.

Lithium

This medication has been associated with Ebstein anomaly, a rare cardiac abnormality that otherwise complicates only 1

per 20,000 births. Ebstein anomaly is characterized by apical displacement of the tricuspid valve, often resulting in severe tricuspid regurgitation and marked right atrial enlargement. A report from the Lithium Baby Registry initially suggested that the risk for Ebstein anomaly was as high as 3 percent. However, subsequent series have identified an attributable risk for Ebstein anomaly and co-occurring right-sided cardiac anomalies of only 1 to 4 cases per 1000 exposed pregnancies (Patorno, 2017; Yacobi, 2008). The NBDPS found that just 1 of 135 cases of Ebstein anomaly occurred in the setting of lithium exposure (Downing, 2019).

Neonatal lithium toxicity stems from exposure near delivery. The manufacturer recommends that if possible, the dosage should be decreased or drug discontinued 2 to 3 days prior to delivery to reduce this risk (West-Ward, 2020). Findings may persist for up to 2 weeks and may include cardiac arrhythmias, hypoglycemia, nephrogenic diabetes insipidus, and a "floppy infant syndrome" (American College of Obstetricians and Gynecologists, 2019f). The latter may include hypotonia, respiratory distress or apnea, bradycardia, cyanosis, and feeding difficulties (West-Ward, 2020).

Selective Serotonin- and Norepinephrine-reuptake Inhibitors

These medications have been studied more than almost any other, apart from Bendectin (p. 146). As a class, they are not considered major teratogens (American College of Obstetricians and Gynecologists, 2019f). The one exception is paroxetine, which has been associated with a slightly higher risk for cardiac anomalies, particularly atrial and ventricular septal defects. Metaanalyses have identified a pooled odds ratio of just 1.3 for paroxetine and cardiac abnormalities (Berard, 2016; Wurst, 2010). However, a review of nearly 1 million pregnancies from the nationwide Medicaid Analytic eXtract identified no significant association between paroxetine use in the first trimester and fetal cardiac abnormalities (Huybrechts, 2014). The American College of Obstetricians and Gynecologists (2019f) recommends that women planning pregnancy avoid paroxetine. Fetal echocardiography should be considered for those with first-trimester paroxetine exposure.

Neonatal effects have been associated with prenatal exposure to selective serotonin-reuptake inhibitors (SSRIs) and selective norepinephrine-reuptake inhibitors (SNRIs). Approximately 25 percent of neonates exposed to SSRIs in late pregnancy manifest one or more nonspecific findings considered to represent poor neonatal adaptation (Costei, 2002; Jordan, 2008). Collectively termed the *neonatal behavioral syndrome*, findings can include jitteriness, irritability, hyper- or hypotonia, feeding abnormalities, vomiting, hypoglycemia, thermoregulatory instability, and respiratory abnormalities. Fortunately, these neonatal behaviors are typically mild and self-limited and last approximately 2 days. Jordan and coworkers (2008) reported that affected newborns were not more likely to require a higher level of care, to experience respiratory abnormalities, or to have prolonged hospitalization. Rarely, neonates exposed to SSRIs in late pregnancy have demonstrated more severe adaptation abnormalities (Ornoy, 2017).

Another concern with late-pregnancy exposure is the possible association of SSRI medications with *persistent pulmonary hypertension of the newborn (PPHN)*. The baseline incidence approximates 2 cases per 1000 term newborns. PPHN is characterized by elevated pulmonary vascular resistance with right-to-left shunting and resultant hypoxemia. Two population-based cohort studies—together involving more than 5 million pregnancies—identified an attributable risk of only 1 to 2 cases per 1000 births (Huybrechts, 2015; Kieler, 2012). Moreover, cases of PPHN associated with SSRI medication have not been severe (Ornoy, 2017).

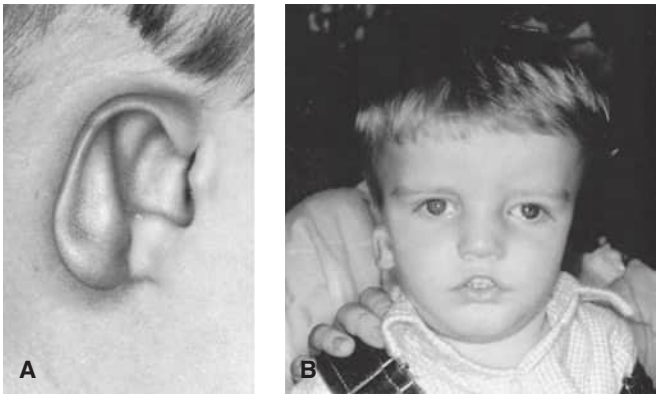


FIGURE 8-3 Retinoic acid embryopathy. **A.** Bilateral microtia or anotia with stenosis of external ear canal. **B.** Flat, depressed nasal bridge and ocular hypertelorism. (Reproduced with permission from permission from Dr. Edward Lammer.)

■ Retinoids

Vitamin A derivatives are among the most potent human teratogens. By inhibiting neural-crest cell migration during embryogenesis, they create a pattern of cranial neural-crest defects—termed *retinoic acid embryopathy*—that involve the CNS, face, heart, and thymus (Fig. 8-3). Specific anomalies may include ventriculomegaly, maldevelopment of the facial bones or cranium, microtia or anotia, micrognathia, cleft palate, conotruncal heart defects, and thymic aplasia or hypoplasia.

Acitretin

This retinoid is used to treat severe psoriasis. It was introduced to replace etretinate, a lipophilic retinoid with such a long half-life (120 days) that birth defects resulted more than 2 years after therapy was discontinued. Although acitretin has a short half-life, it is metabolized to etretinate, and thus remains in the body for prolonged periods (Stiefel Laboratories, 2017). To obviate exposure, the manufacturer of acitretin has developed a pregnancy risk management program. Called "Do Your P.A.R.T"—pregnancy prevention actively required during and after treatment, this program promotes a delay of conception for at least 3 years following therapy discontinuation.

Bexarotene

This retinoid is used to treat refractory cutaneous T-cell lymphoma. When given to rats in doses comparable to those for human therapy, fetuses developed eye and ear abnormalities, cleft palate, and incomplete ossification. For a woman to receive bexarotene, the manufacturer requires two forms of contraception that are initiated 1 month before therapy and continued

for 1 month after it is discontinued. This is coupled with monthly pregnancy testing during treatment (Bausch Health, 2020). Males who have partners who could become pregnant are advised to use condoms during sexual intercourse while taking bexarotene and for 1 month after discontinuing therapy.

Isotretinoin

13-*cis*-Retinoic acid is a vitamin A isomer that stimulates epithelial cell differentiation. It is primarily used to treat recalcitrant nodular acne. First-trimester exposure is associated with a high rate of pregnancy loss, and up to a third of infants have malformations (Lammer, 1985). The iPLEDGE program is an FDA-mandated REMS for isotretinoin and is found at www.ipledgeprogram.com. This web-based, restricted-distribution program requires participation for all patients, physicians, and pharmacies to help eliminate embryo–fetal exposure. Other countries have instituted similar programs, however, inadvertent exposure remains a global concern (Autret-Leca, 2010; Crijns, 2011).

Topical Retinoids

These compounds, initially used to treat acne, have become so popular for sun-damage treatment that they are called *cosmeceuticals* (Panchaud, 2012). The most commonly used topical agents are tretinoin, isotretinoin, and adapalene. Systemic absorption is low, and this argues against plausible teratogenicity.

Isolated case reports have described malformations following topical tretinoin, and it is unknown whether this is due to variability in absorption or perhaps potential individual susceptibility (Kaplan, 2015). A prospective study by the European Network of Teratology Information Services found no higher rates of birth defects or spontaneous losses, and no case of retinoid embryopathy (Panchaud, 2012). A systematic review of 635 pregnancies exposed to topical retinoids identified no higher risk for congenital malformations, spontaneous abortion, stillbirth, low birthweight, or preterm delivery (Kaplan, 2015). Notably, the manufacturer of tazarotene cautions that application over a sufficient body surface area could be comparable to oral treatment. Accordingly, its use in pregnancy is not recommended (Allergan, 2019).

Vitamin A

There are two natural forms of vitamin A. First, *provitamin A carotenoids*, which include beta-carotene, alpha-carotene, and beta-cryptoxanthin, are precursors found in fruits and vegetables. The body converts carotenoids into vitamin A. They have never been shown to cause birth defects (Oakley, 1995).

Second, *preformed vitamin A*, also called retinol, has been associated with cranial neural-crest defects when more than 10,000 IU per day is consumed in the first trimester (Rothman, 1995). Preformed vitamin A is present in liver, fish oils, milk, eggs, and in vitamin pills and dietary supplements. It seems reasonable to avoid doses of preformed preparations that exceed the recommended 3000 IU daily allowance (American Academy of Pediatrics, 2017).

Sex Hormones

Selected functions and effects of male and female hormones on the developing fetus are reviewed in Chapter 3 (p. 31). Androgen exposure may cause varying degrees of virilization in female fetuses and may result in ambiguous genitalia (Fig. 3-3, p. 34).

Thalidomide and Analogues

Possibly the most notorious human teratogen, thalidomide causes malformations in 20 percent of fetuses exposed between 34 and 50 days menstrual age. The characteristic malformation is *phocomelia*—an absence or underdevelopment of one or more long bones. As a result, hands or feet may attach to the trunk, occasionally by a small rudimentary bone. Cardiac defects, gastrointestinal abnormalities, external ear and eye malformations, and other limb-reduction defects also are common following thalidomide exposure. The manufacturer reports that up to 40 percent of affected newborns do not survive the neonatal period (Celgene, 2021).

Thalidomide was marketed outside the United States from 1956 to 1960, before its teratogenicity was appreciated. The ensuing disaster, with thousands of affected children, was instructive of several important teratological principles. First, the placenta is not an effective barrier to the transfer of toxic substances from mother to embryo (Dally, 1998). Second, different species manifest considerable variability in their susceptibility to drugs and chemicals. Namely, thalidomide produced no defects in multiple rodent species and was assumed to be safe for humans. Last, timing of exposure may be closely related to the type of defect (Vargesson, 2015). For example, upper-limb amelia may develop with thalidomide exposure during days 24 to 30 postconception, upper-limb phocomelia with exposure during days 24 to 33, and lower-limb phocomelia with exposure during days 27 to 33.

Thalidomide was first approved in the United States in 1999 and currently is used to treat erythema leprosum nodosum and multiple myeloma (Celgene, 2021). The FDA has mandated a web-based, restricted-distribution program for thalidomide, called THALOMID REMS, which is required before patients, physicians, and pharmacies can access the medication.

Lenalidomide and *pomalidomide* are analogues of thalidomide. Both cross the placenta in animal species. Lenalidomide is used to treat some types of myelodysplastic syndrome and multiple myeloma. It has been found to cause thalidomide-like limb abnormalities in monkeys (Celgene, 2019). Pomalidomide is used to treat refractory multiple myeloma and acquired immunodeficiency syndrome (AIDS)-related Kaposi sarcoma. It is teratogenic in rats and rabbits (Celgene, 2020). Restricted-distribution programs similar to those used for thalidomide have been developed for these analogues.

Thyroid Medications

Methimazole

This thionamide drug is used to treat hyperthyroidism. Methimazole has been associated with a 2-fold increased risk for aplasia cutis congenita, as well as choanal atresia and esophageal atresia (Yoshihara, 2012). This constellation of findings has been termed *methimazole embryopathy*. Aplasia cutis is a rare abnormality characterized by a full-thickness skin defect, usually the scalp,

occasionally with a defect of underlying bone. In a study of more than 1000 methimazole-treated pregnancies, Yoshihara and colleagues (2015) identified the embryopathy in 1 to 2 percent. Treatment of hyperthyroidism in pregnancy is reviewed in Chapter 61.

Radioiodine

Radioactive iodine-131 is used for treatment of thyroid cancer and thyrotoxicosis and for diagnostic thyroid scanning. It is also a component of iodine-131 tositumomab therapy, which is employed to treat a type of non-Hodgkin lymphoma. Radioiodine is contraindicated during pregnancy because it readily crosses the placenta and is concentrated in the fetal thyroid gland by 12 weeks' gestation. It may cause severe or irreversible fetal and neonatal hypothyroidism, which can lead to decreased mental capacity and delayed skeletal maturation. Pregnancy testing should be performed before administration of radioiodine-131, and it is recommended that pregnancy be avoided for 6 to 12 months following treatment (Haugen, 2016). A review of more than 3000 pregnancies in which women delayed conception for at least 6 months after receiving radioactive iodine treatment identified no increase in pregnancy losses or congenital malformations (Kim, 2020). Concerns for the breastfeeding mother stem from breast exposure to the radioisotope.

Warfarin

This anticoagulant is a vitamin K antagonist with a long half-life. Because of its low molecular weight, it readily crosses the placenta and may cause embryotoxic and fetotoxic effects. It is considered contraindicated in pregnancy with one important exception. As discussed in Chapter 52 (p. 922), warfarin is used to treat women with mechanical heart valves who are at high risk for thromboembolism (Bristol-Myers Squibb, 2019).

Warfarin embryopathy is characterized by stippled epiphyses and nasal hypoplasia (Fig. 8-4). In one review of 63 cases attributed to warfarin exposure, 80 percent displayed characteristic findings, which include depressed nasal bridge with nasal hypoplasia and choanal atresia, along with stippled epiphyses of the femur, humerus, calcanei, and distal phalanges (Van Driel, 2002). The embryopathy may result from exposure between 6 and 9 weeks' gestation (Hall, 1980). Prevalence following exposure during this critical period is estimated to be 6 percent. One metaanalysis of cases in which the warfarin dosage was ≤5 mg/d identified embryopathy in 1 percent of exposed fetuses. This suggests that risk may be dose dependent (Hassouna, 2014).

If used beyond the first trimester, warfarin may lead to hemorrhage into fetal structures, which can cause abnormal growth and deformation from scarring (Warkany, 1976). Nearly 50 percent of reported embryopathy cases also have CNS anomalies (van Driel, 2002). Abnormalities can include agenesis of the corpus callosum; cerebellar vermian agenesis, which is the Dandy-Walker malformation; microphthalmia; and optic atrophy. Affected infants are also at risk for blindness, deafness, and developmental delays.

Tobacco

Cigarette smoking is the leading preventable cause of perinatal mortality. At least 7 percent of women report smoking cigarettes during pregnancy (Drake, 2018). Cigarette smoke contains a complex mixture of nicotine, cotinine, cyanide, thiocyanate, carbon monoxide, cadmium, lead, and various hydrocarbons (Stillerman, 2008). In addition to being fetotoxic, many of these substances have vasoactive effects or reduce oxygen levels.

Although tobacco is not considered a major human teratogen, selected birth defects have been reported to occur with greater frequency following exposure. Cigarette smoking and exposure to second-hand smoke have been associated with up to a 1.5-fold risk for orofacial clefts (Kummet, 2016; Sabbagh, 2015). This equates to an attributable risk of approximately 1 case per 2000 births. It is plausible that the vasoactive properties of tobacco smoke could produce congenital defects related to vascular disturbances. For example, the prevalence of Poland sequence, which is caused by an interruption in the vascular supply to one side of the fetal chest and ipsilateral arm, has been reported to occur two times more commonly among cigarette smokers (Martinez-Frias, 1999). The NBDPS similarly found an association between active or passive cigarette smoking and limb reduction defects, and an overall increase in risk of 25 percent (Caspers, 2013). A small increased risk for fetal cardiac anomalies also has been reported and may be dose related (Alverson, 2011; Malik, 2008; Sullivan, 2015).

The most prevalent obstetrical complication from smoking is a dose-dependent reduction in fetal growth. Newborns of mothers who smoke weigh on

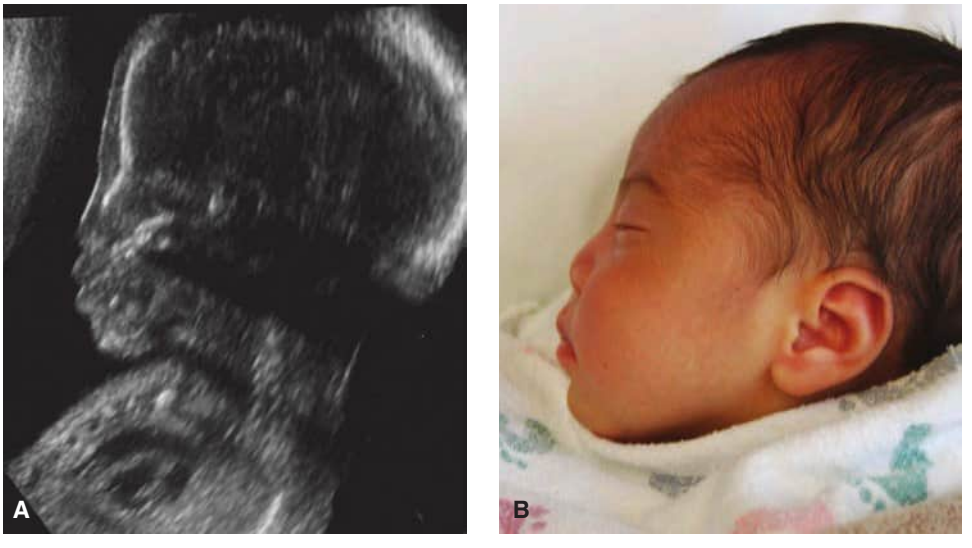


FIGURE 8-4 Warfarin embryopathy or fetal warfarin syndrome: nasal hypoplasia and depressed nasal bridge seen in a fetal sonographic image **(A)** and in the same newborn **(B)**.

average 200 g less than newborns of nonsmokers (D'Souza, 1981). Smoking doubles the risk of low birthweight and raises the risk of fetal-growth restriction two- to threefold (Werler, 1997). As such, cigarette smoking accounts for 15 percent of low-birthweight neonates (Dietz, 2010). Even secondhand smoke increases the risk for low birthweight. Other adverse pregnancy outcomes associated with cigarette smoking include preterm birth, prelabor rupture of membranes, placenta previa, and placenta abruption (American College of Obstetricians and Gynecologists, 2020b). Approximately one third of cases of sudden infant death syndrome have been attributed to cigarette smoking (Anderson, 2019; Dietz, 2010). Risks of childhood asthma and obesity also are increased.

When inquiring about tobacco use, providers should include alternative nicotine delivery products. All forms of nicotine cross the placenta. None is considered safe in pregnancy. Vaping or e-cigarette products heat an "e-liquid" containing nicotine—and often additional contaminants—along with a flavoring agent. Nicotine is associated with adverse effects on fetal brain and lung development (American College of Obstetricians and Gynecologists, 2020b; Spindel, 2016). In adults, vaping has been linked to serious lung injury known as EVALI—e-cigarette or vaping-associated lung injury (Krishnasamy, 2020). Animal studies of hookah use, in which tobacco smoke is filtered through a water bowl, demonstrate lower birthweight and increased markers of cardiac stress (Khabour, 2016).

Smoking cessation should be strongly encouraged. Counseling includes avoidance of secondhand smoke and all nicotine-replacement products, such as patches, gum, and lozenges. A hotline is available from the Centers of Disease Control and Prevention and can be accessed by calling 1-800-QUIT-NOW. The U.S. Preventive Services Task Force has recommended that behavioral interventions be offered at the initial visit and continued throughout pregnancy (Siu, 2015).

■ Herbal Medicinal Products

In large survey studies from North America and Europe, 30 to 60 percent of women report using herbal remedies during pregnancy (Kennedy, 2016; Pallivalapila, 2015). These products are not regulated by the FDA, and there is a paucity of controlled studies assessing their safety and efficacy. The identity, quantity, and purity of each ingredient are usually unknown. Authors of a recent systematic review that included more than 1 million pregnancies concluded that in the absence of more safety data, the use of herbal medicinal products in pregnancy should be discouraged (Munoz Balbontin, 2019). Selected herbal remedies and their reported adverse effects are shown in Table 8-5.

■ Drugs of Abuse

Substance abuse is not uncommon in pregnancy. Assessment of outcomes attributable to illicit drug use is often confounded by factors such as poor maternal health, malnutrition, and infectious disease. Polysubstance abuse further complicates assessment of outcomes associated with any one drug. Moreover, illegal substances may contain toxic contaminants such as lead, cyanide, herbicides, and pesticides. Impurities added as diluents may independently have serious adverse perinatal effects. As noted on page 149, alcohol is a significant teratogen. Because it is legally obtained and ubiquitous, its use confounds the study of illicit drug teratogenicity. Similarly, tobacco use confounds the effect of drugs on fetal growth.

Cocaine

With this CNS stimulant, most adverse outcomes result from its vasoconstrictive and hypertensive effects. Serious potential maternal complications are cerebrovascular hemorrhage, myocardial damage, and placental abruption. Studies of congenital abnormalities and cocaine exposure have yielded conflicting results, but associations with cleft palate, cardiovascular abnormalities, and urinary tract anomalies have been reported (Chasnoff, 1988; Lipshultz, 1991; van Gelder, 2009). Cocaine use is also associated with fetal-growth restriction and preterm delivery. Children exposed as fetuses have risks for behavioral abnormalities and cognitive impairments (Bada, 2011; Gouin, 2011).

Marijuana

This is the recreational drug most commonly used in pregnancy (American College of Obstetricians and Gynecologists, 2019b). Based on data from the National Survey on Drug Use and Health, nearly 4 percent of pregnant women reported using marijuana in 2014 (Brown, 2017). Among women diagnosed with nausea and vomiting of pregnancy, the prevalence of marijuana use increased from 7 to 11 percent from 2009 to 2016 (Young-Wolff, 2019). Of concern is that the increase in prevalence is related to perceived safety and efficacy. In a study of 400 cannabis dispensaries, nearly 70 percent advised a caller posing as a pregnant woman with nausea at 8 weeks' gestation to use marijuana (Dickson, 2018). However, no data support efficacy of marijuana for nausea and vomiting of pregnancy, and there are indeed safety concerns (Metz, 2018).

Cannabinoids are not considered to be major teratogens, but they cross the placenta, and endogenous cannabinoids play key roles in brain development. In animals, cannabinoids are involved in neuronal proliferation, migration, and differentiation (Campolongo, 2011). Adverse developmental outcomes reported in exposed children include decreased attention span and lower scores on tests of visual problem solving and visual-motor coordination (Fried, 2003; Willford 2010).

Pregnancy outcome data are somewhat limited by the confounding risks of concomitant tobacco use. In one metaanalysis of nearly 8000 exposed pregnancies, only those with concomitant tobacco use had increased rates of preterm birth and low-birthweight neonates (Conner, 2016). The American College of Obstetricians and Gynecologists (2019b) has stated that the effects of marijuana may be as serious as those of cigarette smoking or alcohol consumption. Because of neurodevelopmental concerns, women who are pregnant or contemplating pregnancy should avoid marijuana use.

Methamphetamine

This sympathomimetic amine is derived from dextroamphetamine. It enhances dopamine release and blocks its reuptake. Methamphetamine is prescribed to treat attention deficit

TABLE 8-5. Pharmacological Actions and Adverse Effects of Some Herbal Medicines

Herb and Common Name	Potential Pharmacological Effects	Concerns
Aloe (oral ingestion)	Smooth-muscle stimulant	May cause uterine contractions
Almond oil (topical)	Smooth-muscle stimulant	Increase in preterm births
Black cohosh	Smooth-muscle stimulant	Causes uterine contractions; also has an estrogenic compound
Blue cohosh	Smooth-muscle stimulant	Causes uterine contractions; contains compounds teratogenic in multiple animal species
Echinacea: *purple coneflower root*	Activates cell-mediated immunity	Allergic reactions; decreases immunosuppressant effectiveness; possible immunosuppression with long-term use
Ephedra: *ma huang*	Direct and indirect sympathomimetic; tachycardia and hypertension	Hypertension, arrhythmias, myocardial ischemia; stroke; depletes endogenous catecholamines; life-threatening interaction with monoamine oxidase inhibitors
Evening primrose oil	Contains linoleic acids, a prostaglandin precursor	Possible complications if used for labor induction
Garlic: *ajo*	Inhibits platelet aggregation; increased fibrinolysis; antihypertensive activity	Risk of bleeding when combined with other platelet aggregation inhibitors
Ginger	Cyclooxygenase inhibitor, thromboxane synthetase inhibitor; lowers blood glucose	Increased risk of bleeding; hypoglycemia
Ginkgo biloba	Anticoagulant	Risk of bleeding; interferes with monoamine oxidase inhibitors
Ginseng	Lowers blood glucose; inhibition of platelet aggregation	Hypoglycemia; hypertension; risk of bleeding
Kava: *awa, intoxicating pepper, kawa*	Sedation, anxiolysis	Sedation; tolerance and withdrawal
Licorice (glycyrrhizin)	Inhibits cortisol and prostaglandin metabolism	Increased risk of preterm birth
Raspberry leaf	Smooth-muscle stimulant	Increased risk of cesarean when used in late pregnancy or in labor
Valerian: *all heal, garden heliotrope, vandal root*	Sedation	Sedation; hepatotoxicity; benzodiazepine-like acute withdrawal
Yohimbe		Hypertension, arrhythmias

Data from Ang-Lee, 2001; Facchinetti, 2012; Hall, 2012; Munoz Balbontin, 2019; Nordeng, 2011; Strandberg, 2002; Wiesner, 2017.

hyperactivity disorder and narcolepsy. Abuse has been rising in the United States since the late 1980s (American College of Obstetricians and Gynecologists, 2019c). Methamphetamine is not considered teratogenic. However, use in pregnancy is consistently associated with small-for-gestational age newborns, and children are at risk for developmental delays and behavioral abnormalities (Derauf, 2012; Eze, 2016; Gabrhelik, 2021; O'Connor, 2020). Behavioral abnormalities have been described in both infants and school-aged children (Eze, 2016). Hypertensive complications, placental abruption, preterm birth, and stillbirth are other associated adverse outcomes (Gorman, 2014).

Opioids

The dramatic rise in narcotic use among nonpregnant and pregnant individuals has been aptly termed an epidemic. Opioids are not major teratogens. However, the NBDPS did identify a slightly greater risk for spina bifida, gastroschisis, and cardiac abnormalities with periconceptional opioid exposure (Broussard, 2011). The American College of Obstetricians and Gynecologists (2019d) stresses that this potential, small increase in birth defects with maintenance therapy should be weighed against the risks associated with uncontrolled opioid abuse. Heroin addiction is associated with adverse pregnancy outcomes from the effects of repeated narcotic withdrawal on the fetus and placenta. These include preterm birth, placental abruption, fetal-growth restriction, and fetal death.

Neonatal narcotic withdrawal, called the *neonatal abstinence syndrome*, may manifest in 40 to 90 percent of exposed newborns (Blinick, 1973; Creanga, 2012; Dashe, 2002; Zelson, 1973). As discussed in Chapter 33 (p. 605), CNS irritability may progress to seizures if untreated and may be accompanied by tachypnea, apneic episodes, poor feeding, and failure to thrive. At-risk neonates are closely monitored using a scoring

system, and those severely affected are treated with opioids (Finnegan, 1975). The proportion of exposed newborns developing neonatal abstinence syndrome has risen significantly in recent years (Creanga, 2012; Lind, 2015).

The American College of Obstetricians and Gynecologists (2019d) recommends that pregnant women with opioid-use disorder be maintained on opioid-agonist therapy to reduce the risks associated with illicit opioid abuse and associated behaviors. Treatment includes either buprenorphine, which may be given in an office-based setting by a licensed buprenorphine prescriber, or methadone, usually through a licensed outpatient opioid treatment program. A multidisciplinary treatment program is recommended to reduce the likelihood of additional opioid abuse while on maintenance therapy. Withdrawal from methadone during pregnancy is discouraged because of high relapse rates (American College of Obstetricians and Gynecologists, 2019d). At Parkland Hospital, pregnant opioid users who decline maintenance therapy are offered inpatient hospitalization for controlled methadone taper. The goal is to reduce the likelihood of neonatal abstinence syndrome (Dashe, 2002; Stewart, 2013).

Miscellaneous Drugs

Phencyclidine (PCP) or angel dust is not associated with congenital anomalies. More than half of exposed newborns, however, experience withdrawal symptoms characterized by tremors, jitteriness, and irritability. *Toluene* is a common solvent used in paints and glue. Occupational exposure is reported to have significant fetal risks (Wilkins-Haug, 1997). When abused by women in early pregnancy, it is associated with *toluene embryopathy*, which is phenotypically similar to fetal alcohol syndrome. Abnormalities include pre- and postnatal growth deficiency, microcephaly, midface hypoplasia, short palpebral fissures, and wide nasal bridge (Pearson, 1994). Up to 40 percent of exposed children have developmental delays (Arnold, 1994).

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CHAPTER 9

Preconceptional Counseling

The Centers for Disease Control and Prevention (CDC) defines preconceptional health to encompass the overall health of nonpregnant women during their reproductive years (Robbins, 2018). The American College of Obstetricians and Gynecologists (2019b) and the Society for Maternal–Fetal Medicine (2014, 2021) attest to the importance of preconceptional care and promote the following objectives to advance it:

1. Improve knowledge, attitudes, and behaviors of men and women related to preconceptional health
2. Assure that all childbearing-aged women receive preconceptional care services—including evidence-based risk screening, health promotion, and interventions—that will enable them to enter pregnancy in optimal health
3. Implement interconceptional interventions to prevent or minimize recurrent adverse outcomes
4. Reduce the racial and socioeconomical disparities in adverse pregnancy outcomes

Table 9-1 lists the prevalence of many conditions often amenable to preconceptional intervention (Robbins, 2018). These are frequently encountered by generalist obstetrician–gynecologists, who can help optimize health entering pregnancy (Arluck, 2018). For example, by the time most women realize they are pregnant—usually 1 to 2 weeks after the first missed period—the embryo has already begun to form. Thus, many preventive steps—such as folic acid to avoid neural-tube defects—will be ineffective if initiated at this time. Moreover, 45 percent of all pregnancies in the United States are unplanned, and often these are at greatest risk (Finer, 2016). Last, a disproportionate number of indigent women receive less preconceptional care compared with their more affluent counterparts (Easter, 2017).

Few randomized trials evaluate preconceptional care efficacy, in part because withholding such counseling would be unethical.

TABLE 9-1. Preconceptional Health Indicators—United States, 2013–2015

Factor	Prevalence (%)
Diabetes	3.1
Unwanted pregnancy	6.1
Hypertension	10.9
Smoking	16.9
Depression	21.9
Multivitamin use	33.6
Normal weight	44.9
Physical activity	50.4
Effective contraception	56.9

Data from Centers for Disease Control and Prevention, Behavioral Risk Factor Surveillance System, and Pregnancy Risk Assessment Monitoring System.

Also, pregnancy outcomes are dependent on the interaction of various maternal, fetal, and environmental factors. Thus, ascribing a salutary outcome to a specific intervention is difficult (Temel, 2014; Tieu, 2017). However, prospective observational and case-control studies have demonstrated the successes of preconceptional counseling (Yamamoto, 2018). Therefore, routine pregnancy intention screening should be done (Manze, 2020).

COUNSELING SESSION

Obstetricians–gynecologists, internists, family practitioners, and pediatricians have the best opportunity to provide preventive counseling during periodic health maintenance examinations. The occasion of a negative pregnancy test is also an excellent time for education (Skogsdal, 2018). Jack and colleagues (1995) administered a comprehensive preconceptional risk survey to 136 such women, and almost 95 percent reported at least one problem that could affect a future pregnancy (see Table 9-1). Providers should be knowledgeable regarding relevant medical diseases, prior surgery, reproductive disorders, or genetic conditions and be able to interpret data and recommendations provided by other specialists (Simpson, 2014).

Women presenting specifically for preconceptional evaluation are advised that information collection may be time consuming, depending on the number and complexity of factors. The intake evaluation includes a thorough review of the medical, obstetrical, social, and family histories. Useful information is more likely to be obtained by asking specific questions regarding each of these histories and the health of each family member than by asking general, open-ended questions. Some important information can be obtained by questionnaires that address these topics. Answers are reviewed with the couple to ensure appropriate follow-up, including obtaining relevant medical records.

The Fourth Trimester

Another optimal time to begin preconceptional counseling is during the "fourth trimester." This was emphasized by the Presidential Task Force on Redefining the Postpartum Visit (American College of Obstetricians and Gynecologists, 2018e). Designed to optimize postpartum care and provide contraceptive counseling, it also sets the stage for any subsequent pregnancy and for the woman's long-term health. To assist the provider, the American College of Obstetricians and Gynecologists (2019b) has joined the Society of Maternal–Fetal Medicine to provide an Obstetric Care Consensus guide that emphasizes the interpregnancy period.

MEDICAL HISTORY

With specific medical conditions, general points include the pregnancy's effect on the condition and the disorder's influence on the fetus and pregnancy course. Some chronic conditions that may worsen pregnancy outcomes include treated or active cancer, prior peripartum cardiomyopathy, antiphospholipid antibodies, systemic lupus erythematosus, and congenital heart disease (Amant, 2015; Cunningham, 2019; Davis, 2021; Foeller, 2018; Gibbins, 2018; Hopkins, 2018). Importantly, psychological health also is considered (Barker, 2020; Lassi, 2014). Detailed preconceptional information regarding a few exemplary conditions is found in the next sections and in the other topic-specific chapters of this text.

Diabetes Mellitus

Because maternal and fetal pathology associated with hyperglycemia is well known, diabetes is the prototype of a condition for which preconceptional counseling is beneficial. Diabetes-associated risks to both mother and fetus are discussed in detail in Chapter 60 (p. 1068). If a patient maintains glucose levels close to normal, many of these complications can be avoided before conception. Another important aspect of counseling pertains to the frequent use of teratogenic angiotensin-converting enzyme inhibitors in this population (Podymow, 2015).

The American College of Obstetricians and Gynecologists (2018f) has concluded that preconceptional counseling for women with pregestational diabetes is beneficial and cost-effective and should be encouraged. The American Diabetes Association (2004) has promulgated consensus recommendations for preconceptional care for women with diabetes. These guidelines advise an inventory of disease duration and related complications and clinical and laboratory examination for end-organ damage. Perhaps most essential, they encourage a preconceptional hemoglobin A_{1c} level goal below 7 percent. In addition to assessing diabetic control, hemoglobin A_{1c} measurement can also forecast the risks for gestational diabetes and for major anomalies (Fig. 9-1) (Hinkle, 2018; Martin, 2020).

Although no randomized trials attest to the success of preconceptional counseling in women with diabetes, cohort studies do demonstrate its effectiveness (Tieu, 2017). In a prospective study of 5075 affected women, preconceptional counseling improved hemoglobin A_{1c} levels, folic acid compliance, and "optimal" pregnancy preparation (Yamamoto, 2018). Diabetic women who undergo preconceptional counseling also have improved glycemic control before pregnancy and in the first trimester and experience lower rates of adverse outcomes—defined as a perinatal death or major congenital anomaly (Tripathi, 2010). Despite

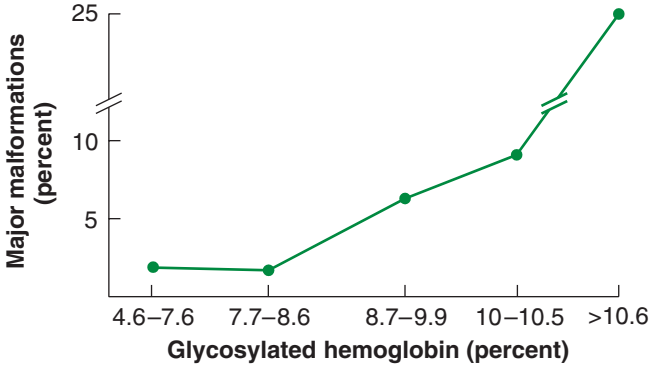

FIGURE 9-1 Relationship between first-trimester glycosylated hemoglobin values and risk for major congenital malformations in 320 women with insulin-dependent diabetes.

TABLE 9-2. First-Trimester Antiepileptic Monotherapy and the Associated Major Malformation Risk

Antiepileptic (n)	Malformations (%)[a]	Relative Risk (95% CI)[b]
Unexposed controls	1.1	Reference
Gabapentin	0.7	1.0 (0.5–1.9)
Lamotrigine	2.0	0.9 (0.7–1.3)
Oxcarbazepine	2.2	—
Levetiracetam	2.4	0.7 (0.4–1.2)
Phenytoin	2.9	1.7 (1.3–2.2)
Carbamazepine	3.0	1.4 (1.1–1.7)
Clonazepam	3.1	1.1 (0.6–2.0)
Topiramate	4.2	1.9 (1.2–2.9)
Phenobarbital	5.5	1.8 (1.4–2.5)
Valproate	9.3	2.9 (2.4–3.7)
Ethosuximide	—	3.0 (1.2–7.1)

Risk compared with that of the unexposed reference population of women without epilepsy.
CI = confidence interval.
Data from [a]Hernández-Díaz, 2012; [b]Veroniki, 2017.

such benefits, in one study of approximately 300 diabetic women in a managed-care plan, only approximately half received preconceptional counseling (Kim, 2005).

Epilepsy

Compared with unaffected women, those with a seizure disorder carry an augmented risk of neonates with structural anomalies. Some early reports indicated that epilepsy conferred an elevated a priori risk for congenital malformations that was independent of anticonvulsant treatment effects. More recent studies have largely failed to confirm this, but it is difficult to refute entirely because women who are controlled without medication generally have less severe disease (Cassina, 2013; Vajda, 2015). Polytherapy is associated with a higher malformation risk compared with monotherapy (Bromley, 2017). Last, in women using antiseizure medications, the risks for miscarriage and stillbirth in do not appear elevated (Aghajanian, 2015; Bech, 2014).

Ideally, medications are adjusted preconceptionally to minimize seizure frequency. From one national registry, the seizure risk during pregnancy was 50 to 70 percent lower in women without a seizure in the year preceding pregnancy compared with a group experiencing seizures in this preceding year (Vajda, 2008). No further advantages accrued if the seizure-free period exceeded a year.

Treatment goals attempt to control seizure frequency with monotherapy and with medications considered less teratogenic (Aguglia, 2009; Tomson, 2009). Discussed in Chapter 63 (p. 1129) and shown in Table 9-2, some one-drug regimens are more teratogenic than others. In particular, valproic acid is avoided if possible, as it has consistently been associated with a greater risk for major congenital malformations than other antiepileptic drugs (Jentink, 2010; Vajda, 2015). Information concerning the teratogenicity of newer antiepileptics is limited (Knight, 2021).

The American Academy of Neurology recommends consideration of antiseizure medication discontinuation before pregnancy in suitable candidates (Jeha, 2005). These include women who satisfy the following criteria: (1) have been seizure-free for 2 to 5 years, (2) display a single seizure type, (3) have a normal neurological examination and normal intelligence, and (4) show electroencephalogram results that have normalized with treatment.

Women with seizures should be advised to take a daily 4-mg oral folic acid supplement. Even so, the value of folate to reduce fetal malformation rates in pregnant women taking anticonvulsant therapy is not entirely clear. In one case-control study, the congenital abnormality risk was reduced by maternal folate supplementation in fetuses exposed to carbamazepine, phenobarbital, phenytoin, and primidone (Kjær, 2008). Conversely, Morrow and coworkers (2009) compared fetal outcomes of women who received preconceptional folic acid with those who did not receive it until later in pregnancy or not at all. In this study, a paradoxical *increase* in the number of major congenital malformations was observed in the group who received preconceptional folate. These investigators concluded that folate metabolism may be only a part of the mechanism by which malformations are induced in women taking these medications.

Immunizations

Preconceptional counseling includes assessment of immunity against common pathogens. Also, depending on health status, travel plans, and time of year, other immunizations may be indicated as discussed in Chapter 10 (p. 189). Several immunization resources are listed in Table 9-3. Vaccines that contain toxoids such as tetanus are suitable before or during gestation. Also, those containing killed bacteria or viruses—such as influenza, pneumococcus, hepatitis B, meningococcus, and rabies vaccines—are not associated with adverse fetal outcomes and are not contraindicated preconceptionally or during pregnancy. Conversely, live-virus vaccines are not recommended during pregnancy. Examples are vaccines against varicella-zoster, measles, mumps, rubella, polio, chickenpox, and yellow fever. Moreover,

TABLE 9-3. Immunization Resources

American College of Obstetricians and Gynecologists website: www.acog.org/programs/immunization-for-women
Centers for Disease Control and Prevention website: www.cdc.gov/vaccines/hcp/
Immunization Action Coalition: www.immunize.org

1 month or longer should ideally pass between vaccination and conception attempts. That said, inadvertent administration of measles, mumps, rubella (MMR) or varicella vaccines during pregnancy should not generally be considered indications for pregnancy termination. Most reports indicate that the fetal risk is only theoretical. Immunization to smallpox, anthrax, and other bioterrorism diseases is discussed if clinically appropriate (Chap. 67, p. 1200).

With some infections, vaccines are unavailable. One recent example is the Zika virus (Brasil, 2016). For this virus, during the 2016 epidemic, the CDC issued travel advisories for pregnant women (Petersen, 2016; Schuler-Faccini, 2016).

GENETIC DISEASES

The CDC (2016) estimates that 3 percent of neonates born each year in the United States will have at least one birth defect. Importantly, such defects are the leading cause of infant mortality and account for 20 percent of deaths. Ethics preclude randomized trials of preconceptional counseling for genetic risk (Hussein, 2018). Instead, the benefits of preconceptional counseling usually are measured by comparing the incidence of new cases before and after initiation of such a program. Specific congenital conditions that clearly benefit from patient education include neural-tube defects, phenylketonuria, thalassemias, and other genetic diseases more common in individuals of Eastern European Jewish descent (King, 2018). Other missed opportunities for genetic consultation were found for women with a personal or family history of birth defects, intellectual disability or autism, and a prior positive genetic carrier screening test (McClatchey, 2018).

Family History

Pedigree construction using the symbols shown in Figure 9-2 is the most thorough method for obtaining a family history as a part of genetic screening. The health and reproductive status of each "blood relative" are individually reviewed for medical illnesses, mental retardation, birth defects, infertility,

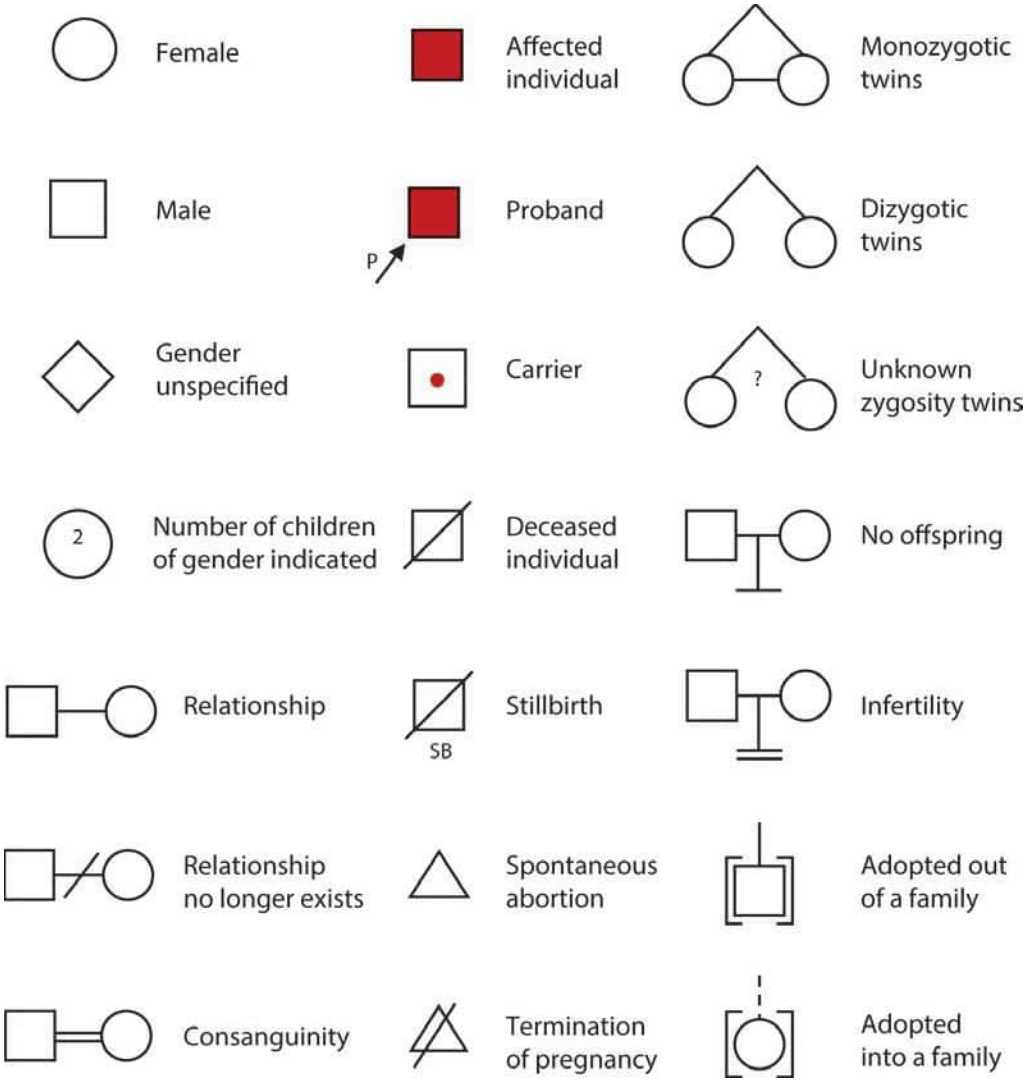

FIGURE 9-2 Symbols used for pedigree construction.

and pregnancy loss. Certain racial, ethnic, or religious backgrounds may indicate elevated risk for specific recessive disorders.

Although most women can provide information regarding their history, their understanding may be limited. Pregnant women may fail to communicate a birth defect in the family or may report it incorrectly. Thus, any disclosed defect or genetic disease is ideally confirmed by reviewing pertinent medical records or by contacting affected relatives for additional information.

Neural-Tube Defects

The incidence of neural-tube defects (NTDs) is 0.9 per 1000 live births, and they are second only to cardiac anomalies as the most frequent structural fetal malformation. Some of these malformations are associated with specific mutations. One example is the 677C → T substitution in the gene that encodes methylene tetrahydrofolate reductase. For this and similar gene defects, one seminal trial showed that preconceptional folic acid therapy significantly reduced the risk for a recurrent NTD by 72 percent (Medical Research Council Vitamin Study Research Group, 1991). More importantly, because more than 90 percent of neonates with NTDs are born to women at low risk, Czeizel and Dudas (1992) showed that universal supplementation reduced the a priori risk of a first NTD.

Because of these findings, all women who may become pregnant are recommended to take daily 400 to 800 μg of folic acid orally before conception and through the first trimester (U.S. Preventive Services Task Force, 2019). Folate fortification of cereal grains has been mandatory in the United States since 1998, and this practice has lowered neural-tube defect rates (Williams, 2015). Despite the demonstrated benefits of folate supplementation, only half of women take folic acid supplementation periconceptionally (de Jong-van den Berg, 2005; Goldberg, 2006).

Phenylketonuria

More than 600 mutations have been identified in the phenylalanine hydroxylase gene. The inherited defect in phenylalanine metabolism exemplifies diseases in which the fetus may not be at risk to inherit the disorder but may be damaged by maternal disease. Specifically, mothers with phenylketonuria (PKU) who eat an unrestricted diet have abnormally high blood phenylalanine levels. This amino acid readily crosses the placenta and can damage developing fetal organs, especially neural and cardiac tissues.

With appropriate preconceptional counseling and adherence to a phenylalanine-restricted diet before pregnancy, the incidence of fetal malformations is dramatically reduced (Camp, 2014; Vockley, 2014). Therefore, the phenylalanine concentration is ideally brought into normal range 3 months before conception and then maintained there throughout pregnancy (American College of Obstetricians and Gynecologists, 2020a). The target phenylalanine blood concentration is 120 to 360 μmol/L (Camp, 2014).

Thalassemias

These disorders of globin-chain synthesis are the most common single-gene disorders worldwide (Forget, 2013; Vichinsky, 2013). As many as 200 million people carry a gene for one of these hemoglobinopathies, and hundreds of mutations are known to cause thalassemia syndromes (Chap. 59, p. 1053). In endemic areas such as Mediterranean and Southeast Asian countries, counseling and other prevention strategies have reduced the incidence of new cases by up to 80 percent (Cao, 2013).

The American College of Obstetricians and Gynecologists (2018a) recommends that individuals of high-risk ancestry be offered carrier screening to allow them informed decision-making regarding reproduction and prenatal diagnosis. One method of early prenatal diagnosis for some thalassemia syndromes is *preimplantation genetic testing (PGT)*, which is coupled with assisted reproductive technology (Chap. 17, p. 348).

Individuals of Eastern European Jewish Descent

Most individuals of Jewish ancestry in North America are descended from Ashkenazi Jewish communities and are at greater risk for having offspring with one of several autosomal recessive disorders. These include Tay-Sachs disease, Gaucher disease, cystic fibrosis, Canavan disease, familial dysautonomia, mucolipidosis IV, Niemann-Pick disease type A, Fanconi anemia group C, and Bloom syndrome. The American College of Obstetricians and Gynecologists (2017a; 2019a) recommends preconceptional counseling and screening for these disorders in this population. Carrier frequency and features of these conditions are discussed in greater detail in Chapter 17 (p. 343).

REPRODUCTIVE HISTORY

During preconceptional screening, information is sought regarding infertility; abnormal pregnancy outcomes that may include miscarriage, ectopic pregnancy, molar pregnancy, and recurrent pregnancy loss; and obstetrical complications such as cesarean delivery, preeclampsia, placental abruption, and preterm delivery (Stubblefield, 2008).

As discussed in Chapter 35 (p. 626), details involving a prior stillbirth are especially important. For example, Korteweg and associates (2008) identified chromosomal abnormalities in 13 percent of stillborns who underwent karyotyping. And, Reddy and colleagues (2012) confirmed that chromosomal microarray analysis (CMA) yields better detection of genetic abnormalities than does standard karyotyping. This primarily stems from CMA's ability to assess nonviable tissue (Chap. 16, p. 325). Identification of a genetic abnormality in a stillborn can help to determine recurrence risk.

PARENTAL AGE

Maternal Age

Women at both ends of the reproductive-age spectrum have unique outcomes to consider. First, according to the CDC, 3.4 percent of births in the United States in 2010 were in women aged 15 to 19 years (Martin, 2012). An international study reported a rate of 11.9 percent for this age group globally (Althabe, 2015). These adolescents are at higher risk for anemia, preterm delivery, and preeclampsia compared with women aged 20 to 35 years (Usta, 2008). The incidence of sexually transmitted diseases—common in adolescents—is even higher during pregnancy (Niccolai, 2003). Unfortunately, because most of their pregnancies are unplanned, adolescents rarely seek preconceptional counseling.

Conceptions after age 35 currently constitute approximately 15 percent of pregnancies in the United States (Martin, 2012). By contrast, these women are more likely to request preconceptional counseling. Motivations may stem from a desire to optimize outcomes at their age or with infertility treatment or both. Some studies—including data from Parkland Hospital presented in Figure 9-3–indicate that risks for obstetrical complications and for perinatal morbidity and mortality rise after age 35 (Waldenström, 2015). The older woman who has a chronic illness or who is in poor physical condition usually has readily apparent risks. For the physically fit woman without medical problems, however, the risks are lower.

Overall, the maternal mortality rate is higher in women aged 35 and older (Chap. 1, p. 5). Creanga and coworkers (2017) analyzed pregnancy-related deaths in the United States for 2011 through 2013. Although women older than 35 years contributed less than 15 percent of all live births, they constituted 31 percent of maternal deaths. For the fetus, maternal age-related risks primarily originate from (1) indicated preterm delivery for maternal complications such as hypertension and diabetes, (2) spontaneous preterm birth, (3) fetal-growth disorders related to chronic maternal disease or multifetal gestation, (4) fetal aneuploidy, and (5) pregnancies resulting from assisted reproductive technology.

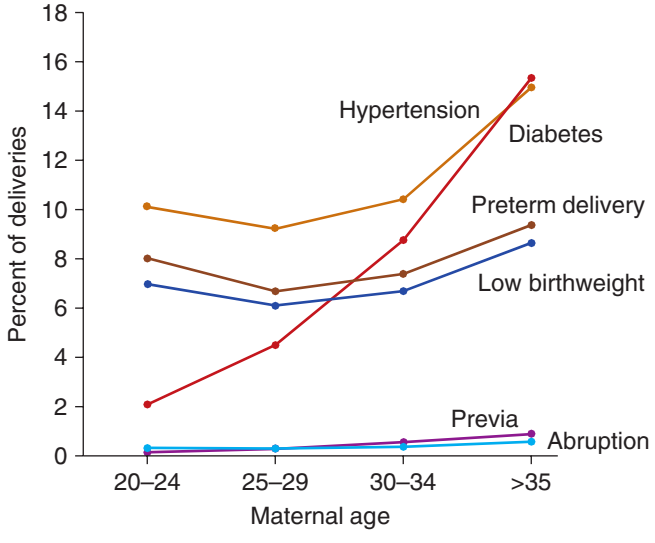

FIGURE 9-3 Incidence of selected pregnancy complications in relation to maternal age among 295,667 women delivered at Parkland Hospital.

Assisted Reproductive Technologies

Recall that older women have subfertility problems. And, although the incidence of dizygotic twinning rises with maternal age, the more important cause of multifetal gestation in older women follows the use of assisted reproductive technology (ART) and ovulation induction. Indeed, according to the CDC, 30 to 40 percent of all multifetal gestations in the United States in 2012 were conceived with the use of ART (Sunderan, 2015). Morbidity and mortality with multifetal pregnancies stem from preterm delivery and placentation complications, such as placenta previa and abruption (Qin, 2016).

With ART, transmission of infectious agents is a risk. For women without human immunodeficiency virus (HIV) infection who plan conception with their HIV-affected partners, the CDC has published prevention strategies (Kawwass, 2017). Also, Zika virus infection acquisition through in vitro fertilization (IVF) has been described (Washington Cross, 2017). Last, some data links ART to higher major congenital malformation rates. In a registry of 308,974 births, 8.3 percent of neonates conceived by ART had major birth defects, and intracytoplasmic injection was also associated with an elevated risk for malformations (Davies, 2012).

Paternal Age

Advanced paternal age has doubled in the United States over the past generation. It is associated with a higher risk of preterm birth and new autosomal-dominant mutations (Chap. 16, p. 320) (Khandwala, 2018). One example is the possible link between increasing paternal age and complex neuropsychiatric conditions (Malaspina, 2015). Parental history and experiences can also exert effects on progeny through epigenomic information not contained in the DNA sequence. Variations in sperm and oocyte cytosine methylation and noncoding RNAs are examples (Cedars, 2015; Lane, 2014).

SOCIAL HISTORY

Recreational Drugs and Smoking

Fetal risks associated with alcohol, marijuana, cocaine, amphetamines, and heroin are discussed in Chapters 8 (p. 148) and 64 (p. 1150). The first step in preventing drug-related fetal risk is an honest assessment of use by the patient (American College of Obstetricians and Gynecologists, 2017c). Toward this end, questioning should be nonjudgmental.

Several validated tools screen for at-risk drinking. One is the well-studied TACE questions (American College of Obstetricians and Gynecologists, 2019d). These four questions investigate having a *tolerance* to alcohol, being *annoyed* by comments about their drinking, attempting to *cut down*, and drinking early in the morning—the *eye opener*.

Of more than 1000 postpartum patients in one Canadian study, a high percentage reported alcohol use concurrent with conception attempts (Tough, 2006). Specifically, nearly half of those planning for pregnancy consumed a mean of 2.2 drinks daily during early gestation and before they recognized their pregnancy. This frequency and pattern clearly underscore the opportunity for preconceptional counseling.

In 2014 to 2015, 17 percent of reproductive-age women in the United States smoked cigarettes according to the CDC (Robbins, 2018). Smoking in pregnancy is consistently associated with numerous adverse perinatal outcomes (Chap. 8, p. 156). These risks are largely mitigated by cessation before pregnancy, highlighting the importance of screening for tobacco use prior to and during pregnancy (Chap. 10, p. 179).

Environmental Exposures

Only a few environmental agents have been shown to cause adverse pregnancy outcomes (McCue, 2019; Windham, 2008). For example, contact with some chemicals may impart significant maternal and fetal risks. Discussed in Chapter 8 (p. 153), excess exposure to methyl mercury or lead is associated with neurodevelopmental disorders. For lead, the American College of Obstetricians and Gynecologists (2018b) endorses guidelines that recommend blood lead testing only if a lead-exposure risk factor is identified. If the levels are >5 µg/dL, counseling is completed, and the lead source is sought and removed. Blood lead levels >45 µg/dL are consistent with lead poisoning, and women in this group may be candidates for chelation therapy (Centers for Disease Control and Prevention, 2019).

In contrast, everyday exposures to *electromagnetic fields* are not linked to adverse fetal outcomes (Robert, 1999). Examples include energy emanated by high-voltage power lines, electric blankets, microwave ovens, and cellular phones.

Diet

Pica is the craving for and consuming of ice, laundry starch, clay, dirt, or other nonfood items. It should be discouraged due to its inherent replacement of healthful food with nutritionally empty products (Chap. 10, p. 191). In some cases, it may represent an unusual physiological response to iron deficiency (Epler, 2017). Many *vegetarian diets* are protein deficient but can be corrected by increasing egg and cheese consumption. *Anorexia* and *bulimia* raise maternal risks of nutritional deficiencies, electrolyte disturbances, cardiac arrhythmias, and gastrointestinal pathology (American Psychiatric Association, 2013). Discussed in Chapter 64 (p. 1149), pregnancy-related complications with these eating disorders include greater risks of low birthweight, smaller head circumference, microcephaly, and small-for-gestational-age newborns.

Obesity is linked with several maternal complications. Discussed in Chapter 51 (p. 905), these include hypertension, preeclampsia, gestational diabetes, labor abnormalities, cesarean delivery, and operative complications (American College of Obstetricians and Gynecologists, 2018d). Obesity also appears to be associated with a range of structural fetal anomalies (Stothard, 2009).

Exercise

Conditioned pregnant women usually can continue to exercise throughout gestation (American College of Obstetricians and Gynecologists, 2020b). Discussed in Chapter 10, covering prenatal care (p. 187), no data suggest that exercise is harmful during pregnancy. However, as pregnancy progresses, balance problems and joint relaxation may predispose to orthopedic injury. During exercise, gravidas should avoid exhaustion, overheating, dehydration, and prolonged supine position.

Intimate-Partner Violence

Pregnancy can exacerbate interpersonal problems and is a time of elevated risk from an abusive partner. According to the American College of Obstetricians and Gynecologists (2012), approximately 324,000 pregnant women are abused each year. Intimate-partner violence (IPV) is associated with greater risk for several pregnancy-related complications that include hypertension, vaginal bleeding, hyperemesis, preterm delivery, and low-birthweight neonates (Chap. 50, p. 891) (Silverman, 2006). Because IPV can escalate during pregnancy, even to the point of homicide, the preconceptional period provides an ideal time for screening and intervention (Cheng, 2010). In support, the American College of Obstetricians and Gynecologists (2019c) provides recommendations and resources for screening both pregnant and nonpregnant women for IPV.

Lesbian, Gay, Bisexual, Transgender, and Queer Individuals

Preconceptional care has traditionally been based on the assumption of heterosexuality and has often excluded lesbian women (Bushe, 2017). The American College of Obstetricians and Gynecologists (2018c) endorses quality health care for all women regardless of sexual orientation. Indeed, in a study by Carpinello and colleagues (2016), three fourths of lesbian couples planned for one partner to conceive. Paradoxically, adolescent bisexual and lesbian women are at greater risk for undesired pregnancies (Charlton, 2018; Hodson, 2017). Of special risks in this group, lesbian and bisexual women have higher incidences of obesity, tobacco and alcohol use, depression, diabetes, and low parity compared with heterosexual women (Mravcak, 2006; O'Hanlan, 2007). In some of these groups, knowledge of surrogacy laws is imperative (Tsai, 2020).

SCREENING TESTS

Highlighted in Table 9-4, women with certain chronic medical diseases ideally would be evaluated before conception. With several of these, optimizing maternal condition will improve pregnancy outcomes.

TABLE 9-4. Selected Preconceptional Counseling Topics

Condition	Reference Chapter	Recommendations for Preconceptional Counseling
Environmental exposure	Chap. 10, p. 188	*Methyl mercury*: Avoid shark, swordfish, king mackerel, and tile fish. Ingest no more than 12 ounces or 2 servings of canned tuna and no more than 6 ounces of albacore per week. *Lead*: Blood lead testing if a risk factor is identified (p. 188); treat if indicated according to recommendations.
Obesity	Chap. 51, p. 902	Calculate BMI yearly from Figure 51-1, p. 903
Eating disorder	Chap. 64, p. 1149	*BMI* $\geq$*25 kg/m*^{2}: Counsel on diet. Test for diabetes and metabolic syndrome if indicated. Consider weight loss prior to conception. *BMI* $\leq$*18.5 kg/m*^{2}: Assess for eating disorder. *Bariatric surgery*: Fertility rate, obstetrical complications.
Physical activity	Chap. 10, p. 187	*Exercise:* Conditioned women may continue to exercise. Counsel on fall prevention. Avoid exhaustion and heat exposure.
Cardiovascular disease	Chap. 52, p. 918 Chap. 8, p. 150	Counsel on cardiac risks during pregnancy; discuss situations in which pregnancy is contraindicated. Optimize cardiac function. Discuss medication teratogenicity (warfarin, ACE inhibitor, ARB) and, if possible, switch to less dangerous agent when conception planned. Offer genetic counseling to those with congenital cardiac anomalies (Table 52-4, p. 920).
Chronic HTN	Chap. 53, p. 944 Chap. 8, p. 150	Counsel on specific risks during pregnancy. Assess those with long-standing HTN for ventricular hypertrophy, retinopathy, and renal disease. Optimize blood pressure control. Assess for teratogenic drug use.
Asthma	Chap. 54, p. 960	Counsel on asthma risks during pregnancy. Optimize pulmonary function preconceptionally. Treat women with pharmacological step therapy for chronic asthma.
Thrombophilia	Chap. 55, p. 976	Question for personal or family history of thrombotic events or recurrent poor pregnancy outcomes. If a thrombophilia is found or known, counsel and offer appropriate anticoagulation regimen.
Renal disease	Chap. 56, p. 1003 Chap. 8, p. 150	*Chronic renal disease:* Counsel on specific risks during pregnancy. Optimize blood pressure control before conception. Counsel women taking ACE inhibitors and ARBs about teratogenicity.
Gastrointestinal disease	Chap. 57, p. 1021 Chap. 8, p. 152	*Inflammatory bowel disease*: Counsel affected women on subfertility risks and risks of adverse pregnancy outcomes. Discuss teratogenicity of methotrexate and the other immunomodulators. Offer effective contraception during their use.
Hepatobiliary disease	Chap. 58, p. 1037	*Hepatitis B*: Vaccinate all high-risk women before conception (Table 10-7, p. 189). Counsel chronic carriers on transmission prevention to partners and fetus. Treat if indicated. *Hepatitis C*: Screen high-risk women. Counsel affected women on risks of disease and transmission. If nonpregnant treatment indicated, discuss ramifications and appropriateness of pregnancy.
Hematological disease	Chap. 59, p. 1048	*Iron-deficiency anemia*: Iron supplementation. *Sickle-cell disease*: Screen all black women. Counsel those with trait or disease. Test partner if desired. *Thalassemias*: Screen women of Southeast Asian or Mediterranean ancestry.
Diabetes	Chap. 60, p. 1070	Optimize glycemic control to minimize teratogenicity of hyperglycemia. Evaluate for end-organ damage such as retinopathy, nephropathy, hypertension, and others. Discontinue ACE inhibitors.
Thyroid disease	Chap. 61, p. 1089	Screen those with thyroid disease symptoms. Ensure iodine-sufficient diet. Treat overt hyper- or hypothyroidism. Counsel on risks to pregnancy outcome.
Connective tissue disease	Chap. 62, p. 1109 Chap. 8, p. 144	*Rheumatoid arthritis*: Counsel on flare risk after pregnancy. Discuss methotrexate and leflunomide teratogenicity, as well as possible effects of other immunomodulators. Switch these agents before conception. Stop NSAIDs by 27 weeks' gestation. *Lupus*: Counsel on risks during pregnancy. Assess renal involvement. Optimize disease before conception. Discuss mycophenolate mofetil and cyclophosphamide teratogenicity as well as possible effects of newer immunomodulators. Switch these agents before conception.

(*continued*)

TABLE 9-4. Continued

Condition	Reference Chapter	Recommendations for Preconceptional Counseling
Substance abuse	Chap. 64, p. 1150	*Opioid use disorder (OUD)*: codeine, oxycodone, heroin, and other opioids.
Psychiatric disorders	Chap. 64, p. 1143	*Depression*: Screen for symptoms of depression. Counsel on risks of treatment and of untreated illness and the high risk of exacerbation during pregnancy and the puerperium.
Neurological disorders	Chap. 63, p. 1128	*Seizure disorder*: Optimize seizure control using monotherapy if possible.
Dermatological disease	Chap. 8, p. 155	Discuss isotretinoin and etretinate teratogenicity and effective contraception during their use; switch agents before conception.
Cancer	Chap. 66, p. 1164	Counsel on fertility preservation options before cancer therapy and on decreased fertility following certain agents. Discuss appropriateness of pregnancy balanced with need for ongoing cancer therapy and prognosis of the disease state.
Infectious diseases	Chap. 67, p. 1183	*Influenza*: Vaccinate all women who will be pregnant during flu season. Vaccinate high-risk women prior to flu season. *COVID-19*: Vaccinate candidates. *Malaria*: Counsel to avoid travel to endemic areas during conception. If unable, offer effective contraception during travel or provide chemoprophylaxis for those planning pregnancy. *Zika virus*: See travel restrictions by CDC. *Rubella*: Screen for rubella immunity. If nonimmune, vaccinate and counsel on the need for effective contraception during the subsequent month. *Tdap*: *tetanus, diphtheria, pertussis:* Update vaccination in all reproductive-aged women. *Varicella*: Question regarding immunity. If nonimmune, vaccinate.
STIs	Chap. 68, p. 1206	*Gonorrhea, syphilis, chlamydial infection*: Screen high-risk women and treat as indicated. *Human immunodeficiency virus*: Screen at-risk women. Counsel affected women on risks during pregnancy and on perinatal transmission. Discuss initiation of treatment before pregnancy to decrease transmission risk. Offer effective contraception to those not desiring conception. *Human papilloma virus*: Provide Pap smear screening per guidelines (Chap. 66, p. 1164). Vaccinate candidate patients. *Herpes virus*: Provide serological screening to asymptomatic women with affected partners. Counsel affected women on risks of perinatal transmission and on preventative measures during the third trimester and labor.

ACE = angiotensin-converting enzyme; ARB = angiotensin-receptor blocker; BMI = body mass index; CDC = Centers for Disease Control and Prevention; HTN = hypertension; NSAID = nonsteroidal antiinflammatory drug; STI = sexually transmitted infection.

Adapted from American College of Obstetricians and Gynecologists, 2017a, 2019b, 2021; Centers for Disease Control and Prevention, 2021; Jack, 2008.

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CHAPTER 10

Prenatal Care

The American Academy of Pediatrics and the American College of Obstetricians and Gynecologists (2017) define prenatal care as "A comprehensive antepartum program involves a coordinated approach to medical care, continuous risk assessment, and psychosocial support that optimally begins before pregnancy and extends throughout the postpartum and interpregnancy period." As promulgated by John Ballantyne, such care has been a bedrock to improve pregnancy outcomes for more than 100 years (Reiss, 2000).

PRENATAL CARE IN THE UNITED STATES

Almost a century after its introduction, prenatal care has become one of the most frequently used health services in the United States. According to the Centers for Disease Control and Prevention (CDC), only 1.6 percent of women who gave birth in 2016 received no prenatal care (Osterman, 2018). African-American and Hispanic women have high rates of inadequate or no prenatal care that reach 10 and 7.7 percent, respectively. This figure is greater for adolescents, particularly those younger than 15 years, compared with older age groups. These data highlight areas of potential improvement by the health-care system.

Prenatal Care Effectiveness

Care designed during the early 1900s focused on lowering the extremely high maternal mortality rate. Prenatal care undoubtedly contributed to the dramatic decline in maternal deaths from 690 per 100,000 births in 1920 to 50 per 100,000 by 1955 (Loudon, 1992). Data from 1998 to 2005 from the Pregnancy Mortality Surveillance System identified a fivefold increased risk for maternal death in women who received no prenatal care (Berg, 2010).

Goldenberg and McClure (2018) have emphasized the importance of prenatal care to reduce stillbirth rates as well. In a study of almost 29 million births, the risk for preterm birth, stillbirth, early and late neonatal death, and infant death rose linearly with decreasing prenatal care utilization (Partridge, 2012). Similarly, from Parkland Hospital, Leveno and associates (2009) found that a significant decline in preterm births correlated closely with any use of prenatal care by medically indigent women. And in women with diabetes, adherence to prenatal care resulted in lower rates of neonatal admissions to the intensive care unit (Sperling, 2018a).

Group prenatal care is acceptable and effective (American College of Obstetricians and Gynecologists, 2018g). Ickovics and coworkers (2016) compared this with individual prenatal care. Group care provided traditional pregnancy surveillance in a group setting with special focus on support, education, and active health-care participation. Women enrolled in group care had significantly better pregnancy outcomes. Carter and colleagues (2017) cited similar results. Childbirth education classes are also reported to result in better pregnancy outcomes (Afshar, 2017). Pregnancy in adolescents carries special risk, and guidelines have been developed that focus on this age group (Fleming, 2015).

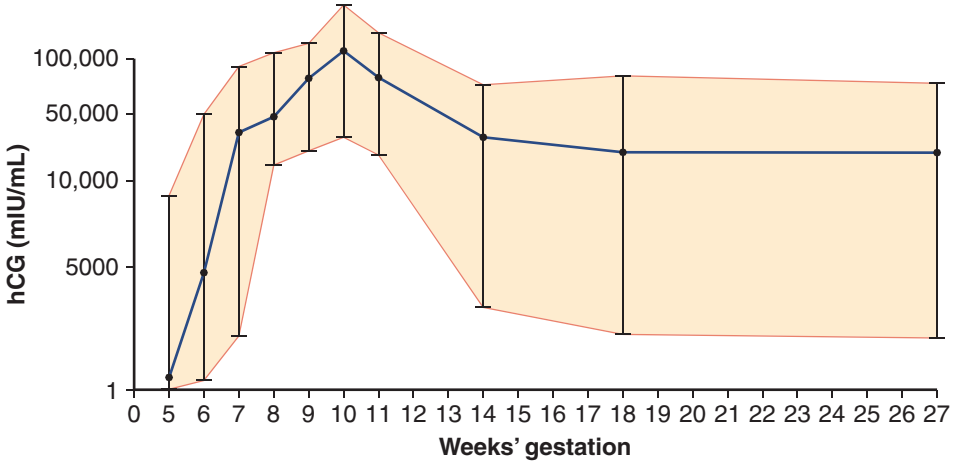

FIGURE 10-1 Mean concentration (95% CI) of human chorionic gonadotropin (hCG) in serum of women throughout normal pregnancy.

corpus luteum, which is the principal site of progesterone formation during the first 6 weeks of pregnancy.

With a sensitive test, the hormone can be detected in maternal serum or urine by 8 to 9 days after ovulation. The doubling time of serum hCG concentration is 1.4 to 2.0 days. As shown in Figure 10-1, serum levels range widely and increase from the day of implantation. Lower levels of hCG rise more rapidly than higher levels (Barnhart, 2016). Peak hCG levels are reached at 60 to 70 days. Thereafter, the concentration declines slowly to a plateau at approximately 16 weeks' gestation.

DIAGNOSIS OF PREGNANCY

Pregnancy is usually identified when a woman presents with symptoms and possibly a positive home urine pregnancy test result. Typically, these women receive confirmatory testing of urine or blood for human chorionic gonadotropin (hCG). Further, presumptive signs or diagnostic findings of pregnancy may be found during the clinical examination. Sonography is often used, especially if miscarriage or ectopic pregnancy is a concern.

Symptoms and Signs

Amenorrhea in a healthy reproductive-aged woman who previously has experienced spontaneous, cyclical, predictable menses is highly suggestive of pregnancy. Menstrual cycles vary appreciably in length among women and even in the same woman (Chap. 5, p. 83). Thus, amenorrhea is not a reliable pregnancy indicator until 10 or more days have passed after expected menses. Occasionally, uterine bleeding that mimics menstruation is noted after conception. During the first month of pregnancy, these episodes are likely the consequence of blastocyst implantation. Still, first-trimester bleeding should prompt evaluation for an abnormal pregnancy.

Of other symptoms, maternal perception of fetal movement depends on factors such as parity and habitus. In general, after a first successful pregnancy, a woman may first perceive fetal movements between 16 and 18 weeks' gestation. A primigravida may not appreciate fetal movements until approximately 2 weeks later. At about 20 weeks, depending on maternal habitus, an examiner can begin to detect fetal movements. Of pregnancy signs, changes in the lower reproductive tract, uterus, and breasts develop early.

Pregnancy Tests

Detection of hCG in maternal blood and urine is the basis for endocrine assays of pregnancy. Syncytiotrophoblast produces hCG in amounts that increase exponentially during the first trimester. hCG and luteinizing hormone (LH) share the same receptor in tissues. Thus, a main function of hCG is to prevent involution of the

Measurement of hCG

This hormone is a glycoprotein with high carbohydrate content. The general structure of hCG is a heterodimer composed of two dissimilar subunits, designated α and β, which are noncovalently linked. The α-subunit is identical to those of LH, follicle-stimulating hormone (FSH), and thyroid-stimulating hormone (TSH), but the β-subunit is structurally distinct. Thus, antibodies were developed with high specificity for the hCG β-subunit. This specificity allows its detection, and numerous commercial immunoassays are available for measuring serum and urine hCG levels. Each immunoassay detects a slightly different mixture of hCG variants, its free subunits, or its metabolites—however, all are appropriate for pregnancy testing (Braunstein, 2014). Depending on the assay used, the sensitivity for the laboratory detection limit of hCG in serum is 1.0 mIU/mL or even lower.

False-positive hCG test results are rare. A few women have circulating serum factors that may bind erroneously with the test antibody directed to hCG in a given assay. The most common factors are heterophilic antibodies. These are produced by an individual and bind to the animal-derived test antibodies used in a given immunoassay. Thus, women who have worked closely with animals are more likely to develop these antibodies, and alternative laboratory techniques are available (American College of Obstetricians and Gynecologists, 2017a). Elevated hCG levels may also reflect molar pregnancy and its associated neoplasms (Chap. 13, p. 238). Other rare causes of positive assays without pregnancy are (1) exogenous hCG injection used for weight loss, (2) renal failure with impaired hCG clearance, (3) physiological pituitary hCG, and (4) hCG-producing tumors that most commonly originate from gastrointestinal sites, ovary, bladder, or lung (McCash, 2017).

Home Pregnancy Tests

More than 60 different types of over-the-counter pregnancy test kits are available in the United States (Grenache, 2015). Unfortunately, many of these are not as accurate as advertised (Johnson, 2015). For example, Cole and associates (2011) found that a detection limit of 12.5 mIU/mL would be required to diagnose

95 percent of pregnancies at the time of missed menses. However, they reported that only one brand had this degree of sensitivity. Two other brands gave false-positive or invalid results. In fact, with an hCG concentration of 100 mIU/mL, clearly positive results were displayed by only 44 percent of brands. Accordingly, only approximately 15 percent of pregnancies could be diagnosed at the time of the missed menses. Some manufacturers of even newer home urine assays claim >99-percent accuracy for tests done on the day of—and some up to 4 days before—the expected day of menses. Again, careful analysis suggests that these assays are often not as sensitive as advertised.

■ Sonographic Recognition of Pregnancy

Transvaginal sonography is commonly used to accurately establish gestational age and confirm pregnancy location. A *gestational sac* is the first sonographic evidence of pregnancy, and it may be seen with transvaginal sonography by 4 to 5 weeks' gestation. It should not be confused with a *pseudogestational sac*. The latter, or *pseudosac*, is a fluid collection within the endometrial cavity, which can occur in the setting of ectopic pregnancy (Fig. 12-3, p. 223). Further evaluation may be warranted if this is the only sonographic finding, particularly in a woman with pain or bleeding. A normal gestational sac implants eccentrically in the endometrium, whereas a pseudosac is seen in the midline of the endometrial cavity. Other potential indicators of early intrauterine pregnancy are an anechoic center surrounded by a single echogenic rim—the *intradecidual sign*—or two concentric echogenic rings surrounding the gestational sac—the *double decidual sign* (Fig. 10-2). If sonography yields equivocal findings, the term *pregnancy of unknown location (PUL)* is applied (Bobdiwala, 2019). In these cases, serial serum hCG levels and transvaginal sonography can help differentiate a normal intrauterine pregnancy from an extrauterine pregnancy or an early miscarriage (Chap. 12, p. 222).

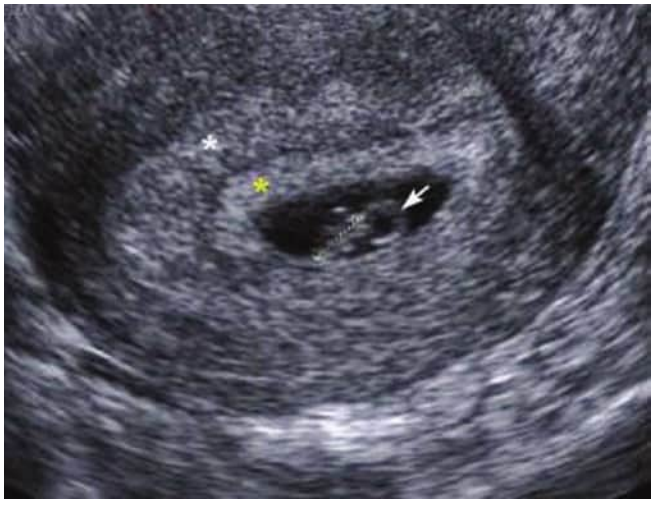

FIGURE 10-2 Transvaginal sonogram of a first-trimester intrauterine pregnancy. The double decidual sign is noted surrounding the gestational sac and is defined by the decidua parietalis (*white asterisk*) and the decidua capsularis (*yellow asterisk*). The arrow notes the yolk sac, and the crown-rump length of the embryo is marked with measuring calipers. (Reproduced with permission from Dr. Elysia Moschos.)

If the *yolk sac*—a brightly echogenic ring with an anechoic center—is seen within the gestational sac, an intrauterine location for the pregnancy is confirmed. The yolk sac can normally be seen by the middle of the fifth week. As shown in Figure 10-2, after 6 weeks, an embryo is seen as a linear structure immediately adjacent to the yolk sac. Cardiac motion is typically noted at this point.

INITIAL PRENATAL EVALUATION

Prenatal care is ideally initiated early. Major goals are to (1) define the health status of the mother and fetus, (2) estimate the gestational age, and (3) initiate a plan for continued obstetrical care. Typical components of the initial visit are summarized in Table 10-1. Subsequent care may range from relatively infrequent routine visits to prompt hospitalization because of serious maternal or fetal disease.

■ Prenatal Record

Use of a standardized record within a perinatal health-care system greatly aids antepartum and intrapartum management. Standardizing documentation allows communication and care continuity between providers and enables objective measures of care quality to be evaluated over time and across different clinical settings (Gregory, 2006). A prototype is provided by the American Academy of Pediatrics and the American College of Obstetricians and Gynecologists (2017) in their *Guidelines for Perinatal Care*, 8th edition.

Definitions

Several definitions are pertinent to establishment of an accurate prenatal record.

1. *Nulligravida*—a woman who currently is not pregnant and has never been pregnant.
2. *Gravida*—a woman who currently is pregnant or has been in the past, irrespective of the pregnancy outcome. With the establishment of the first pregnancy, she becomes a *primigravida*, and with successive pregnancies, a *multigravida*.
3. *Nullipara*—a woman who has never completed a pregnancy beyond 20 weeks' gestation. She may not have been pregnant or may have had a spontaneous or elective abortion(s) or an ectopic pregnancy.
4. *Primipara*—a woman who has been delivered only once of a fetus or fetuses born alive or dead with an estimated gestation duration of 20 or more weeks. In the past, a 500-g birthweight threshold was used to define parity. This threshold is now controversial. Namely, many states still use this weight to differentiate a stillborn fetus from an abortus, but the survival of neonates with birthweights <500 g is no longer uncommon (Chap. 1, p. 2).
5. *Multipara*—a woman who has completed two or more pregnancies with gestational ages at least 20 weeks. Parity is determined by the number of pregnancies reaching 20 weeks. It is not increased to a higher number if multiples are delivered in a given pregnancy. Moreover, stillbirth does not lower this number.

TABLE 10-1. Typical Components of Routine Prenatal Care

	Text Referral	First Visit	Weeks 15–20	Weeks 24–28	Weeks 29–41
History					
Complete	Chap. 10, p. 179	•			
Updated			•	•	•
Physical Examination					
Complete	Chap. 10, p. 180	•			
Blood pressure	Chap. 40, p. 688	•	•	•	•
Maternal weight	Chap. 10, p. 181	•	•	•	•
Pelvic/cervical examination	Chap. 10, p. 180	•			
Fundal height	Chap. 10, p. 180	•	•	•	•
Fetal heart rate/fetal position	Chap. 10, p. 182	•	•	•	•
Laboratory Tests					
Hematocrit or hemoglobin	Chap. 59, p. 1048	•		•	
Blood type and Rh factor	Chap. 18, p. 353	•			
Antibody screen	Chap. 18, p. 353	•		**A**	
Pap smear screening	Chap. 66, p. 1164	•			
Glucose tolerance test	Chap. 60, p. 1079			•	
Fetal aneuploidy screening	Chap. 17, p. 335	**B**[a] and/or	**B**		
Neural-tube defect screening	Chap. 17, p. 338		**B**		
Cystic fibrosis screening	Chap. 17, p. 342	**B** or	**B**		
Urine protein assessment	Chap. 4, p. 68	•			
Urine culture	Chap. 56, p. 996	•			
Rubella serology	Chap. 67, p. 1190	•			
Syphilis serology	Chap. 68, p. 1208	•			**C**
Gonococcal screening	Chap. 68, p. 1211	**D**			**D**
Chlamydial screening	Chap. 68, p. 1212	•			**C**
Hepatitis B serology	Chap. 58, p. 1037	•			**D**
HIV serology	Chap. 68, p. 1219	**B**			**D**
Group B streptococcus culture	Chap. 67, p. 1195				**E**
Tuberculosis screening	Chap. 54, p. 966	**F**			

[a]First-trimester aneuploidy screening may be offered between 10 and 14 weeks.
A Performed at 28 weeks, if indicated.
B Test should be offered.
C High-risk women should be retested at the beginning of the third trimester.
D High-risk women should be screened at the first prenatal visit and again in the third trimester.
E Rectovaginal culture should be obtained between 35 and 37 weeks.
F High-risk women should be screened at the first prenatal visit.
HIV = human immunodeficiency virus.

In some locales, the obstetrical history is summarized by a series of digits connected by dashes. These refer to the number of term newborns, preterm neonates, abortuses younger than 20 weeks, and children currently alive. For example, a woman who is para 2–1–0–3 has had two term deliveries, one preterm delivery, no abortuses, and has three living children. Because these are nonconventional, it is helpful to specify the outcome of any pregnancy that did not end normally.

Normal Pregnancy Duration

The normal duration of pregnancy calculated from the first day of the last normal menstrual period is very close to 280 days or 40 weeks. A quick estimate of a pregnancy due date based on menstrual data can be made as follows: add 7 days to the first day of the last period and subtract 3 months. For example, if the first day of the last menses was October 5, the due date is 10-05 minus 3 (months) plus 7 (days) = 7–12 or July 12 of the following year. This calculation is the *Naegele rule*. However, menstrual cycle length varies among women and renders many of these calculations inaccurate. This, combined with the frequent use of first-trimester sonography, has changed the method of determining an accurate gestational age.

The American College of Obstetricians and Gynecologists (2017e), the American Institute of Ultrasound in Medicine, and the Society for Maternal-Fetal Medicine have emphasized that first-trimester ultrasound is the most accurate method to

establish or reaffirm gestational age. For pregnancies conceived by assisted reproductive technologies, embryo age or transfer date is used to assign gestational age. If available, the gestational ages calculated from the last menstrual period and from first-trimester ultrasound are compared, and this estimated date of delivery is recorded. Reconciling any discordance between these two values is discussed in Chapter 14 (p. 248).

Trimesters

It has become customary to divide pregnancy into three equal epochs or trimesters of approximately 3 calendar months. More recently a "fourth trimester" has been recognized to emphasize the need for comprehensive postpartum care (American College of Obstetricians and Gynecologists, 2018i). This is discussed in Chapter 36 (p. 634). Historically, the first trimester extends through completion of 14 weeks, the second through 28 weeks, and the third through 42 weeks. The fourth is the 12 weeks after delivery. Thus, prenatally, there are three periods of 14 weeks each. Certain major obstetrical problems tend to cluster in each of these three time periods. For example, most spontaneous abortions take place during the first trimester, whereas most women with hypertensive disorders due to pregnancy are diagnosed during the third trimester.

In modern obstetrics, the clinical use of trimesters to describe a specific pregnancy is imprecise. For example, it is inappropriate in cases of uterine hemorrhage to categorize the problem temporally as "third-trimester bleeding." Appropriate management for the mother and her fetus will vary remarkably depending on whether bleeding begins early or late in the third trimester (Chap. 42, p. 733). Because precise knowledge of fetal age is imperative for obstetrical management, the clinically appropriate unit is *weeks of gestation completed.* Clinicians designate gestational age using completed weeks and days. For example, $33^{4/7}$ weeks or 33 + 4 describes pregnancy duration of 33 completed weeks and 4 days.

Previous and Current Health Status

As elsewhere in medicine, history-taking begins with queries concerning medical or surgical disorders. Detailed information regarding previous pregnancies is essential, as many obstetrical complications tend to recur in subsequent pregnancies. The *menstrual* and *contraceptive histories* also are important. As noted earlier, gestational age may be less accurate for those with irregular menses. Moreover, some methods of birth control favor ectopic implantation following method failure (Chap. 38, p. 665).

Psychosocial Screening. The American Academy of Pediatrics and the American College of Obstetricians and Gynecologists (2017) define psychosocial issues as nonbiomedical factors that affect mental and physical well-being. Women should be screened regardless of social status, education level, race, or ethnicity. Such screening should seek barriers to care, communication obstacles, nutritional status, unstable housing, desire for pregnancy, safety concerns that include intimate-partner violence, depression, stress, and use of substances such as tobacco, alcohol, and illicit drugs. This screening is performed on a regular basis, at least once per trimester, to identify important issues and reduce adverse pregnancy outcomes. Coker and colleagues (2012) compared pregnancy outcomes in women before and after implementation of a universal psychosocial screening program and found that screened women were less likely to have preterm or low-birthweight newborns, as well as other adverse outcomes. Specific screens for depression are presented in Chapter 64 (p. 1143).

Cigarette Smoking. These data are included on the birth certificate, and the number of pregnant women who smoke continues to decline. From 2000 to 2010, the prevalences were 12 to 13 percent (Tong, 2013). By 2016, the incidence was 7.2 percent according to the National Center for Health Statistics (Drake, 2018). Concurrent with the decline in cigarette use, there has been an increase in electronic cigarettes/vaping with a reported prevalence of 0.6 to 15 percent (Whittington, 2018). In a survey of more than 3000 mothers in Oklahoma and Texas, 7 percent reported using electronic vapor products prior to conception and in the postpartum period. Of these women, according to the CDC, 1.4 percent used them during the last 3 months of pregnancy (Kapaya, 2019).

According to the American Society for Reproductive Medicine (2018), smoking is associated with subfertility. Higher rates of miscarriage, stillbirth, low birthweight, and preterm delivery also are linked to smoking during pregnancy (Dahlin, 2016; Luke, 2018; Tong, 2013). Compared with nonsmokers, risks of placenta previa, placental abruption, and premature membrane rupture are increased twofold. Potential teratogenic effects are reviewed in Chapter 8 (p. 156). Thus, the U.S. Preventive Services Task Force recommends that clinicians offer counseling and effective intervention options to pregnant smokers at the first and subsequent prenatal visits (Siu, 2015). Although benefits are greatest if smoking ceases early in pregnancy or preferably preconceptionally, quitting at any stage of pregnancy can improve perinatal outcomes (Soneji, 2019).

Compared with simple counseling to quit, person-to-person psychosocial interventions are significantly more successful in achieving smoking abstinence in pregnancy (Fiore, 2008). One example is a brief counseling session covering the "5As" of smoking cessation (Table 10-2). This approach can be accomplished in 15 minutes or less and is effective when initiated by health-care providers (American College of Obstetricians and Gynecologists, 2020b).

Behavioral interventions and nicotine replacement products are successful in reducing smoking rates (Patnode, 2015). However, nicotine replacement has not been sufficiently evaluated to determine its effectiveness and safety in pregnancy. Trials evaluating such therapy have yielded conflicting evidence (Coleman, 2015; Spindel, 2016). Two randomized trials also produced inconclusive results. In the Smoking and Nicotine in Pregnancy (SNAP) trial, Cooper and associates (2014) reported that a temporary cessation of smoking may have been associated with improved infant development. In the Study of Nicotine Patch in Pregnancy (SNIPP) trial, no differences in smoking cessation rates or birthweights were found (Berlin, 2014). Similar preliminary results were reported for sustained-release bupropion (Nanovskaya, 2017). Olson and colleagues (2019) reported that financial incentives were helpful to encourage smoking cessation.

TABLE 10-2. Five A's of Smoking Cessation

ASK about smoking at the first and subsequent prenatal visits.
ADVISE with clear, strong statements that explain the risks of continued smoking to the woman, fetus, and newborn.
ASSESS the patient's willingness to attempt cessation.
ASSIST with pregnancy-specific, self-help smoking cessation materials. Offer a direct referral to the smokers' quit line (1-800-QUIT NOW) to provide ongoing counseling and support.
ARRANGE to track smoking abstinence progress at subsequent visits.

Adapted from American College of Obstetricians and Gynecologists, 2020b; Fiore, 2008.

Because of limited available evidence to support pharmacotherapy for smoking cessation in pregnancy, the American College of Obstetricians and Gynecologists (2020b) recommends that if nicotine replacement therapy is used, it should be done with close supervision and after careful consideration of the risks of smoking versus nicotine replacement.

Alcohol. Ethyl alcohol or ethanol is a potent teratogen that causes the *fetal alcohol spectrum disorders.* Fetal alcohol syndrome, the most severe form of these disorders, is characterized by growth restriction, facial abnormalities, and central nervous system dysfunction. The estimated prevalence of these disorders is 11 to 50 per 1000 (May, 2018).

As discussed in Chapter 8 (p. 150), women who are pregnant or considering pregnancy should abstain from drinking any alcoholic beverages (Sarman, 2018). The CDC analyzed data from the Behavioral Risk Factor Surveillance System from 2015 to 2017 and estimated that 12 percent of pregnant women used alcohol (Denny, 2019). The American College of Obstetricians and Gynecologists (2021a) in collaboration with the CDC has developed the *Fetal Alcohol Spectrum Disorders (FASD) Prevention Program*, which provides resources for providers and is available at www.acog.org/alcohol.

Illicit Drugs. An estimated 10 percent of fetuses are exposed to one or more illicit drugs. Agents may include heroin and other opiates, cocaine, amphetamines, barbiturates, and marijuana (American Academy of Pediatrics, 2017). As discussed in Chapter 8 (p. 157), chronic use of large quantities is harmful to the fetus (Metz, 2015). Well-documented sequelae include fetal-growth restriction, low birthweight, and drug withdrawal soon after birth. Adverse effects of marijuana are less convincing. Women who use such drugs frequently do not seek prenatal care, which in itself is associated with risks for preterm and low-birthweight neonates (Eriksen, 2016).

For women who abuse heroin, methadone maintenance can be initiated within a registered methadone treatment program to reduce complications of illicit opioid use and narcotic withdrawal, to encourage prenatal care, and to avoid drug culture risks (American College of Obstetricians and Gynecologists, 2017g). Available programs can be found through the treatment locator of the Substance Abuse and Mental Health Services Administration at www.samhsa.gov. Methadone dosages usually are initiated at 10 to 30 mg orally daily and titrated as needed. In some women, careful methadone taper may be an appropriate option (Stewart, 2013). Buprenorphine alone or in combination with naloxone also may be offered and managed by physicians with specific credentialing. These therapeutic options are considered in greater detail in Chapter 64 (p. 1150).

Intimate-Partner Violence. This term refers to a pattern of assault and coercive behavior that may include physical injury, psychological abuse, sexual assault, progressive isolation, stalking, deprivation, intimidation, and reproductive coercion (Miller, 2019). Such violence is recognized as a major public health problem. Unfortunately, most abused women continue to be victimized during pregnancy. With the possible exception of preeclampsia, intimate-partner violence (IPV) is more prevalent than any major medical condition detectable through routine prenatal screening (American Academy of Pediatrics, 2017). The estimated prevalence during pregnancy lies between 4 and 8 percent. IPV is associated with an increased risk of several adverse perinatal outcomes that include preterm delivery, fetal-growth restriction, and perinatal death (Chap. 50, p. 891).

The American College of Obstetricians and Gynecologists (2019c) has provided methods for IPV screening and recommends their use at the first prenatal visit, again at least once per trimester, and again at the postpartum visit. Such screening should be done privately and away from family members and friends. Patient self-administered or computerized screenings appear to be as effective for disclosure as clinician-directed interviews (Ahmad, 2009; Chen, 2007). Physicians should be familiar with state laws that may require reporting of IPV. Coordination with social services can be invaluable in these cases. The National Domestic Violence Hotline (1–800–799-SAFE [7233]) is a nonprofit telephone referral service that provides individualized information regarding city-specific shelter locations, counseling resources, and legal advocacy.

Clinical Evaluation

Thorough, general physical and pelvic examinations should be completed at the initial prenatal encounter. The cervix is visualized using a speculum lubricated with warm water or water-based lubricant gel. Bluish-red passive hyperemia of the cervix is characteristic, but not diagnostic, of pregnancy. Dilated, occluded cervical glands bulging beneath the ectocervical mucosa—*nabothian cysts*—may be prominent. The cervix is not normally dilated except at the external os. To identify cytological abnormalities, a Pap test is performed according to current guidelines noted in Chapter 66 (p. 1164). Specimens for identification of *Chlamydia trachomatis* and *Neisseria gonorrhoeae* are obtained when indicated (p. 181).

Bimanual examination is completed by palpation. Special attention is given to the consistency, length, and dilation of the

cervix; to uterine and adnexal size; to the bony pelvic architecture; and to any vaginal or perineal anomalies. Often, later in pregnancy, fetal presentation also can be determined. Lesions of the cervix, vagina, or vulva are further evaluated as needed by colposcopy, biopsy, or culture. The perianal region is inspected, and digital rectal examination is performed as required for complaints of rectal pain, bleeding, or mass.

Gestational Age Assessment

Precise knowledge of gestational age is essential for prenatal care, because several pregnancy complications may develop and optimal treatment will depend on fetal age. Menstrual history is best confirmed by first-trimester sonography (Chap. 14, p. 248). That said, gestational age can also be estimated with considerable precision by a carefully performed clinical uterine size examination that is coupled with last menstrual period dating. Uterine size similar to a small orange roughly correlates with a 6-week gestation; a large orange, with an 8-week pregnancy; and a grapefruit, with one at 12 weeks (Margulies, 2001).

Laboratory Tests

Recommended routine tests at the first prenatal encounter are listed in Table 10-1. Initial blood tests include a complete blood count, a determination of blood type and Rh status, and an antibody screen. The Institute of Medicine recommends universal human immunodeficiency virus (HIV) testing as a routine part of prenatal care. This testing is explained to the patient, who may decline. The American College of Obstetricians and Gynecologists (2018j) continues to support this practice. If a woman declines, this is recorded in the prenatal record. All pregnant women are screened also for hepatitis B virus infection, syphilis, and immunity to rubella at the initial visit.

Based on their prospective investigation of 1000 women, Murray and coworkers (2002) concluded that in the absence of hypertension, routine urinalysis beyond the first prenatal visit was unnecessary. A urine culture is recommended by most, because treating bacteriuria significantly reduces the likelihood of developing symptomatic urinary tract infections in pregnancy (Chap. 56, p. 996).

Cervical Infections

C trachomatis is isolated from the cervix in 2 to 13 percent of pregnant women. The American Academy of Pediatrics and the American College of Obstetricians and Gynecologists (2017) recommend that all women be screened for chlamydia during the first prenatal visit, with additional third-trimester testing for those at increased risk. Risk factors include unmarried status, recent change in sexual partner or multiple concurrent partners, age younger than 25 years, inner-city residence, history or presence of other sexually transmitted diseases, and little or no prenatal care. For those testing positive, treatment described in Chapter 68 (p. 1212) is followed by a second testing—a *test of cure*—3 to 4 weeks after treatment completion.

N gonorrhoeae typically causes cervicitis or urethritis in pregnancy. Infrequently, it may also cause septic arthritis (Bleich, 2012). Risk factors for gonorrhea are similar to those for chlamydial infection. The American Academy of Pediatrics and the American College of Obstetricians and Gynecologists (2017) recommend that pregnant women with risk factors or those living in an area of high *N gonorrhoeae* prevalence be screened at the initial prenatal visit and again in the third trimester. Treatment is given for gonorrhea and simultaneously for possible coexisting chlamydial infection (Chap. 68, p. 1211). Test of cure is recommended following treatment.

Pregnancy Risk Assessment

Many factors can adversely affect maternal and fetal well-being. Some are evident at conception, but many become apparent during the course of pregnancy. The designation of "high-risk pregnancy" is overly vague for an individual woman and is best avoided if a more specific diagnosis can be assigned. Some common risk factors for which consultation is recommended by the American Academy of Pediatrics and the American College of Obstetricians and Gynecologists (2017) are shown in Table 10-3. Some conditions may require the involvement of a maternal-fetal medicine specialist, geneticist, neonatologist, anesthesiologist, cardiologist, or other specialist.

SUBSEQUENT PRENATAL VISITS

These are traditionally scheduled at 4-week intervals until 28 weeks, then every 2 weeks until 36 weeks, and weekly thereafter. Women with complicated pregnancies—for example, with twins or diabetes—often require return visits at 1- to 2-week intervals (Power, 2013). In 1986, the Department of Health and Human Services convened an expert panel to review the content of prenatal care. This report was subsequently reevaluated and revised in 2005 (Gregory, 2006). The panel recommended, among other things, early and continuing risk assessment that is patient specific. It also endorsed flexibility in clinical visit spacing; health promotion and education, including preconceptional care; medical and psychosocial interventions; standardized documentation; and expanded prenatal care objectives that include family health up to 1 year after birth.

The World Health Organization conducted a multicenter randomized trial with almost 25,000 women that compared routine prenatal care with an experimental model designed to minimize visits (Villar, 2001). In the new model, women were seen once in the first trimester and screened for certain risks. Those without anticipated complications—80 percent of those screened—were seen again at 26, 32, and 38 weeks. Compared with routine prenatal care, which required a median of eight visits, the new model required a median of only five. No disadvantages were attributed to the regimen with fewer visits, and these findings are consistent with other randomized trials.

Prenatal Surveillance

At each return visit, the well-being of mother and fetus are assessed (see Table 10-1). Fetal heart rate, growth, and activity are evaluated. Maternal blood pressure and weight and their extent of change are assessed. Symptoms such as abdominal pain, nausea and vomiting, bleeding, vaginal fluid leakage, headache, altered vision, and dysuria are sought. After 20 weeks' gestation, uterine examination measures size from the symphysis to the fundus with

TABLE 10-3. Conditions for Which Maternal-Fetal Medicine Consultation May Be Beneficial

Medical History and Conditions
Cardiac disease—moderate to severe disorders
Diabetes mellitus with evidence of end-organ damage or uncontrolled hyperglycemia
Family or personal history of genetic abnormalities
Hemoglobinopathy
Chronic hypertension if uncontrolled or associated with renal or cardiac disease
Renal insufficiency if associated with significant proteinuria (≥500 mg/24 hour), serum creatinine ≥1.5 mg/dL, or hypertension
Pulmonary disease if severe restrictive or obstructive, including severe asthma
Human immunodeficiency virus infection
Prior pulmonary embolus or deep-vein thrombosis
Severe systemic disease, including autoimmune conditions
Bariatric surgery
Epilepsy if poorly controlled or requires more than one anticonvulsant
Cancer, especially if treatment is indicated in pregnancy
Obstetrical History and Conditions
CDE (Rh) or other blood group alloimmunization (excluding ABO, Lewis)
Prior or current fetal structural or chromosomal abnormality
Desire or need for prenatal diagnosis or fetal therapy
Periconceptional exposure to known teratogens
Infection with or exposure to organisms that cause congenital infection
Higher-order multifetal gestation
Severe disorders of amnionic fluid volume

a traditional tape measure. In late pregnancy, vaginal examination often provides valuable information. This may include confirmation of the presenting part and its station, clinical estimation of pelvic capacity and configuration, fetal ballottement as a reflection of sufficient amnionic fluid volume, and cervical consistency, effacement, and dilation (Chap. 22, p. 426).

Fundal Height

Between 20 and 34 weeks' gestation, the height of the uterine fundus measured in centimeters correlates closely with gestational age in weeks. This measurement is used to monitor fetal growth and amnionic fluid volume. It is measured along the abdominal wall from the top of the symphysis pubis to the top of the fundus. Importantly, the bladder must be emptied before fundal measurement. Obesity or the presence of uterine masses such as leiomyomas also may limit fundal height measurement accuracy. Moreover, using fundal height alone, fetal-growth restriction may be undiagnosed in up to a third of cases (American College of Obstetricians and Gynecologists, 2021b; Haragan, 2015).

Fetal Heart Sounds

Instruments incorporating Doppler ultrasound are usually used to easily detect fetal heart action, and in the absence of maternal obesity, heart sounds are almost always detectable by 10 weeks with such instruments (Chap. 24, p. 447). The fetal heart rate ranges from 110 to 160 beats per minute and is typically heard as a double sound. Using a standard nonamplified stethoscope, the fetal heart is audible by 20 weeks in 80 percent of women, and by 22 weeks, heart sounds are expected to be heard in all (Herbert, 1987). Because the fetus moves freely in amnionic fluid, the site on the maternal abdomen where fetal heart sounds can be heard best will vary.

Additionally, with ultrasonic auscultation, one may hear the *funic souffle*, which is a sharp, whistling sound that is synchronous with the fetal pulse. It is caused by the rush of blood through the umbilical arteries and may not be heard consistently. In contrast, the *uterine souffle* is a soft, blowing sound that is synchronous with the maternal pulse. It is produced by the passage of blood through the dilated uterine vessels and is heard most distinctly near the lower portion of the uterus.

Sonography

Ultrasound imaging provides invaluable information regarding fetal anatomy, growth, and well-being. As such, it is recommended that all pregnant women be offered at least one prenatal sonographic examination (American College of Obstetricians and Gynecologists, 2018l). Continuing trends suggest that the number of these examinations performed per pregnancy is increasing. Data from commercial insurance plans indicate that even low-risk pregnancies receive an average of 4 to 5 ultrasound examinations (O'Keeffe, 2013). Sonography should be performed only for valid medical indications. Additionally, needed information is obtained using the lowest possible ultrasound exposure settings, which is the as low as reasonably achievable (ALARA) principle (American Institute of Ultrasound in Medicine, 2016).

■ Subsequent Laboratory Tests

If initial results were normal, most tests need not be repeated. Hematocrit or hemoglobin determination, along with serology

for syphilis if it is prevalent in the population, is repeated at 28 to 32 weeks (Hollier, 2003; Kiss, 2004). For women at increased risk for HIV acquisition during pregnancy, repeat testing is recommended in the third trimester, preferably before 36 weeks (American College of Obstetricians and Gynecologists, 2018j). Similarly, women who engage in behaviors that place them at high risk for hepatitis B virus infection are retested at the time of delivery. Women who are D (Rh) negative and are unsensitized should have an antibody screening test repeated at 28 to 29 weeks. Anti-D immunoglobulin is given if they remain unsensitized (Chap. 18, p. 354).

Group B Streptococcal Infection

The CDC (2010b) recommends that vaginal and rectal group B streptococcal (GBS) cultures be obtained in all women between 35 and 37 weeks' gestation, and the American College of Obstetricians and Gynecologists (2020f) endorses this recommendation. Intrapartum antimicrobial prophylaxis is provided to those whose culture results are positive. Women with GBS bacteriuria, preterm labor, or a previous infant with invasive disease are given empirical intrapartum prophylaxis. Trials are in progress to test an investigational vaccine (Madhi, 2016). These infections are described further in Chapter 67 (p. 1194).

Gestational Diabetes

All pregnant women are screened for gestational diabetes mellitus, whether by history, clinical factors, or routine laboratory testing. Although laboratory testing between 24 and 28 weeks' gestation is the most sensitive approach, there may be women at low risk who are less likely to benefit from testing (American College of Obstetricians and Gynecologists, 2019d). Gestational diabetes is discussed in Chapter 60 (p. 1079).

Genetic Screening

Serum screening for fetal aneuploidy is routinely offered to all pregnant women—in the first trimester at 10 to 14 weeks, in the second trimester at 15 to 20 weeks, or as cell-free DNA screening at any point after 10 weeks (American College of Obstetricians and Gynecologists, 2020d). Additionally, the College recommends that both cystic fibrosis carrier screening and screening for spinal muscular atrophy should be offered to all women considering pregnancy or who are currently pregnant, provided that carrier or disease status is not already known (American College of Obstetricians and Gynecologist, 2017b).

Historically, carrier screening for selected genetic abnormalities was offered only to women at increased risk based on ethnic or racial background. One example is screening for Tay-Sachs disease in those of Ashkenazi Jewish descent. However, given our increasingly diverse, multiethnic society, previous assumptions about carrier risk may no longer apply. Although ethnicity-specific carrier screening remains an option, providers should also consider panethnic and expanded carrier screening strategies (American College of Obstetricians and Gynecologists, 2017c). These are discussed further in Chapter 17 (p. 342). All genetic screening is optional, and ideally, genetic carrier screening and counseling should be performed before pregnancy.

Neural-Tube Defects

Traditionally, screening for neural-tube defects has been performed as part of second-trimester aneuploidy screening. An elevation of maternal serum alpha-fetoprotein (MSAFP) levels then prompted additional evaluation with ultrasound and/or amniocentesis. With the advent of other screening modalities for aneuploidy, second-trimester MSAFP testing is less frequently obtained. For example, the expansion of second-trimester fetal anatomical surveillance has been used to screen and identify neural-tube defects (American College of Obstetricians and Gynecologists, 2017f).

NUTRITIONAL COUNSELING

Weight Gain Recommendations

In 2009, the Institute of Medicine and National Research Council revised guidelines for weight gain in pregnancy and continued to stratify suggested weight gain ranges based on prepregnancy body mass index (BMI) (Table 10-4). The same recommendations apply to women in all age, race, and ethnic groups. The American College of Obstetricians and Gynecologists (2018n) endorses these measures.

When the initial Institute of Medicine guidelines were formulated, concern focused on low-birthweight newborns. However, current emphasis is directed to the obesity epidemic. The specific and relatively narrow range of recommended weight gains for obese women emphasizes the renewed interest in *lower* weight gains during pregnancy. Obesity is associated with significantly greater risks for gestational hypertension, preeclampsia, gestational diabetes, macrosomia, cesarean delivery, and other complications (Chap. 51, p. 905). The risk appears proportionate to prenatal weight gain. In a Maternal-Fetal Medicine Units Network cohort of more than 29,000 pregnant women, 51 percent had weight gain above and 21 percent below the guidelines

TABLE 10-4. Recommendations for Total and Rate of Weight Gain During Pregnancy

Category (BMI)	Total Weight Gain Range (lb)[a]	Weight Gain in 2nd and 3rd Trimesters Mean in lb/wk (range)
Underweight (<18.5)	28–40	1 (1–1.3)
Normal weight (18.5–24.9)	25–35	1 (0.8–1)
Overweight (25.0–29.9)	15–25	0.6 (0.5–0.7)
Obese (≥30.0)	11–20	0.5 (0.4–0.6)

[a]Empirical recommendations for weight gain in twin pregnancies include: normal BMI, 37–54 lb; overweight women, 31–50 lb; and obese women, 25–42 lb.
BMI = body mass index.
Modified from the Centers for Disease Control and Prevention, 2019b; Institute of Medicine and National Research Council, 2009.

(Kominiarek, 2018). Those with excessive weight gain had higher rates of hypertension and cesarean delivery. This risk is even greater in chronically hypertensive women (Ornaghi, 2018).

Conversely, among 100,000 women with normal prepregnancy BMI, DeVader and colleagues (2007) found that those who gained <25 lb during pregnancy had a lower risk for preeclampsia, failed induction, cephalopelvic disproportion, cesarean delivery, and large-for-gestational age neonates. This cohort, however, had an increased risk for small-for-gestational age newborns.

Severe Undernutrition

Meaningful studies of nutrition in human pregnancy are exceedingly difficult to design because experimental dietary deficiency is not ethical. In those instances in which severe nutritional deficiencies have been induced as a consequence of social, economic, or political disaster, coincidental events have often created many variables, the effects of which are not amenable to quantification. Some past experiences suggest, however, that in otherwise healthy women, a state of near starvation is required to establish clear differences in pregnancy outcome. These are discussed in Chapter 47 (p. 827).

Weight Retention After Pregnancy

Not all the weight gained during pregnancy is lost during and immediately after delivery. Schauberger and coworkers (1992) studied prenatal and postpartum weights in 795 women. Their average weight gain was 28.6 lb or 12.9 kg. As shown in Figure 10-3, most maternal weight loss was at delivery—approximately 12 lb or 5.4 kg—and in the ensuing 2 weeks—approximately 9 lb or 4 kg. An additional 5.5 lb or 2.5 kg was lost between 2 weeks and 6 months postpartum. Thus, average retained pregnancy weight was 2.1 lb or 1 kg. Excessive weight gain is manifest by accrual of fat and may be partially retained as long-term fat (Berggren, 2016; Widen, 2015). Overall, the more weight that was gained during pregnancy, the more that was lost postpartum. And breastfeeding duration is inversely related to weight retention (Jiang, 2018).

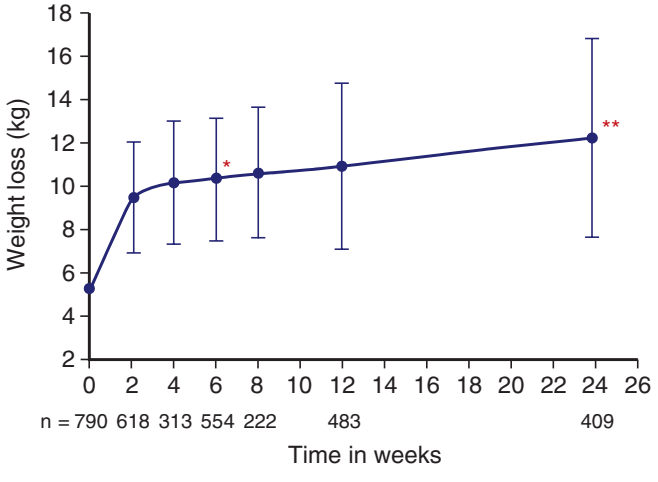

FIGURE 10-3 Cumulative weight loss from last antepartum visit to 6 months postpartum. On average, 1 kg will be retained after pregnancy. *Significantly different from 2-week weight loss; **Significantly different from 6-week weight loss. (Redrawn with permission from Schauberger CW, Rooney BL, Brimer LM: Factors that influence weight loss in the puerperium. Obstet Gynecol 79:424, 1992.)

Dietary Reference Intakes—Recommended Allowances

Periodically, the Institute of Medicine (2006, 2011) publishes recommended dietary allowances, including those for pregnant or lactating women. Some of its latest recommendations are summarized in Table 10-5. Certain prenatal vitamin–mineral supplements may lead to intakes well in excess of the recommended allowances. Moreover, the use of excessive supplements, which often are self-prescribed, has led to concern regarding nutrient toxicities during pregnancy. *Those with potentially toxic effects include iron, zinc, selenium, and vitamins A, B_6, C, and D.*

Calories

As shown in Figure 10-4, pregnancy requires an additional 80,000 kcal, mostly during the last 20 weeks. To meet this demand, a caloric increase of 100 to 300 kcal/d is recommended

TABLE 10-5. Recommended Daily Dietary Allowances for Pregnant and Lactating Women

	Pregnant	Lactating
Fat-Soluble Vitamins		
Vitamin A	770 µg	1300 µg
Vitamin D[a]	15 µg	15 µg
Vitamin E	15 mg	19 mg
Vitamin K[a]	90 µg	90 µg
Water-Soluble Vitamins		
Vitamin C	85 mg	120 mg
Thiamin	1.4 mg	1.4 mg
Riboflavin	1.4 mg	1.6 mg
Niacin	18 mg	17 mg
Vitamin B_6	1.9 mg	2 mg
Folate	600 µg	500 µg
Vitamin B_{12}	2.6 µg	2.8 µg
Minerals		
Calcium[a]	1000 mg	1000 mg
Sodium[a]	1.5 g	1.5 g
Potassium[a]	4.7 g	5.1 g
Iron	27 mg	9 mg
Zinc	11 mg	12 mg
Iodine	220 µg	290 µg
Selenium	60 µg	70 µg
Other		
Protein	71 g	71 g
Carbohydrate	175 g	210 g
Fiber[a]	28 g	29 g

[a]Recommendations measured as adequate intake.
Modified from the American Academy of Pediatrics, 2017; Institute of Medicine, 2006, 2011.

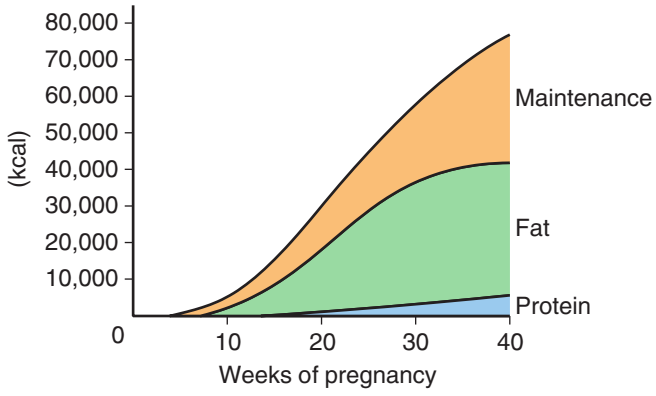

FIGURE 10-4 Cumulative kilocalories required for pregnancy. (Redrawn with permission from Chamberlain G, Broughton-Pipkin F [eds]: Clinical Physiology in Obstetrics, 3rd ed. Oxford, Blackwell Science, 1998.)

during pregnancy (American Academy of Pediatrics and American College of Obstetricians and Gynecologists, 2017). This greater intake, however, should not be divided equally during the course of pregnancy. The Institute of Medicine (2006) recommends adding 0, 340, and 452 kcal/d to the estimated nonpregnant energy requirements in the first, second, and third trimesters, respectively. The addition of 1000 kcal/d or more results in fat accrual (Jebeile, 2015).

Whenever caloric intake is inadequate, protein is metabolized rather than being spared for its vital role in fetal growth and development. Total physiological requirements during pregnancy are not necessarily the sum of ordinary nonpregnant requirements plus those specific to pregnancy. For example, the additional energy required during pregnancy may be compensated in whole or in part by reduced physical activity (Hytten, 1991).

Protein

Protein requirements rise to meet the demands for growth and remodeling of the fetus, placenta, uterus, and breasts, and for the expanded maternal blood volume (Chap. 4, p. 51). During the second half of pregnancy, approximately 1000 g of protein are deposited, amounting to 5 to 6 g/d (Hytten, 1971). To accomplish this, protein intake that approximates 1 g/kg/d is recommended (see Table 10-5). Data suggest this should be doubled in late gestation (Stephens, 2015). Most amino-acid levels in maternal plasma fall markedly, including ornithine, glycine, taurine, and proline (Hytten, 1991). Exceptions during pregnancy are glutamic acid and alanine, the concentrations of which rise.

Preferably, most protein is supplied from animal sources, such as meat, milk, eggs, cheese, poultry, and fish. These furnish amino acids in optimal combinations. Milk and dairy products are considered nearly ideal sources of nutrients, especially protein and calcium, for pregnant or lactating women. Ingestion of specific fish and potential methylmercury toxicity are discussed later (p. 188).

Minerals

The intakes recommended by the Institute of Medicine (2006) for various minerals are listed in Table 10-5. With the exception of iron and iodine, practically all diets that supply sufficient calories for appropriate weight gain will contain enough minerals to prevent deficiency.

Iron requirements substantively rise during pregnancy, and reasons for this are discussed in Chapter 4 (p. 60). Of the approximately 300 mg of iron transferred to the fetus and placenta and the 500 mg incorporated into the expanding maternal hemoglobin mass, nearly all is used after midpregnancy. During that time, iron requirements imposed by pregnancy and maternal excretion total approximately 7 mg/d (Pritchard, 1970). Few women have sufficient iron stores or dietary intake to supply this amount. Thus, the American Academy of Pediatrics and the American College of Obstetricians and Gynecologists (2017) endorse the recommendation by the National Academy of Sciences that at least 27 mg of elemental iron be supplemented daily to pregnant women. This amount is contained in most prenatal vitamins.

As little as 30 mg of elemental iron, supplied as ferrous gluconate, sulfate, or fumarate, and taken daily throughout the latter half of pregnancy, provides sufficient iron to meet pregnancy requirements and protect preexisting iron stores (Scott, 1970). This amount will also provide for iron requirements of lactation. Notably, in iron preparations, the number of milligrams of compound is followed by the milligrams of elemental iron, which is enclosed by parentheses. The pregnant woman may benefit from 60 to 100 mg of elemental iron per day if she is obese, has a multifetal gestation, begins supplementation late in pregnancy, takes iron irregularly, or has a depressed hemoglobin level. The woman who is overtly anemic from iron deficiency responds well to oral supplementation with iron salts. In response, serum ferritin levels rise more than the hemoglobin concentration (Daru, 2016).

Iodine also is needed, and the recommended iodine allowance is 220 µg/d (see Table 10-5). The use of iodized salt and bread products is recommended during pregnancy to offset the increased fetal requirements and maternal renal losses of iodine. Despite this, iodine intake has declined substantially in the past 15 years, and in some areas it is probably inadequate (Caldwell, 2013; Chittimoju, 2019). Severe maternal iodine deficiency predisposes offspring to endemic cretinism, which is characterized by multiple severe neurological defects. In parts of China and Africa, where this condition is common, iodide supplementation very early in pregnancy prevents some cretinism cases (Cao, 1994). To obviate this, most prenatal supplements now contain various quantities of iodine (Patel, 2019).

Calcium is retained by the pregnant woman during gestation and approximates 30 g. Most of this is deposited in the fetus late in pregnancy (Pitkin, 1985). This amount of calcium represents only approximately 2.5 percent of total maternal calcium, most of which is in bone and can readily be mobilized for fetal growth. As another potential use, routine calcium supplementation to prevent preeclampsia is ineffective (Chap. 40, p. 704).

Zinc deficiency if severe may lead to poor appetite, suboptimal growth, and impaired wound healing. During pregnancy, the recommended daily intake approximates 12 mg. But, the safe level of zinc supplementation for pregnant women is not clearly established. Vegetarians have lower zinc intakes (Foster, 2015). The bulk of studies support zinc supplementation only

in zinc-deficient women in poor-resource countries (Nossier, 2015; Ota, 2015).

Magnesium deficiency as a consequence of pregnancy has not been recognized. Undoubtedly, during prolonged illness with no magnesium intake, the plasma level might become critically low, as it would in the absence of pregnancy. We have observed this deficiency during pregnancies in some with previous intestinal bypass surgery. Instead, as a preventive agent, Sibai and colleagues (1989) randomly assigned 400 normotensive primigravidas to receive 365-mg elemental magnesium supplementation or placebo tablets from 13 to 24 weeks' gestation. Supplementation did not improve any measures of pregnancy outcome.

Trace metals include copper, selenium, chromium, and manganese, which all have important roles in certain enzyme functions. In general, most are provided by an average diet. Selenium deficiency is manifested by a frequently fatal cardiomyopathy in young children and reproductive-aged women. Conversely, selenium toxicity resulting from oversupplementation also has been observed. Selenium supplementation is not needed in American women.

Potassium concentrations in maternal plasma decline by approximately 0.5 mEq/L by midpregnancy (Brown, 1986). Potassium deficiency develops in the same circumstances as in nonpregnant individuals. One common example in pregnant women is hyperemesis gravidarum.

Fluoride metabolism is not altered appreciably during pregnancy (Maheshwari, 1983). Horowitz and Heifetz (1967) concluded that no additional offspring benefits accrued from maternal ingestion of fluoridated water if the newborn ingested such water from birth. Sa Roriz Fonteles and associates (2005) studied microdrill biopsies of deciduous teeth and concluded that antenatal fluoride provided no additional fluoride uptake compared with postnatal fluoride alone. Finally, supplemental fluoride ingested by lactating women does not raise the fluoride concentration in breast milk (Ekstrand, 1981).

Vitamins

The increased requirements for most vitamins during pregnancy shown in Table 10-5 usually are supplied by any general diet that provides adequate calories and protein. The exception is folic acid during times of unusual requirements, such as pregnancy complicated by protracted vomiting, hemolytic anemia, or multiple fetuses. That said, in impoverished countries, routine multivitamin supplementation reduced the incidence of low-birthweight and growth-restricted fetuses but did not alter preterm delivery or perinatal mortality rates (Fawzi, 2007).

Folic acid supplementation in early pregnancy can lower neural-tube defect risks (Chap. 15, p. 276). For example, the CDC (2004) estimated that the number of affected pregnancies had decreased from 4000 per year to approximately 3000 per year after mandatory fortification of cereal products with folic acid in 1998. Perhaps more than half of all neural-tube defects can be prevented with daily intake of 400 µg of folic acid throughout the periconceptional period (Centers for Disease Control and Prevention, 2019a). Evidence also suggests that folate insufficiency has a global effect on brain development (Ars, 2016). Putting 140 µg of folic acid into each 100 g of grain products may increase the folic acid intake of the average American woman of childbearing age by 100 µg/d. Because nutritional sources alone are insufficient, however, folic acid supplementation is still recommended.

A woman with a prior child with a neural-tube defect can reduce the 2- to 5-percent recurrence risk by more than 70 percent with a daily 4-mg folic acid supplement taken during the month before conception and during the first trimester. As emphasized by the American Academy of Pediatrics and the American College of Obstetricians and Gynecologists (2017), this dose should be consumed as a separate supplement and not as multivitamin tablets. This practice avoids excessive intake of fat-soluble vitamins.

Vitamin A, although essential, has been associated with congenital malformations when taken during pregnancy in high doses (>10,000 IU/d). These malformations are similar to those produced by the vitamin A derivative isotretinoin (Accutane), which is a potent teratogen (Chap. 8, p. 155). Beta-carotene, the precursor of vitamin A found in fruits and vegetables, does not produce vitamin A toxicity. Most prenatal vitamins contain vitamin A in doses considerably below the teratogenic threshold. Dietary intake of vitamin A in the United States appears to be adequate, and additional supplementation is not routinely recommended. In contrast, vitamin A deficiency is an endemic nutritional problem in the developing world (McCauley, 2015). Vitamin A deficiency, whether overt or subclinical, is associated with night blindness and with an increased risk of maternal anemia and spontaneous preterm birth (West, 2003).

Vitamin B_{12} plasma levels drop in normal pregnancy, mostly as a result of reduced plasma levels of their carrier proteins—*transcobalamins*. Vitamin B_{12} occurs naturally only in foods of animal origin, and strict vegetarians may give birth to neonates whose B_{12} stores are low. Likewise, because breast milk of a vegetarian mother contains little vitamin B_{12}, the deficiency may become profound in the breastfed infant (Higginbottom, 1978). Excessive ingestion of vitamin C also can lead to a functional deficiency of vitamin B_{12}. Although its role is still controversial, vitamin B_{12} deficiency may be an independent factor associated with neural-tube defects (Molloy, 2018).

Vitamin B_6, which is pyridoxine, does not require supplementation in most gravidas (Salam, 2015). For women at high risk for inadequate nutrition, a daily 2-mg supplement is recommended. As discussed on page 191, vitamin B_6, when combined with the antihistamine *doxylamine*, is helpful in many cases of nausea and vomiting of pregnancy.

Vitamin C allowances during pregnancy are 80 to 85 mg/d—approximately 20 percent more than when nonpregnant (see Table 10-5). A reasonable diet should readily provide this amount, and supplementation is unnecessary (Rumbold, 2015). Maternal plasma levels decline during pregnancy, whereas cord blood levels are higher. This is a phenomenon observed with most water-soluble vitamins.

Vitamin D is a fat-soluble vitamin. After being metabolized to its active form, it boosts the efficiency of intestinal calcium absorption and promotes bone mineralization and growth. Unlike most vitamins that are obtained exclusively from dietary intake, vitamin D is also synthesized endogenously with exposure to sunlight. Vitamin D deficiency is common during pregnancy. This is especially

true in high-risk groups such as women with limited sun exposure, vegetarians, and ethnic minorities—particularly those with darker skin (Bodnar, 2007). Maternal deficiency can cause disordered skeletal homeostasis, congenital rickets, and fractures in the newborn (American College of Obstetricians and Gynecologists, 2017j). However, vitamin D supplementation in women with asthma *may* decrease the likelihood of childhood asthma in their offspring (Litonjua, 2016). The Food and Nutrition Board of the Institute of Medicine (2011) established that an adequate intake of vitamin D during pregnancy and lactation was 15 µg/d (600 IU/d). In women suspected of having vitamin D deficiency, serum levels of 25-hydroxyvitamin D can be obtained. Even then, the optimal levels in pregnancy have not been established (De-Regil, 2016).

Pragmatic Nutritional Surveillance

Although researchers continue to study the ideal nutritional regimen for the pregnant woman and her fetus, basic tenets for the clinician include:

1. Advise the pregnant woman to eat food types she wants in reasonable amounts and salted to taste.
2. Ensure that food is amply available for socioeconomically deprived women.
3. Monitor weight gain and align goals with the Institute of Medicine recommendations.
4. Explore food intake by dietary recall periodically to discover the occasional nutritionally errant diet.
5. Give tablets of simple iron salts that provide at least 30 mg of elemental iron daily. Give folate supplementation before and in the early weeks of pregnancy. Provide iodine supplementation in areas of known dietary insufficiency.
6. Recheck the hematocrit or hemoglobin concentration at 28 to 32 weeks' gestation to detect significant anemia.

COMMON CONCERNS

Employment

More than half of the children in the United States are born to working mothers. Several federal laws have been passed to protect pregnant workers. These prohibit employers from excluding women from job categories on the basis that they are or might become pregnant. The Family and Medical Leave Act of 1993 requires that covered employers must grant up to 12 work weeks of unpaid leave to an employee for the birth and care of a newborn child.

In the absence of complications, most women can continue to work until labor onset (American Academy of Pediatrics and American College of Obstetricians and Gynecologists, 2017). Some types of work, however, may increase pregnancy complication risks. According to the American College of Obstetricians and Gynecologists (2018b), risks of preterm birth are slightly to modestly increased with standing or walking at work >3 hours daily, lifting and carrying >5 kg, or physically exerting oneself at work. In a prospective study of more than 900 healthy nulliparas, women who worked had a fivefold higher risk of preeclampsia (Higgins, 2002). Thus, any occupation that subjects the gravida to severe physical strain should be avoided. Ideally, no work or play is continued to the extent that undue fatigue develops. Adequate periods of rest should be provided.

Exercise

In general, pregnant women do not need to limit exercise, provided they do not become excessively fatigued or risk injury (Davenport, 2016). Clapp and associates (2000) reported that both placental size and birthweight were significantly greater in women who exercised. Duncombe and coworkers (2006) reported similar findings in 148 women. In contrast, Magann and colleagues (2002) prospectively analyzed exercise behavior in 750 healthy women and found that working women who exercised had smaller neonates and more dysfunctional labors.

The American College of Obstetricians and Gynecologists (2020a) advises a thorough clinical evaluation before recommending an exercise program. In the absence of contraindications listed in Table 10-6, pregnant women are encouraged to engage in regular, moderate-intensity physical activity for at least 150 minutes each week. Such activity has been shown to not adversely alter uterine artery Doppler studies (Szymanski, 2018). Each activity should be reviewed individually for its potential risk. Examples of safe activities are walking, running, swimming, stationary cycling, and low-impact aerobics. However, they should refrain from activities with a high risk of falling or abdominal trauma. Similarly, scuba diving is avoided because the fetus is at increased risk for decompression sickness (Reid, 2018).

In the setting of certain pregnancy complications, it is wise to abstain from exercise and even limit physical activity. Some women with pregnancy-associated hypertensive disorders, preterm labor, placenta previa, or severe cardiac or pulmonary disease may accrue advantages from being sedentary. Also, those with multiple or suspected growth-restricted fetuses may be served by greater rest.

TABLE 10-6. Some Contraindications to Exercise During Pregnancy

Significant cardiovascular or pulmonary disease: chest pain, calf pain or swelling
Significant risk for preterm labor: cerclage, multifetal gestation, significant bleeding, threatened preterm labor, ruptured membranes
Obstetrical complications: preeclampsia, placenta previa, anemia, poorly controlled diabetes or epilepsy, morbid obesity, fetal-growth restriction

Summarized from American College of Obstetricians and Gynecologists, 2017g; The American Academy of Pediatrics, 2017.

Seafood Consumption

Fish are an excellent source of protein, are low in saturated fats, and contain omega-3 fatty acids. It is recommended that pregnant women ingest 8 to 12 ounces of fish weekly, but no more than 6 ounces of albacore or "white" tuna (U.S. Environmental Protection Agency, 2019). Because nearly all fish and shellfish contain trace amounts of mercury, pregnant and lactating women are advised to avoid specific types of fish with potentially high methylmercury levels. These include shark, swordfish, king mackerel, and tile fish. If the mercury content of locally caught fish is unknown, overall fish consumption should be limited to 6 ounces per week. Finally, to help avert listeriosis, eating raw or undercooked fish is avoided (American College of Obstetricians and Gynecologists, 2017j).

Lead Screening

Maternal lead exposure is associated with several adverse maternal and fetal outcomes across a range of maternal blood lead levels (Taylor, 2015). These include gestational hypertension, miscarriage, low birthweight, and neurodevelopmental impairments in exposed pregnancies. The levels at which these risks rise remains unclear. However, recognizing that such exposure remains a significant health issue for reproductive-aged women, the CDC (2010a) provides guidance for screening and managing exposed pregnant and lactating women. These guidelines, which have been endorsed by the American College of Obstetricians and Gynecologists (2018f), recommend blood lead testing only if a risk factor is identified. If the levels are >5 μg/dL, the lead source is sought and removed. Subsequent blood levels are obtained. Blood lead levels >45 μg/dL are consistent with lead poisoning, and women in this group may be candidates for chelation therapy. Affected pregnancies are best managed in consultation with lead poisoning treatment experts. National and state resources are available at the CDC website: www.cdc.gov/nceh/lead/.

Automobile and Air Travel

Pregnant women are encouraged to wear properly positioned three-point restraints as protection against automobile accident injury (Chap. 50, p. 892). The lap portion of the restraining belt is placed under the abdomen and across her upper thighs. The belt should be comfortably snug. The shoulder belt also is firmly positioned between the breasts. Airbags should not be disabled for the pregnant woman.

In general, air travel in a properly pressurized aircraft has no harmful effect on pregnancy. Thus, in the absence of obstetrical or medical complications, the American College of Obstetricians and Gynecologists (2018a) has concluded that pregnant women can safely fly up to 36 weeks' gestation. It is recommended that they observe the same precautions for air travel as the general population. Seatbelts are used while seated. Support stockings, periodic lower extremity movement, and at least hourly ambulation help lower the venous thromboembolism threat. Significant risks with travel, especially international travel, are infectious disease acquisition and development of complications remote from adequate health-care resources.

Coitus

In healthy pregnant women, sexual intercourse usually is not harmful. Whenever miscarriage, placenta previa, or preterm labor threatens, however, coitus is avoided. Nearly 10,000 women enrolled in a prospective investigation by the Vaginal Infection and Prematurity Study Group were interviewed regarding sexual activity (Read, 1993). They reported a decreased frequency of coitus with advancing gestation. By 36 weeks, 72 percent had intercourse less than once weekly. The decline is attributed to lower desire and fear of harming the pregnancy (Staruch, 2016).

Intercourse specifically late in pregnancy is not harmful. Sayle and colleagues (2001) reported no increased—and actually a decreased—risk of delivery within 2 weeks of intercourse. Tan and associates (2007) studied women scheduled for nonurgent labor induction and found that spontaneous labor ensued at equal rates in groups either participating in or abstaining from intercourse.

Oral-vaginal intercourse is occasionally hazardous. Aronson and Nelson (1967) described a fatal air embolism late in pregnancy as a result of air blown into the vagina during cunnilingus. Other near-fatal cases have been described (Bernhardt, 1988).

Dental Care

Examination of the teeth is included in the prenatal examination, and good dental hygiene is encouraged. Indeed, periodontal disease is linked to preterm labor. Unfortunately, although its treatment improves dental health, it does not prevent preterm birth (Daalderop, 2018). Dental caries are not aggravated by pregnancy. Importantly, pregnancy is not a contraindication to dental treatment including dental radiographs (American Academy of Pediatrics and American College of Obstetricians and Gynecologists, 2017).

Immunization

Current recommendations for immunization during pregnancy are summarized in Table 10-7. Well-publicized concerns regarding a causal link between childhood exposure to the thimerosal preservative in some vaccines and neuropsychological disorders have led some parents to vaccine prohibition. Although controversy continues, these associations have been proven groundless. Thus, many vaccines may be used in pregnancy (Munoz, 2019). The American College of Obstetricians and Gynecologists (2020c) stresses the importance of integrating an effective vaccine strategy into the care of both obstetrical and gynecological patients. The College further emphasizes that information on the safety of vaccines given during pregnancy is subject to change, and recommendations can be found on the CDC website at www.cdc.gov/vaccines.

Influenza and tetanus–diphtheria–acellular pertussis (Tdap) vaccinations are recommended routinely for all pregnant women (Munoz, 2019; Sperling, 2018b). Others are recommended for specific indications (see Table 10-7). Women who are susceptible to rubella should receive measles, mumps, and rubella (MMR) vaccination postpartum. This vaccine is contraindicated during pregnancy.

TABLE 10-7. Recommendations for Immunization During Pregnancy and Postpartum

Immunobiological Agent	Indications for Immunization During Pregnancy	Dose Schedule	Comments
Live Attenuated Virus Vaccines			
Measles	Contraindicated—see immune globulins	Single dose SC, preferably as MMR[a]	Vaccinate susceptible women postpartum; breastfeeding is not a contraindication
Mumps	Contraindicated	Single dose SC, preferably as MMR	Vaccinate susceptible women postpartum
Rubella	Contraindicated, but congenital rubella syndrome has never been described after vaccine	Single dose SC, preferably as MMR	Teratogenicity of vaccine is theoretical and not confirmed to date; vaccinate susceptible women postpartum
Poliomyelitis oral = live attenuated; injection = enhanced-potency inactivated virus	Not routinely recommended for women in the United States, except women at increased risk of exposure[b]	Primary: Two doses of enhanced-potency inactivated virus SC at 4- to 8-week intervals and a 3rd dose 6–12 months after 2nd dose Immediate protection: One dose oral polio vaccine (in outbreak setting)	Vaccine indicated for susceptible women traveling in endemic areas or in other high-risk situations
Yellow fever	Travel to high-risk areas	Single dose SC	Limited theoretical risk outweighed by risk of yellow fever
Varicella	Contraindicated, but no adverse outcomes reported in pregnancy	Two doses needed: 2nd dose given 4–8 weeks after 1st dose	Teratogenicity of vaccine is theoretical; vaccination of susceptible women should be considered postpartum
Zoster	Contraindicated	Single dose	Teratogenicity is theoretical
Smallpox (vaccinia)	Contraindicated in pregnant women and in their household contacts	One dose SC, multiple pricks with lancet	Only vaccine known to cause fetal harm
Other			
Influenza	All pregnant women, regardless of trimester during flu season (October–May)	One dose IM every year	Inactivated or recombinant virus vaccine
Rabies	Indications for prophylaxis not altered by pregnancy; each case considered individually	Public health authorities to be consulted for indications, dosage, and route of administration	Killed-virus vaccine
Human papillomavirus	Not recommended	Three-dose series IM at 0, 1, and 6 months	Nonavalent vaccine is inactivated virus; no teratogenic effects have been observed
Hepatitis B	Preexposure and postexposure for women at risk of infection, e.g., chronic liver or kidney disease	Three-dose series IM at 0, 1, and 6 months	Used with hepatitis B immune globulin for some exposures; exposed newborn needs birth-dose vaccination and immune globulin as soon as possible; all infants should receive birth dose of vaccine
Hepatitis A	Preexposure and postexposure if at risk (international travel); chronic liver disease	Two-dose schedule IM, 6 months apart	Inactivated virus

(*continued*)

TABLE 10-7. Continued

Immunobiological Agent	Indications for Immunization During Pregnancy	Dose Schedule	Comments
Inactivated Bacterial Vaccines			
Pneumococcus	(1) For chronic metabolic, liver, cardiac, or lung ds. (2) For immunosuppression, general malignancy, chronic renal disease, or asplenia	One lifetime dose: (1) One dose PPSV23 (2) One dose PCV13 with PPSV23 given 8 weeks later	Indications not altered by pregnancy Polyvalent polysaccharide vaccine; safety in the first trimester has not been evaluated
Meningococcus	Indications not altered by pregnancy; vaccination recommended in unusual outbreaks	One dose MenACWY or MPSV4; tetravalent vaccine; two doses for asplenia	Antimicrobial prophylaxis if significant exposure
Typhoid	Not recommended routinely except for close, continued exposure or travel to endemic areas	Killed Primary: 2 injections IM 4 weeks apart Booster: One dose; schedule not yet determined	Killed, injectable vaccine or live attenuated oral vaccine; oral vaccine preferred
Anthrax	See text	Six-dose primary vaccination, then annual booster vaccination	Preparation from cell-free filtrate of *B anthracis*; no dead or live bacteria; teratogenicity of vaccine theoretical
Toxoids			
Tetanus-diphtheria-acellular pertussis (Tdap)	Recommended in every pregnancy, preferably between 27 and 36 weeks to maximize passive antibody transfer	Primary: Two doses IM at 1–2 month interval with 3rd dose 6–12 months after the 2nd Booster: Single dose IM every 10 years, as a part of wound care if ≥5 years since last dose, or once per pregnancy	Combined tetanus-diphtheria toxoids with acellular pertussis (Tdap) preferred; updating immune status should be part of antepartum care
Specific Immune Globulins			
Hepatitis B	Postexposure prophylaxis	Depends on exposure	Usually given with hepatitis B virus vaccine; exposed newborn needs immediate prophylaxis
Rabies	Postexposure prophylaxis	Half dose at injury site, half dose in deltoid	Used in conjunction with rabies killed-virus vaccine
Tetanus	Postexposure prophylaxis	One dose IM	Used in conjunction with tetanus toxoid
Varicella	Should be considered for exposed pregnant women to protect against maternal, not congenital, infection	One dose IM within 96 hours of exposure	Indicated also for newborns or women who developed varicella within 4 days before delivery or 2 days following delivery
Standard Immune Globulins			
Hepatitis A: Hepatitis A virus vaccine should be used with hepatitis A immune globulin	Postexposure prophylaxis and those at high risk	0.02 mL/kg IM in one dose	Immune globulin should be given as soon as possible and within 2 weeks of exposure; infants born to women who are incubating the virus or are acutely ill at delivery should receive one dose of 0.5 mL as soon as possible after birth

[a]Two doses necessary for students entering institutions of higher education, newly hired medical personnel, and travel abroad.
[b]Inactivated polio vaccine recommended for nonimmunized adults at increased risk.
Ds. = disease; ID = intradermally; IM = intramuscularly; MMR = measles, mumps, rubella; PO = orally; SC = subcutaneously.
From the American College of Obstetricians and Gynecologists, 2018o; Centers for Disease Control and Prevention, 2011; Kim, 2016; Munoz, 2019.

Caffeine

Whether adverse pregnancy outcomes are related to caffeine consumption is somewhat controversial. As summarized from Chapter 11 (p. 200), heavy intake of coffee each day—approximately five cups or 500 mg of caffeine—slightly raises the miscarriage risk. Studies of "moderate" intake—less than 200 mg daily—did not find a higher risk.

It is unclear if caffeine consumption is associated with preterm birth or impaired fetal growth. Clausson and coworkers (2002) found no association between caffeine consumption <500 mg/d and low birthweight, fetal-growth restriction, or preterm delivery. Bech and associates (2007) randomly assigned more than 1200 pregnant women who drank at least three cups of coffee per day to caffeinated versus decaffeinated coffee. They found no difference in birthweight or gestational age at delivery between groups. The CARE Study Group (2008), however, evaluated 2635 low-risk pregnancies and reported a 1.4-fold risk for fetal-growth restriction among those whose daily caffeine consumption was >200 mg/d compared with those who consumed <100 mg/d. The American College of Obstetricians and Gynecologists (2018g) concludes that moderate consumption of caffeine—less than 200 mg/d—does not appear to be associated with miscarriage or preterm birth, but that the relationship between caffeine consumption and fetal-growth restriction remains unsettled.

Nausea and Heartburn

Nausea and vomiting are common complaints during the first half of pregnancy. These vary in severity and usually commence between the first and second missed menstrual period and continue until 14 to 16 weeks' gestation. Although nausea and vomiting tend to be worse in the morning—thus termed *morning sickness*—both symptoms frequently continue throughout the day. Lacroix and associates (2000) found that nausea and vomiting were reported by three fourths of pregnant women and lasted an average of 35 days. Half had relief by 14 weeks' gestation, and 90 percent by 22 weeks' gestation. In 80 percent of these women, nausea lasted all day.

Treatment of pregnancy-associated nausea and vomiting seldom provides complete relief, but symptoms can be minimized. Eating small meals at frequent intervals is valuable. One systematic literature search reported that the herbal remedy ginger was likely effective (Borrelli, 2005). Mild symptoms usually respond to vitamin B_6 given with doxylamine, but some women require phenothiazine or H_1-receptor blocking antiemetics (American College of Obstetricians and Gynecologists, 2018h). In some with *hyperemesis gravidarum*, vomiting is so severe that dehydration, electrolyte and acid-base disturbances, and starvation ketosis become serious problems (Chap. 57, p. 1014).

Heartburn is another common complaint of gravidas and is caused by gastric content reflux into the lower esophagus. The greater frequency of regurgitation during pregnancy most likely results from upward displacement and compression of the stomach by the uterus, combined with relaxation of the lower esophageal sphincter. Avoiding bending over or lying flat can be preventive. In most pregnant women, symptoms are mild and relieved by a regimen of more frequent but smaller meals. Antacids may provide considerable relief (Phupong, 2015). Specifically, aluminum hydroxide, magnesium trisilicate, or magnesium hydroxide are given alone or in combination. Management of heartburn or nausea that does not respond to simple measures is discussed in Chapter 57 (p. 1017).

Pica and Ptyalism

The craving for strange foods is termed pica. Worldwide, its prevalence among pregnant women is estimated to be 30 percent (Fawcett, 2016). At times, nonfoods such as ice (pagophagia), starch (amylophagia), or clay (geophagia) may predominate. This desire is considered by some to be triggered by severe iron deficiency (Epler, 2017). Although such cravings usually abate after deficiency correction, not all pregnant women with pica are iron deficient. Indeed, if strange "foods" dominate the diet, iron deficiency will be aggravated or will develop eventually. Patel and colleagues (2004) prospectively completed a dietary inventory on more than 3000 women during the second trimester. The prevalence of pica was 4 percent. The most common nonfood items ingested were starch in 64 percent, dirt in 14 percent, sourdough in 9 percent, and ice in 5 percent.

Women during pregnancy are occasionally distressed by profuse salivation—*ptyalism*. Although usually unexplained, ptyalism sometimes appears to follow salivary gland stimulation by the ingestion of starch. It commonly occurs with hyperemesis gravidarum (Bronshtein, 2018).

Headache or Backache

Headaches are common in pregnancy. At least 5 percent of pregnancies are estimated to be complicated by new-onset or new-type headache (Spierings, 2016). Acetaminophen is suitable for treatment of most, and an in-depth discussion is found in Chapter 63 (p. 1127).

Low back pain to some extent is reported by nearly 70 percent of gravidas (Liddle, 2015). Minor degrees follow excessive strain or significant bending, lifting, or walking. It can be reduced by squatting rather than bending when reaching down, by using a back-support pillow when sitting, and by avoiding high-heeled shoes. Back pain complaints increase with progressing gestation and are more prevalent in obese women and those with a history of low back pain. In some cases, troublesome pain may persist for years after the pregnancy (Norén, 2002).

Severe back pain should not be attributed simply to pregnancy until a thorough orthopedic examination has been conducted. Severe pain has other uncommon causes that include pregnancy-associated osteoporosis, disc disease, vertebral osteoarthritis, or septic arthritis (Smith, 2008). More commonly, muscular spasm and tenderness are classified clinically as acute strain or fibrositis. Although evidence-based clinical research directing care in pregnancy is limited, low back pain usually responds well to analgesics, heat, and rest. Acetaminophen may be used as needed. Nonsteroidal antiinflammatory drugs also may be beneficial but are used only in short courses to avoid fetal effects (Chap. 8, p. 151). Muscle relaxants that include cyclobenzaprine or baclofen may be added when needed. Once acute pain is improved, stabilizing and strengthening exercises provided by physical therapy help improve spine and hip stability, which is essential for the increased load of

pregnancy. For some, a support belt that stabilizes the sacroiliac joint may be helpful (Gutke, 2015).

Varicosities and Hemorrhoids

Venous leg varicosities have a congenital predisposition and accrue with advancing age. They can be aggravated by factors that raise lower-extremity venous pressures, such as an enlarging uterus. Femoral venous pressures in the supine gravida rise from 8 mm Hg in early pregnancy to 24 mm Hg at term. Thus, leg varicosities typically worsen as pregnancy advances, especially with prolonged standing. Symptoms vary from cosmetic blemishes and mild discomfort at the end of the day to severe discomfort that requires prolonged rest with feet elevation. Treatment is generally limited to periodic rest with leg elevation, elastic stockings, or both. Surgical correction during pregnancy generally is not advised, although rarely the symptoms may be so severe that injection, ligation, or even stripping of the veins is necessary. Superficial varicosities are a risk factor for deep-vein thrombosis and pulmonary embolism (Chap. 55, p. 980).

Vulvar varicosities frequently coexist with leg varicosities, but they may appear without other venous pathology. Uncommonly, they become massive and almost incapacitating (Pratilas, 2018). If these large varicosities rupture, either spontaneously or at the time of delivery, blood loss can be severe. Treatment is with specially fitted pantyhose that will also minimize lower extremity varicosities. With particularly bothersome vulvar varicosities, a foam rubber pad suspended across the vulva by a belt can be used to exert pressure on the dilated veins.

Hemorrhoids are rectal vein varicosities and may first appear during pregnancy as pelvic venous pressures rise. Commonly, they are recurrences of previously encountered hemorrhoids. Up to 40 percent of pregnant women develop these (Poskus, 2014). Pain and swelling usually are relieved by topically applied anesthetics, warm soaks, and stool-softening agents. With thrombosis of an external hemorrhoid, pain can be considerable. This may be relieved by incision and removal of the clot following injection of a local anesthetic.

Sleeping and Fatigue

Beginning early in pregnancy, many women experience fatigue and need greater amounts of sleep. The soporific effect of progesterone contributes but may be compounded in the first trimester by nausea and vomiting. In the latter stages, general discomforts, urinary frequency, and dyspnea can be additive. Sleep-disordered breathing may be associated with significant morbidities such as hypertensive disorders of pregnancy, stillbirth, and preterm delivery (Brown, 2018; Dominguez, 2018). Moreover, sleep efficiency appears to progressively diminish as pregnancy advances. Wilson and associates (2011) performed overnight polysomnography and observed that women in the third trimester had poorer sleep efficiency, more awakenings, and less of both stage 4 (deep) and rapid-eye-movement sleep. Women in the first trimester also were affected, but to a lesser extent. Daytime naps and mild sedatives at bedtime such as diphenhydramine (Benadryl) can be helpful.

Cord Blood Banking

Cord blood contains hemopoietic stem cells that can be used to treat more than 70 types of diseases. These include immunological and genetic diseases and some forms of cancer. Of the two cord blood bank types, public banks promote allogeneic donation, for use by a related or unrelated recipient, similar to blood product donation. Private banks store stem cells for future autologous use and charge fees for initial processing and annual storage.

The American College of Obstetricians and Gynecologists (2020e) has concluded that if a woman requests data on umbilical cord banking, information regarding advantages and disadvantages of public versus private banking should be explained. Some states have passed laws that require physicians to inform patients about cord blood banking options. Importantly, few transplants have been performed by using cord blood stored in the absence of a known indication in the recipient (Screnci, 2016). The likelihood that cord blood would be used for the child or family member of the donor couple is considered remote. Instead, it is recommended that directed donation be considered when an immediate family member carries the diagnosis of a specific condition known to be treatable by hemopoietic transplantation.

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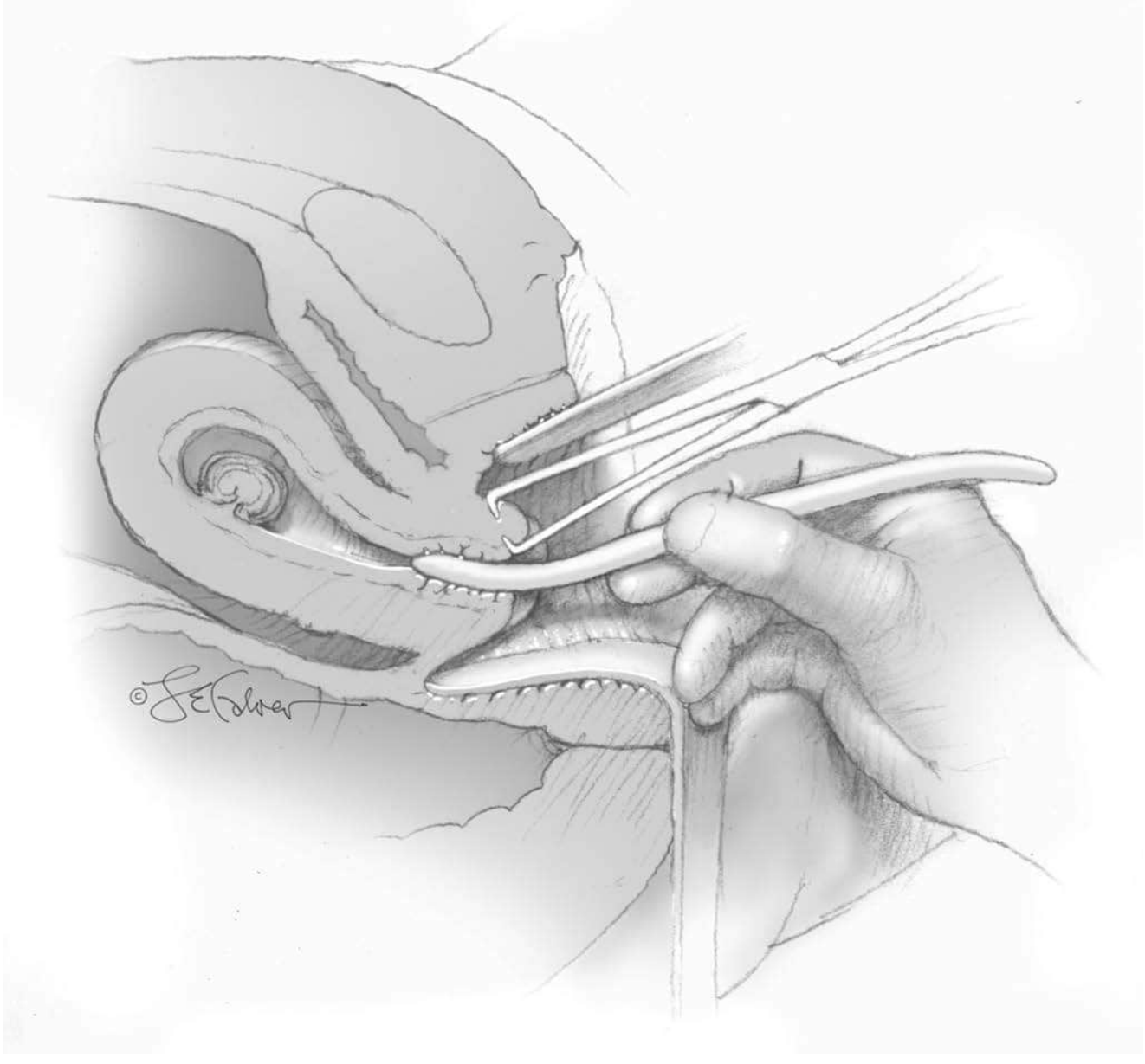
SECTION 5

FIRST- AND SECOND-TRIMESTER PREGNANCY LOSS



CHAPTER 11

First- and Second-Trimester Pregnancy Loss

Miscarriage is a common event in pregnancy. Most early losses stem from genetic abnormalities, and thus the opportunity for prevention is small. Women with later miscarriage or with recurrent miscarriage more likely have a chronic etiology that may be modified. In contrast to these spontaneous losses, pregnancy termination may be elected. For both induced abortion and miscarriage, management options include surgery or medication, and providers should have an understanding of these methods and their potential complications.

NOMENCLATURE

Abortion is defined as the spontaneous or induced termination of pregnancy before fetal viability. Many prefer *miscarriage* for spontaneous loss. *Induced abortion* describes termination with surgery or medication of a live fetus that has not reached viability.

Definitions of an abortus vary among organizations. The National Center for Health Statistics and the World Health Organization define *abortion* as loss or termination of a pregnancy with a fetus aged younger than 20 weeks' gestation or weighing <500 g. These criteria, however, are somewhat contradictory because the mean birthweight of a 20-week fetus approximates 330 g, whereas 500 g is the mean for 22 weeks (Hadlock, 1991). Further confusion may derive from criteria that are set by state laws and define abortion even more widely.

Incongruity also exists for the term *early pregnancy loss* itself. The American College of Obstetricians and Gynecologists (2019b) defines this as a nonviable, intrauterine pregnancy (IUP) within the first $12^{6/7}$ weeks of gestation that consists of either an empty gestational sac or one containing an embryo or fetus without fetal heart activity. *Recurrent pregnancy loss* is variably defined but is meant to identify women with repetitive miscarriage (p. 203).

Other definitions help distinguish intrauterine from ectopic gestations. The term *pregnancy of unknown location (PUL)* describes a pregnancy identified by human chorionic gonadotropin (hCG) level testing but without a confirmed sonographic location. In this context, five categories are proposed for early pregnancies: definite ectopic pregnancy, probable ectopic pregnancy, PUL, probable IUP, and definite IUP (Barnhart, 2011). Diagnostic and management options for ectopic gestation are described in Chapter 12.

Last, spontaneous abortion includes subcategories of threatened, incomplete, complete, missed, and inevitable abortions. These are discussed in the next sections. Septic abortion is used to further classify any of these that are complicated by infection.

FIRST-TRIMESTER SPONTANEOUS ABORTION

Pathogenesis

More than 80 percent of spontaneous abortions occur within the first 12 weeks of gestation. With first-trimester losses, demise

of the embryo or fetus nearly always precedes spontaneous expulsion. Death is usually accompanied by hemorrhage into the decidua basalis. This is followed by adjacent tissue necrosis that stimulates uterine contractions and expulsion. An intact gestational sac is usually filled with fluid. *Anembryonic miscarriage* or *preembryonic loss* describes the group with no identifiable embryo. The term *blighted ovum* is less preferred. An *embryonic miscarriage or embryonic loss* displays an embryo without cardiac activity during ultrasound evaluation (Kolte, 2015; Pinar, 2018).

In second-trimester losses, the fetus usually does not die before expulsion. Thus, other sources for abortion are sought and described on page 213.

Incidence

Rates for miscarriage vary according to the study population. In pregnancies aged 5 to 20 weeks' gestation, the incidence ranges from 10 to 20 percent and is higher in earlier weeks (Ammon Avalos, 2012). To evaluate rates starting at conception, researchers have tested daily urinary samples for β-hCG in women trying to conceive and found that approximately 20 percent of pregnancies failed very early (Wang, 2003). These *biochemical pregnancy losses* are clinically silent and are identified only by dropping β-hCG levels (Kolte, 2015).

Certain factors influence the clinically apparent miscarriage rate and are described next. It is unknown if these same factors also affect biochemical pregnancy loss.

Fetal Factors

Of all miscarriages, approximately half are *euploid abortions,* that is, carrying a normal chromosomal complement. The other half of all miscarriages has a chromosomal abnormality. This percentage appears to persist even from evaluations with newer cytogenetic techniques (Sahoo, 2017). However, outside of research, routine use of chromosomal microarray testing of first-trimester fetal tissues is not endorsed by the American College of Obstetricians and Gynecologists (2020d). The American Society for Reproductive Medicine (2012) recognize its value only if cytogenetic analysis alters future care of a patient.

Both abortion and chromosomal anomaly rates decline with advancing gestational age (Eiben, 1990). Of chromosomally abnormal embryos, 75 percent aborts by 8 weeks' gestation. The rate of abortion with euploid fetuses peaks at approximately 13 weeks (Kajii, 1980).

Of chromosomal abnormalities, 95 percent are caused by maternal gametogenesis errors, and 5 percent by paternal errors (Jacobs, 1980). Thus, the aneuploid abortion incidence rises dramatically after maternal age exceeds 35 years (Eiben, 1990). Indeed, maternal age is a primary factor underlying the spontaneous loss of aneuploid fetuses (Nybo Andersen, 2000). To a lesser degree, increasing paternal age is also associated with a greater abortion risk (Nguyen, 2019). Not yet well studied, chromosomal abnormalities in spermatozoa likely play a role (Pohl, 2021).

Most common abnormalities are trisomy, found in 50 to 60 percent; monosomy X, in 9 to 13 percent; and triploidy, in 11 to 12 percent (Jenderny, 2014; Sahoo, 2017). *Trisomies* typically result from isolated nondisjunction, and rates rise with maternal age (Boué, 1975). Trisomies of chromosomes 13, 16, 18, 21, and 22 are most common. Less often, a trisomy forms from a balanced structural chromosomal rearrangements. These may originate from either parent and are found in 2 to 4 percent of couples with recurrent pregnancy loss (p. 204).

Monosomy X (45,X) is the single most frequent specific chromosomal abnormality. This is *Turner syndrome*, which usually results in miscarriage, but liveborn females are described in Chapter 3 (p. 36). Conversely, *autosomal monosomy* is rare and incompatible with life.

Triploidy is an additional haploid set of chromosomes, and cells thus contain a total of 69 chromosomes. The extra haploid set can be either maternally or paternally derived. Maternally derived *digynic triploidy* typically results from a meiosis error and fertilization of a diploid ovum by a normal haploid sperm. Paternally derived *diandric triploidy* usually forms from the fertilization of a normal haploid ovum by two haploid spermatozoa and leads to partial molar pregnancy (Chap. 13, p. 237). Triploid fetuses frequently spontaneously abort early, and the few carried longer are all grossly deformed.

Maternal Factors

Medical Disorders

In chromosomally normal pregnancy losses, maternal contributions can play a role. For example, a prominent miscarriage risk is associated with poorly controlled diabetes mellitus, obesity, thyroid disease, and systemic lupus erythematosus. In these, inflammatory mediators may be an underlying theme to pregnancy loss (Kalagiri, 2016; Sjaarda, 2017). In chapters on these disorders, the miscarriage rate and attempts to lower it are discussed. In contrast, thrombophilias are no longer linked to miscarriage (American College of Obstetricians and Gynecologists (2020b).

For women undergoing cancer treatment, direct therapeutic radiation can cause miscarriage. Suggested safe parameters are found in Chapter 49 (p. 872). Similarly, the effects of chemotherapy on miscarriage rates are not well defined. Particularly worrisome are women with an ongoing pregnancy after early exposure to the teratogen methotrexate, described in Chapter 8 (p. 152). Cancer survivors previously treated with abdominopelvic radiotherapy and now subsequently pregnant may carry a greater risk for miscarriage (Chap. 66, p. 1164).

Surgical Procedures

The miscarriage risk associated with surgery is not well studied. But, as discussed in Chapter 49 (p. 867), *uncomplicated* surgical procedures performed during early pregnancy are unlikely to raise this risk (Mazze, 1989).

If indicated, ovarian tumors can generally be resected without inciting miscarriage. An exception involves early removal of the corpus luteum or the entire ovary in which it resides. If performed before 10 weeks' gestation, supplemental progesterone should be given and is described in Chapter 66 (p. 1170).

Trauma seldom causes first-trimester miscarriage, and although Parkland Hospital is a busy trauma center, this is an infrequent association. Major trauma—especially abdominal—can cause fetal loss but is more likely as pregnancy advances (Chap. 50, p. 891).

Nutrition

Sole deficiency of one nutrient or moderate deficiency of all does not appear to raise miscarriage risks. Even in extreme cases—for example, hyperemesis gravidarum—abortion is rare. Dietary quality may play a small role, and some data suggest miscarriage risk may decline in women who eat a diet rich in fruits, vegetables, whole grains, and fish (Gaskins, 2015). Unlike obesity, underweight is not associated with a greater miscarriage risk (Balsells, 2016).

With caffeine, reports link heavy intake of approximately five cups of coffee per day—about 500 mg of caffeine—with a slightly greater abortion risk (Cnattingius, 2000; Klebanoff, 1999). Values vary depending on brewing style, but an 8-ounce cup of coffee contains 80 to 100 mg of caffeine. Black or green tea has half this dose (Food and Drug Administration, 2018). Currently, the American College of Obstetricians and Gynecologists (2020e) concludes consumption of <200 mg/d likely is not a major miscarriage risk and that any associated risk with higher intake is unsettled. Metaanalyses support an increasing dose-related risk (Chen, 2016; Li, 2015).

Behavioral Factors

Approximately 7 percent of pregnant women acknowledge cigarette smoking (Kondracki, 2019). One metaanalysis found a slight dose-related relationship between current smoking and early pregnancy loss (Pineles, 2014). The serious later risks of persistent smoking on pregnancy outcomes are discussed in Chapter 8 (p. 156).

Alcohol consumption carries miscarriage risk mainly in those with chronic or heavy use (Feodor Nilsson, 2014). The potent teratogenic effects in these instances are also discussed in Chapter 8 (p. 149).

Environmental Factors

Despite the many infections acquired in pregnancy, these uncommonly cause early miscarriage. The important maternofetal consequences of specific infections in later pregnancy are discussed in Chapters 67 and 68.

Environmental toxins suggested to have a possible link to miscarriage include bisphenol A, phthalates, polychlorinated biphenyls, and dichlorodiphenyltrichloroethane (DDT) (Krieg, 2016). Even fewer studies implicate occupational exposures. Data suggest a slight increased miscarriage risk in health-care workers exposed to radiation or antineoplastic drugs (Anderson, 2020). The National Institute for Occupational Safety and Health publishes guidelines on potentially hazardous drugs (Connor, 2016). Evidence implicating occupational anesthetic gases in miscarriage is not robust (Oliveira, 2021). Still, gas scavenging systems and workplace exposure limits are recommended (McGlothin, 2014).

■ Spontaneous Abortion Clinical Classification

Threatened Abortion

This is defined as bleeding through a closed cervical os in the first 20 weeks of pregnancy and with a live embryo or fetus. It may portend abortion, or it may be associated with conceptus implantation. Other bleeding sources to exclude are ectopic pregnancy, cervical infection, and dysplastic or neoplastic cervical lesions.

Almost one fourth of women develop bleeding during early gestation that is attributed to threatened abortion (Everett, 1997). Bleeding or spotting may persist for days or weeks. It may be accompanied by suprapubic discomfort, mild cramps, pelvic pressure, or persistent low backache. Of symptoms, bleeding is by far the most predictive factor for subsequent pregnancy loss.

Vaginal bleeding or abdominal pain in early pregnancy should prompt hematocrit and blood type assessment. One primary goal is to exclude ectopic pregnancy, and strategic use of β-hCG levels and transvaginal sonography (TVS) is outlined in Chapter 12 (p. 222). A second goal is to determine IUP viability. With an IUP, the gestational sac—an anechoic fluid collection that represents the exocoelomic cavity—may be seen by 4.5 weeks (Fig. 10-2, p. 177). At this time, β-hCG levels generally measure 1500 to 2000 mIU/mL (Barnhart, 1994; Timor-Tritsch, 1988). Connolly and colleagues (2013), however, noted that a threshold as high as 3500 mIU/mL may be needed to identify the gestational sac in some cases that ultimately yield a viable singleton IUP.

One caveat during TVS is that a gestational sac may appear similar to a *pseudogestational sac*, which is an anechoic intrauterine fluid collection (Fig. 12-3, p. 223). This pseudosac may be blood derived from a bleeding ectopic pregnancy and is easier to exclude once a yolk sac is seen. Typically, the yolk sac is visible by 5.5 weeks and with a mean gestational-sac diameter of 10 mm. Thus, the diagnosis of an IUP should be made cautiously if the yolk sac is not yet seen (American College of Obstetricians and Gynecologists, 2020h). Fetal cardiac activity can typically be detected at 6 to 6.5 weeks.

A subchorionic hematoma may also be seen sonographically with threatened miscarriage (Fig. 11-1). In general, this collection does not portend a greater miscarriage risk (Naert, 2019).

Once threatened abortion is diagnosed, observation is the norm. Acetaminophen-based analgesia will help relieve

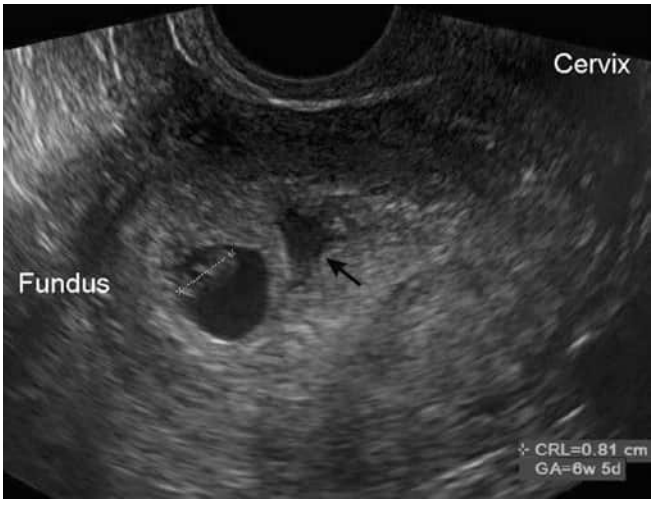


FIGURE 11-1 In this transvaginal sonogram sagittal view of the uterus, a subchorionic hematoma is seen as a very hypoechoic collection (*arrow*). It lies adjacent to the round anechoic gestational sac that contains a nearly 7-week embryo (*calipers*). (Reproduced with permission from Jason McWhirt, ARDMS.)

cramping discomfort. The randomized Progesterone in Spontaneous Miscarriage (PRISM) trial found no advantage to progesterone supplementation to lower miscarriage rates in women with first-trimester bleeding (Coomarasamy, 2019). Bed rest does not improve outcomes and may cause harms such a deep-vein thrombosis (McCall, 2013). We do counsel against intercourse until bleeding subsides. In unusual cases, bleeding with threatened abortion can lead acute severe anemia or hypovolemia. Pregnancy evacuation is generally indicated. Less often, transfusion and further observation is elected.

Even if miscarriage does not follow threatened abortion, later rates of preterm birth and placental abruption are slightly increased (Saraswat, 2010). Weiss and coworkers (2004) noted greater risks for later adverse outcomes if early bleeding was heavy rather than light. Despite these associations, we typically do not add sonography or other surveillance later in pregnancy solely for a first-trimester diagnosis of threatened abortion.

Incomplete Abortion

During miscarriage, the cervix opens and placental separation causes bleeding. Before 10 weeks' gestation, the fetus and the placenta are frequently expelled together, but later, they often deliver separately. Thus, tissue may remain entirely within the uterus or partially extrude through the cervix. Products lying loosely within the cervical canal can be easily extracted or teased out with ring forceps. For uterine infection or for hemodynamically unstable women with heavy bleeding, prompt surgical evacuation is performed.

For less urgent cases, three management options are curettage, expectant management, or misoprostol (Cytotec), which is prostaglandin E_1 (PGE_1) (Kim, 2017). With all three, treatment complications such as infection and need for transfusion are infrequent. However, misoprostol and expectant care can be associated with unpredictable bleeding. Thus, some women will still require unscheduled curettage, which studies have used as a failure endpoint. Expectant management of spontaneous incomplete abortion has failure rates that approximate 25 percent in randomized trials (Nielsen, 1999; Trinder, 2006). Medication therapy carries failure rates of 5 to 30 percent (Shochet, 2012; Trinder, 2006). Many of the studies assessing treatment have used an 800-µg vaginal, a 400-µg sublingual, or a 600-µg oral misoprostol dose. Last, curettage usually results in a quick resolution that is 95- to 100-percent successful. However, it is invasive, carries surgical risks, and is not necessary for all women (p. 211).

Complete Abortion

At times, the entire pregnancy is expelled. With completion, bleeding ebbs, and the internal cervical os subsequently closes over the next hour or so. Patients are encouraged to bring in passed tissue, and a gestation should be documented within blood clots or within a decidual cast (Fig. 11-2). The latter is the thickened endometrium, in the shape of the uterine cavity, that may slough with miscarriage.

If a gestational sac is not identified within the expelled tissue, TVS helps differentiate a complete abortion from a threatened abortion or ectopic pregnancy. Findings of complete abortion include a thin endometrium without a gestational sac. However, this does not guarantee a recent IUP. One study evaluated

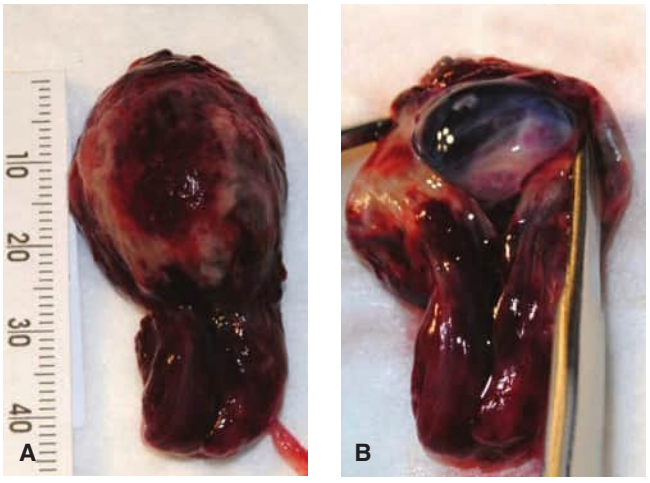


FIGURE 11-2 A. Decidual cast from a complete abortion. **B.** Opening the cast reveals a clear translucent gestational sac, which confirms the diagnosis.

152 women with heavy bleeding and an empty uterus with endometrial thickness <15 mm. Six percent were subsequently found to have an ectopic pregnancy (Condous, 2005). Thus, a complete abortion cannot be surely diagnosed unless: (1) true products of conception are seen grossly or (2) sonography documents first an IUP and then later an empty cavity. In unclear settings, serial serum β-hCG levels aid clarification. With complete abortion, these levels drop quickly (Table 11-1).

Missed Abortion

This describes dead products of conception that have been retained for days or weeks within a uterus with a closed cervical

TABLE 11-1. Percentage Decline of Initial Serum β-hCG Levels Following Complete Spontaneous Abortion

Initial hCG (mIU/mL)	Percentage Decline[a] by day 2 Expected % (Minimum %)	by day 4 Expected % (Minimum %)	by day 7 Expected % (Minimum %)
50	68 (12)	78 (26)	88 (34)
100	68 (16)	80 (35)	90 (47)
300	70 (22)	83 (45)	93 (62)
500	71 (24)	84 (50)	94 (68)
1000	72 (28)	86 (55)	95 (74)
2000	74 (31)	88 (60)	96 (79)
3000	74 (33)	88 (63)	96 (81)
4000	75 (34)	89 (64)	97 (83)
5000	75 (35)	89 (66)	97 (84)

[a]The percentage decline is given as the expected decline. The minimum expected decline in parentheses is the 95th percentile value. Declines less than this minimum may reflect retained either intrauterine or extrauterine trophoblast.
hCG = human chorionic gonadotropin.
Data from Barnhart, 2004; Chung, 2006.

TABLE 11-2. Guidelines for Early Pregnancy Loss Diagnosis

Sonographic Findings
CRL ≥7 mm and no heartbeat
MSD ≥25 mm and no embryo
An initial US scan shows a gestational sac with yolk sac, and after ≥11 days no embryo with a heartbeat is seen
An initial US scan shows a gestational sac without a yolk sac, and after ≥2 weeks no embryo with a heartbeat is seen
Modalities
Transvaginal preferable to transabdominal US
M-mode imaging used to document and measure heartbeat
Pulsed Doppler US methods generally not used to evaluate a normal early embryo

CRL = crown-rump length; MSD = mean sac diameter; US = ultrasound.
From American College of Obstetricians and Gynecologists, 2019b; Brown, 2018; Doubilet, 2013.

os. Diagnosis is imperative prior to intervention and avoids interruption of a potentially live IUP. Again, TVS and β-hCG levels are primary tools. With the latter, levels that plateau or drop are typical.

With TVS, a 1- to 2-mm embryo adjacent to the yolk sac can be seen at 5 to 6 weeks' gestation. As listed in Table 11-2, absence of an embryo in a sac with a mean sac diameter (MSD) ≥25 mm signifies pregnancy loss. The MSD is calculated by summing the length, width, and height of a gestational sac and dividing the sum by three. Fetal cardiac activity can typically be detected at 6 to 6.5 weeks, with a crown-rump length (CRL) of 1 to 5 mm, and an MSD of 13 to 18 mm (Goldstein, 1992; Levi, 1990). A CRL threshold ≥7 mm plus absent cardiac activity also is used to diagnose nonviability (Doubilet, 2013). For cases in which a gestational sac has no embryo or yolk sac, additional time and repeat TVS are recommended. M-mode should be used to document cardiac activity and measure the rate (Brown, 2018). Pulsed Doppler is not used routinely and is reserved for specific diagnostic purposes because of theoretical temperature elevation in exposed fetal tissues (Chap. 14, p. 247).

Less robust sonographic markers may portend pregnancy failure. A yolk sac diameter >7 mm in pregnancies <10 weeks' gestation is one (Rodgers, 2015). The fetal heart rate in the first trimester rises from 110 to 130 beats per minute (bpm) at 6 weeks' gestation to 160 to 170 bpm at 8 weeks (Achiron, 1991; Rauch, 2009). A slower heart rate is unfavorable, especially one <85 bpm (DeVilbiss, 2020). Even with cardiac activity, fetuses with a small MSD may presage embryonic loss. A difference <5 mm between the MSD and CRL values raises concern (Bromley, 1991). Last, an irregular gestational sac contour may portend loss (Nyberg, 1986).

With embryonic or fetal death confirmed, expectant observation, surgery, or medication is an option. Nonsurgical options balance less invasiveness against heavier associated bleeding, longer completion times, and lower success rates. Of options, expectant care underperforms medication or surgery, and failure rates range from 15 to 50 percent (Luise, 2002; Trinder, 2006; Zhang, 2005). Also, weeks may pass between pregnancy failure diagnosis and actual spontaneous miscarriage.

As a medication option, misoprostol can be given, and a single 800-μg dose vaginally is a common standard. It may be repeated once in 1 to 2 days, and one large trial reported that 22 percent of women required a second dose (Zhang, 2005). Overall, failure rates range from 15 to 40 percent (Petersen, 2013; Trinder, 2006). Success rates are improved by a 200-mg oral dose of mifepristone (Mifeprex) given 24 hours prior to misoprostol (Schreiber, 2018). In the United States, access to this antiprogestin is limited by the Food and Drug Administration (FDA) to providers participating in the manufacturer's Risk Evaluation and Mitigation Strategy (REMS) (Danco Laboratories, 2021). Contraindications mirror those listed in the section describing induced abortion (p. 212).

Inevitable Abortion of a Previable Fetus

Either rupture of placental membranes or marked ballooning of membranes into the vagina may lead to inevitable abortion. The latter is discussed in the cervical insufficiency section (p. 205).

Preterm prelabor rupture of membranes (PPROM) at a *previable* gestational age complicates 0.5 percent of pregnancies (Hunter, 2012). Instead, *periviable birth* is defined as delivery between $20^{0/7}$ and $25^{6/7}$ weeks and is discussed in Chapter 45 (p. 785). Clinically with PPROM, abundant vaginal fluid that pools during sterile speculum examination confirms the diagnosis. Patient coughing or Valsalva maneuver may accentuate this. Other diagnostic steps can include pH testing, microscopic examination, and sonographic assessment of amnionic fluid volume, and these are outlined in Chapter 22 (p. 426).

Rupture may be spontaneous, and risks are prior PPROM, prior second-trimester delivery, and tobacco use (Kilpatrick, 2006). Iatrogenic fluid leakage can follow amniocentesis or fetal surgery. In some second-trimester cases, fluid may have collected previously between the amnion and chorion and reflects only chorion leakage.

Spontaneous rupture in the first trimester is nearly always followed by either uterine contractions or infection, and termination is typical. With second-trimester spontaneous PPROM at a previable age, 40 to 50 percent of women will deliver within the first week, and 70 to 80 percent will do so after 2 to 5 weeks (American College of Obstetricians and Gynecologists, 2020f). Average latency is 2 weeks (Hunter, 2012; Kibel, 2016). Significant maternal complications attend previable PPROM and include uterine infection, sepsis, placental abruption, postpartum hemorrhage, and retained placenta (Dotters-Katz, 2017b; Waters, 2009). In one study, 56 percent of women suffered one or more of these complications (van der Marel, 2016). With significant bleeding or fever, the uterus should be evacuated. Surgical evacuation or medication options for this vary by gestational age and surgeon skill. Methods mirror those for second-trimester elective abortion, described later (p. 213).

For cases in which previable delivery is inevitable or elected, neonatal consultation aids decision-making and helps form expectations for the family. For fetuses with a life-limiting

condition, such as extreme prematurity, *perinatal palliative care* is a strategy that emphasizes comfort (American College of Obstetricians and Gynecologists, 2019c). Care team members can include obstetric and neonatal professionals, chaplaincy, and mental health specialists.

In cases without bleeding or fever, expectant management is an option in the well-counseled patient. Many will choose termination due to the earlier-described maternal risks and tenuous neonatal outcomes. Early fetal mortality stems from pulmonary hypoplasia, severe intraventricular hemorrhage, and sepsis. Of those managed expectantly with PPROM at <20 weeks, the percentage of infants who are discharged home ranges from 12 to 23 percent (Hunter, 2012; Sim, 2020; van der Martel, 2016). Common neonatal morbidities are respiratory distress syndrome, bronchopulmonary hypoplasia or dysplasia, necrotizing enterocolitis, and sepsis. Overall, prognosis is improved if previable PPROM occurs at a later gestation, latency is longer, and oligohydramnios is absent. With the last, poor lung development and fetal skeletal deformations can result from scant amnionic fluid.

If expectant care is elected, initial hospital evaluation, diminished physical activity, and observation for fever or labor are reasonable. After 24 hours, if there is no bleeding, cramping, or fever, a woman may resume ambulation and is discharged home. She is instructed to watch for fever, contractions, or bleeding. Antibiotics are considered and given for 7 days to extend latency (Dotters-Katz, 2017a). However, lung-maturing corticosteroids, magnesium sulfate neuroprophylaxis, group B streptococcus antibiotic prophylaxis, cesarean delivery, and tocolytics are not recommended before 22 weeks' gestation (American College of Obstetricians and Gynecologists, 2019d). Once a viable age is reached, readmission until delivery is our practice. PPROM care at viable gestational ages is described in Chapter 45 (p. 799).

In procedure-related PPROM, iatrogenic leaks are typically higher in the uterus and tend to self-seal. For leaks from amniocentesis, management is typically conservative, and brief bedrest yields high pregnancy continuation rates. For rupture after fetal surgery, investigational treatments can address surgical leaks (Chmait, 2017). One is an occlusive plug—termed an amniopatch—that forms following intraamnionic instillation of autologous platelets and cryoprecipitate. Another is amnioinfusion to counter the effects of oligohydramnios but is not robustly supported by current data (Roberts, 2014; van Kempen, 2019).

In subsequent pregnancies, the risk for recurrent preterm birth is great in women with prior previable PPROM. In one cohort study, 46 percent delivered their next pregnancy before 37 weeks, and 17 percent delivered before reaching 24 weeks (Monson, 2016).

Septic Abortion

With spontaneous or induced abortion, organisms may invade myometrial tissues and extend to cause parametritis, peritonitis, and septicemia. This may complicate both medication and surgical methods. Classic clinical findings include fever, lower abdominal pain, uterine tenderness, and foul vaginal discharge. Vaginal bleeding and sonographic evidence of retained uterine tissue are others. Urinary tract infection should be excluded by urinalysis, and a complete blood count assesses leukocytosis.

Most bacteria causing septic abortion are part of the normal vaginal flora. Thus, vaginal culture is not informative, however, we obtain blood cultures for those with sepsis. Particularly worrisome are severe necrotizing infections and toxic shock syndrome (TSS) caused by group A streptococcus—*S pyogenes* (Daif, 2009). Maternal deaths from *Clostridium perfringens* or *C sordellii* also have been described. With TSS, women show severe endothelial injury, capillary leakage, hemoconcentration, hypotension, tachycardia, and marked leukocytosis but may not be febrile initially.

With septic abortion, management includes prompt administration of broad-spectrum antibiotics as discussed in Chapter 37 (p. 651). If products are retained, suction evacuation is performed. Most women respond to this treatment within 1 to 2 days and are discharged when afebrile. Additional oral antibiotics are likely unnecessary (Savaris, 2011). In a very few women, severe sepsis syndrome develops, and intensive supportive care is essential. Although rare, widespread peritonitis despite curettage and clinical decline in the patient should raise concerns. Imaging that shows intraabdominal free air or air within the uterine wall typically prompts laparotomy (Eschenbach, 2015). If the uterus is necrotic, hysterectomy is indicated.

Anti-D Immunoglobulin

With spontaneous or induced abortion, 2 percent of D-negative women will become alloimmunized if not provided passive isoimmunization. With surgical dilation and curettage, this rate may reach 5 percent. The American College of Obstetricians and Gynecologists (2019e) recommends a 300-μg intramuscular dose of anti-Rho (D) immunoglobulin for all gestational ages. Doses can also be graduated. Namely, a 50-μg or 120-ug dose is given for pregnancies ≤12 weeks and a 300-μg one for those ≥13 weeks. This is administered immediately following surgical evacuation. For medication abortion or expectant management, the injection is given within 72 hours of pregnancy failure diagnosis.

With *threatened* abortion, immunoglobulin prophylaxis is controversial because of sparse evidence-based data (Hannafin, 2006). It is reasonable to administer anti-D immunoglobulin for a threatened abortion, and this is our practice.

RECURRENT MISCARRIAGE

Affecting approximately 1 percent of fertile couples, recurrent pregnancy loss (RPL) is classically defined as three or more consecutive pregnancy losses at <20 weeks' gestation or with a fetal weight <500 g. However, data show the risk for a subsequent loss to be similar whether a woman has two or three prior miscarriages (Bhattacharya, 2010). The American Society for Reproductive Medicine (2020) now defines RPL as two or more failed pregnancies confirmed by sonographic or histopathological examination. *Primary RPL* refers to multiple losses in a woman who has never delivered a liveborn, and *secondary RPL* refers to multiple pregnancy losses in a patient with a prior live birth. Remarkably, chances for a successful pregnancy are >50 percent even after five miscarriages (Table 11-3) (Brigham, 1999). RPL evaluation addresses its major causes, described next.

TABLE 11-3. Predicted Success Rate of Subsequent Pregnancy According to Age and Number of Previous Miscarriages

Age (yrs)	No. of Previous Miscarriages: Predicted Success of Subsequent Pregnancy (%)			
	2	3	4	5
20	92	90	88	85
25	89	86	82	79
30	84	80	76	71
35	77	73	68	62
40+	65	59	53	47

Etiology

Widely accepted causes of RPL include some parental chromosomal abnormalities, antiphospholipid antibody syndrome, specific endocrinopathies, and certain structural uterine abnormalities. Thus, current RPL evaluation includes karyotyping of both parents; measuring antiphospholipid antibody levels; assessing HbA_{1c}, thyroid-stimulating hormone (TSH), and prolactin levels; and performing saline-infusion sonography (SIS) or hysterosalpingography (American Society for Reproductive Medicine, 2012).

The timing of recurrent loss can offer clues, and in some women, each miscarriage may occur near the same gestational age (Heuser, 2010). Approximately 50 percent of women have idiopathic RPL (Habayeb, 2004).

Parental Chromosomal Abnormalities

In first-trimester RPL, the incidence of genetic abnormalities is significantly lower than in sporadic miscarriage (Stephenson, 2002). A notable exception is a parent that carries a reciprocal translocation or Robertsonian translocation (Fan, 2016). Their genesis and reproductive sequelae are discussed in Chapter 16 (p. 316). These account for only 2 to 4 percent of RPL cases, but karyotyping of both parents is a recognized part of RPL evaluation.

After thorough genetic counseling, couples with an abnormal karyotype can be offered in vitro fertilization (IVF) followed by preimplantation genetic testing (PGT) or offered donor gametes (Chap. 17, p. 348). However, birth rates with IVF plus PGT are not superior to expectant management for this cause of RPL (Murugappan, 2016). Importantly, in couples with RPL who are *chromosomally normal,* PGT is not recommended solely for the indication of RPL.

Anatomical Factors

Several genital tract abnormalities have been implicated in RPL, but direct linkage is not robust. According to Devi Wold and associates (2006), 15 percent of women with ≥3 consecutive miscarriages will have a congenital or acquired uterine anomaly. Thus, SIS and hysteroscopy are primary evaluation tools.

Uterine leiomyomas are common, and some may cause miscarriage, especially if located near the placental implantation site. However, data suggesting a significant link to RPL are not convincing and poor quality (Saravelos, 2011). The American Society for Reproductive Medicine (2017) notes that hysteroscopic excision of large submucosal leiomyomas in women with RPL can be considered.

Uterine synechiae, often called *Asherman syndrome,* result from broad destruction of endometrium and subsequent scarring, which can follow uterine curettage or hysteroscopic surgeries. With SIS, multiple hypoechoic bridging bands are seen to span the endometrial cavity, which is filled with anechoic saline. Treatment is hysteroscopic adhesiolysis, but success rates are lower with more severe initial disease.

Uterine polyps have been found more frequently in women with RPL, but causality is unclear. These are seen during hysteroscopy or SIS as a mass lesion extending from the uterine wall into the endometrial cavity. Application of color Doppler during SIS classically reveals a single feeder vessel reaching the mass. Hysteroscopic polypectomy can be considered.

For all these acquired lesions, correction can be considered for those with significant uterine cavity distortion. However, evidence supporting improved birth rates is not robust (American Society for Reproductive Medicine, 2012). Moreover, reproductive benefits are balanced against intrauterine adhesions that may form after any intracavitary surgery.

Congenital uterine anomalies often originate from abnormal müllerian duct formation. Depending on their anatomy, some may raise risks for miscarriage or preterm delivery. Of these, septate uterus is most closely linked with miscarriage. Hysteroscopic resection has been associated with improved live birth rates in some but not all studies (Rikken, 2017). It can be considered for RPL (American Society for Reproductive Medicine, 2016). Chapter 3 (p. 42) contains a fuller discussion of uterine abnormalities and their other obstetrical effects.

Immunological Factors

Miscarriages are more common in women with systemic lupus erythematosus (SLE) (Clowse, 2008). Many of these women and also some without SLE carry *antiphospholipid antibodies*. These are a family of autoantibodies that bind to phospholipid-binding plasma proteins and are associated with RPL (Alijotas-Reig 2019). As shown in Table 11-4, the *antiphospholipid antibody syndrome (APS)* is defined by these antibodies in combination with various forms of reproductive loss or vascular thrombosis (American College of Obstetricians and Gynecologists, 2019a). Chapter 62 (p. 1114) describes pregnancy loss with APS and treatment.

Endocrine Factors

Of recurrent miscarriages, 8 to 12 percent are caused by endocrine factors (Arredondo, 2006). First, the well-known abortifacient action of uncontrolled diabetes mellitus is detailed in Chapter 60 (p. 1070). Optimal periconceptional glycemic control will mitigate many of these losses.

Overt hypothyroidism and severe iodine deficiency also raise miscarriage rates (Chap. 61, p. 1094). Correction with supplementation reverses these actions. Subclinical hypothyroidism, however, does not appear to increase miscarriage rates (Dong, 2020). Antithyroid antibodies are a common associate of subclinical hypothyroidism or overt hypothyroidism. A recent

TABLE 11-4. Clinical and Laboratory Criteria for Diagnosis of Antiphospholipid Antibody Syndrome[a]

Clinical Criteria

Obstetrical:

≥3 unexplained consecutive spontaneous miscarriages <10 weeks' gestation

or

≥1 unexplained fetal death(s) ≥10 weeks' gestation

or

Severe preeclampsia or placental insufficiency necessitating delivery before 34 weeks

Vascular: ≥1 episode(s) of arterial, venous, or small-vessel thrombosis in any tissue

Laboratory Criteria[b]

Presence of lupus anticoagulant according to guidelines of the International Society on Thrombosis and Hemostasis

or

Medium or high serum levels of IgG or IgM anticardiolipin antibodies

or

Anti-β_2 glycoprotein-I IgG or IgM antibody

[a]At least one clinical and one laboratory criteria must be present for diagnosis.
[b]These tests must be positive on two or more occasions at least 12 weeks apart.
IgG = immunoglobulin G; IgM = immunoglobulin M.
Modified from Branch, 2010; Miyakis, 2006.

metaanalysis found positive associations between these antibodies and a greater risk for sporadic and recurrent miscarriages (Xie, 2020). However, levothyroxine supplementation in this group does not improve subsequent pregnancy outcomes (Sun, 2020). For evaluation of RPL, measuring levels of serum TSH, but not antithyroid antibodies, is reasonable.

Other endocrinopathies are inconclusively implicated. One is progesterone deficiency caused by a luteal-phase defect. Progesterone supplementation, compared with placebo, did not improve the live birth rate in those with RPL in one large trial (Coomarasamy, 2015). Limited data implicate hyperprolactinemia (Hirahara, 1998). Obesity, polycystic ovarian syndrome, and insulin resistance are also linked to RPL (Cavalcante, 2019; Craig, 2002; Mayrhofer, 2020). However, the interplay between these makes assigning individual causality difficult.

SECOND-TRIMESTER ABORTION

Etiology

The timespan that defines a midtrimester fetal loss extends from the end of the first trimester until the fetus weighs <500 g or gestational age reaches 20 weeks. The spontaneous loss rate in the second trimester is much lower than in the first.

Unlike earlier miscarriages that frequently stem from chromosomal aneuploidies, causes of these later fetal losses are more diverse (Table 11-5). Their ultimate presentations may be miscarriage, PPROM, or fetal demise prior to labor (Morris, 2016). Some second-trimester abortions are induced because of fetal abnormalities or patient choice.

Second-trimester losses are subclassified similarly to first-trimester ones (p. 200). Management is similar in many regards to that used for second-trimester induced abortion, described on page 214. One exception is cervical cerclage, which may be employed for cervical insufficiency.

Cervical Insufficiency

Previously called incompetent cervix, this is characterized classically by painless cervical dilation in the second trimester. It can be followed by prolapse and ballooning of the amnionic membranes into the vagina, and ultimately, expulsion of an immature fetus. This sequence often repeats in future pregnancies.

Of causes, prior cervical trauma is implicated. One cohort study of more than 15,000 women with prior cervical conization found a fourfold risk of pregnancy loss before 24 weeks' gestation (Albrechtsen, 2008). However, in women solely with prior conization but no prior preterm birth, outcomes are not improved by prophylactic cerclage (Zeisler, 1997). In other instances, abnormal cervical development, including that from diethylstilbestrol (DES), may play a role (Hoover, 2011). Marfan and Ehlers-Danlos syndromes also carry increased risk of cervical insufficiency (Meijboom, 2006; Spiegel, 2020).

Surgical Indications

For women with an unequivocal history of second-trimester painless delivery, prophylactic cerclage placement is an option and reinforces a weak cervix by an encircling suture. However,

TABLE 11-5. Some Causes of Midtrimester Spontaneous Pregnancy Losses

Fetal Anomalies	**Placental Causes**
Structural	Abruption, previa
Chromosomal	Vasculopathy
	Chorioamnionitis
Maternal Disorders	**Uterine Defects**
Autoimmune	Congenital
Infections	Leiomyomas
Metabolic	Incompetent cervix

some women have a history and clinical findings that make it difficult to verify—*classic* cervical insufficiency. In one randomized trial of almost 1300 women, cerclage was found to be beneficial—13 versus 17 percent—to prolong pregnancy past 33 weeks (MacNaughton, 1993).

The physical finding of early dilation of the internal cervical os and visible membranes is another indicator of insufficiency. In one systematic review, cerclages that were placed based on such examination findings provided superior perinatal outcomes compared with expectant management (Ehsanipoor, 2015).

Last, some use TVS to determine cerclage need. In those with any prior spontaneous preterm birth, the Society for Maternal-Fetal Medicine (2016) recommends transvaginal cervical length screening. The American College of Obstetricians and Gynecologists (2021) also recommends this screening. Surveillance extends between 16 and 24 weeks' gestation, and examinations, described in Chapter 14 (p. 254), are performed every 1 to 4 weeks. In those without prior preterm birth or in those with multifetal gestation, cervical length is not specifically measured. The cervix should be viewed during the sonographic anatomical anatomy examination at 18 to 22 weeks' gestation. Chapter 45 (p. 794) discusses recommendations for cerclage placement based on cervical length to prevent preterm birth.

Presurgical Preparation

Contraindications to cerclage include bleeding, contractions, or ruptured membranes, any of which substantially raise the likelihood of labor and failure. Prophylactic *elective cerclage* before dilation is preferable, and timing between 12 and 14 weeks' gestation allows early intervention. Still, it avoids surgery in the first trimester, which is when most predestined spontaneous losses occur, and screening for aneuploidy and malformation is completed. Cervical neoplasia screening in suitable candidates and gonorrhea and chlamydial infection testing are done. Obvious cervical infection is treated.

At times, the cervix instead is found to be dilated, effaced, or both, and an *emergency cerclage* is performed. Notably, in more-advanced pregnancy, the risk of stimulating preterm labor or of rupturing membranes with the surgery is greater. At Parkland Hospital, cerclage procedures are not done after 23 to 24 weeks' gestation. Others, however, describe placement later than this (Caruso, 2000; Terkildsen, 2003).

When outcomes of cerclage are evaluated, women with similar clinical presentations are ideally compared. In a study of elective cerclage by Owen and associates (2009), approximately a third of women delivered before 35 weeks, and complications were few. By contrast, in a 10-year review of 75 women undergoing emergency cerclage, only half were delivered after 36 weeks (Chasen, 1998). Importantly, only 44 percent of those with bulging membranes at the time of cerclage reached 28 weeks. Terkildsen and associates (2003) had similar experiences. Our experiences at Parkland Hospital are that emergency cerclage has a high failure rate, and women are counseled accordingly.

If the clinical indication for cerclage is questionable, a woman may instead be observed. Most undergo cervical examinations weekly or every 2 weeks to assess effacement and dilation. Unfortunately, rapid effacement and dilation can develop despite such precautions (Witter, 1984).

Vaginal Cerclage

Of the two vaginal cerclage operations, most use the simpler procedure developed by McDonald (1963) (Fig. 11-3). The more complicated operation is a modification of the procedure

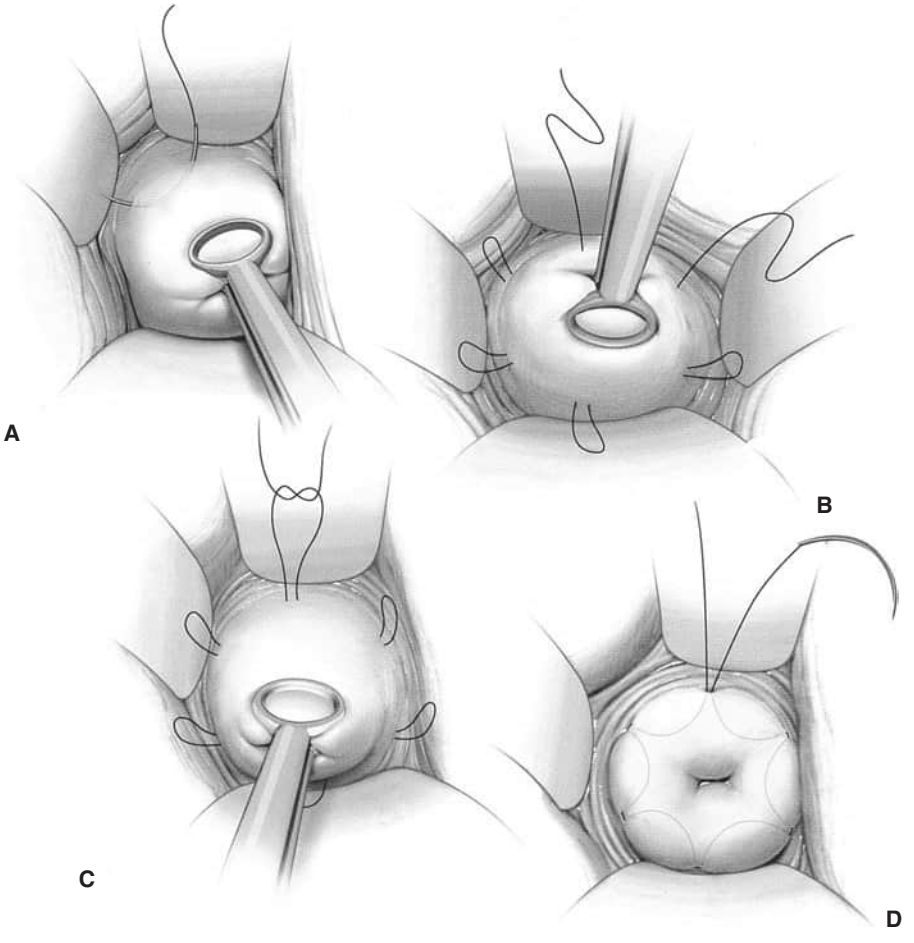


FIGURE 11-3 McDonald cerclage procedure for incompetent cervix. **A.** Start of the cerclage procedure with a no. 2 monofilament suture being placed in the body of the cervix very near the level of the internal os. **B.** Continuation of suture placement in the body of the cervix so as to encircle the os. **C.** Encirclement completed. **D.** The suture is tightened around the cervical canal sufficiently to reduce the diameter of the canal to 5 to 10 mm, and then the suture is tied. The effect of the suture placement on the cervical canal is apparent. A second suture placed somewhat higher may be of value if the first is not in close proximity to the internal os.

described by Shirodkar (1955) (Fig. 11-4). When either technique is performed electively, women with a classic history of cervical insufficiency have good outcomes (Caspi, 1990; Kuhn, 1977). For either vaginal or abdominal cerclage, evidence is insufficient to recommend perioperative antibiotic prophylaxis (American College of Obstetricians and Gynecologist, 2020a). Few data are available and do not support prophylactic tocolysis (Smith, 2015).

Regional analgesia is suitable and preferred. After this, the woman is placed in standard lithotomy position. The vagina and perineum are cleaned for surgery, and the bladder is drained. Some operators do not use potentially irritating antiseptic solution if amnionic membranes are exposed and instead use warm saline (Pelosi, 1990). Although steps are described here, a thorough and illustrated review of technique is provided by Hawkins (2017).

For suturing, options include a no. 1 or 2 nylon or polypropylene monofilament suture or 5-mm Mersilene tape. During placement, the suture is placed as cephalad along the cervical length as possible, is anchored into the dense cervical stroma, yet avoids the bladder. Two tandem cerclage suture rings are not more effective than one (Giraldo-Isaza, 2013).

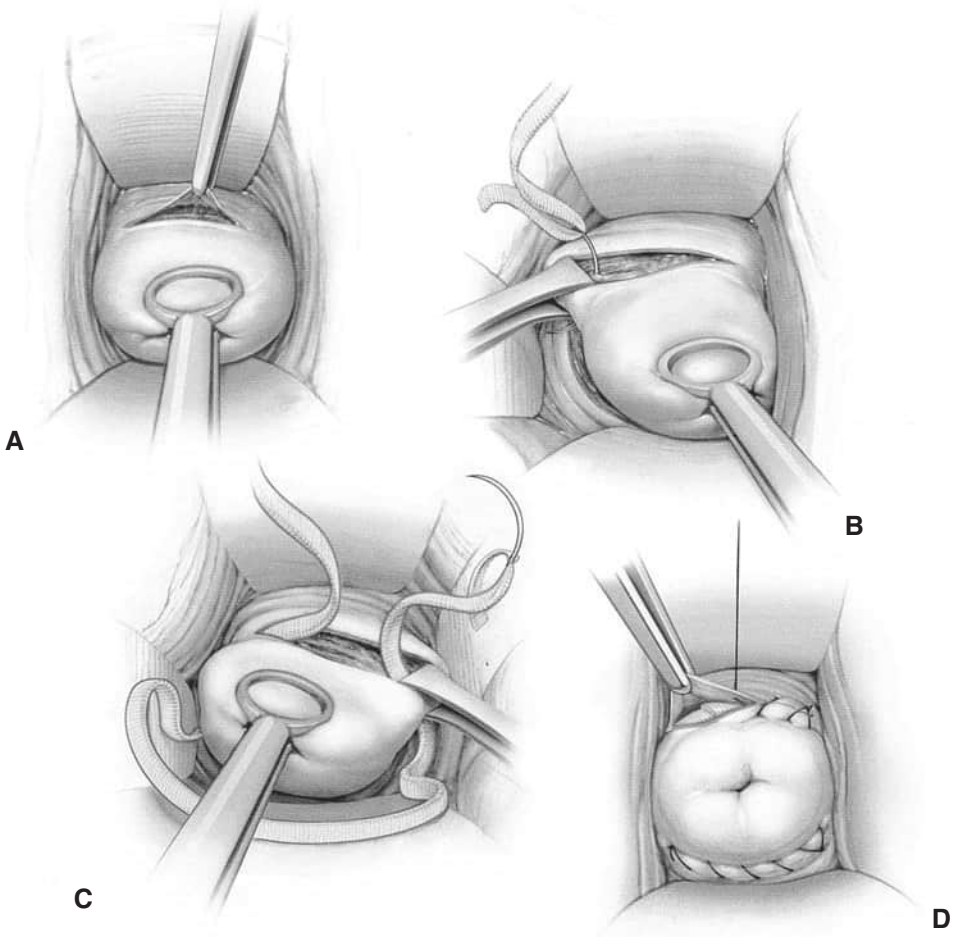


FIGURE 11-4 Modified Shirodkar cerclage for incompetent cervix. **A.** A transverse incision is made in the mucosa overlying the anterior cervix, and the bladder is pushed cephalad. **B.** A 5-mm Mersilene tape on a swaged-on or Mayo needle is passed anterior to posterior. **C.** The tape is then directed posterior to anterior on the other side of the cervix. Allis clamps are placed so as to bunch the cervical tissue. This diminishes the distance that the needle must travel submucosally and aids tape placement. **D.** The tape is snugly tied anteriorly, after ensuring that all slack has been taken up. The cervical mucosa is then closed with continuous stitches of chromic suture.

Emergency cerclage placement with a thinned dilated cervix is more difficult, and tissue tearing and membrane puncture are risks. Gentle replacement of the prolapsed amnionic sac back into the uterus can aid suturing. Options include steep Trendelenburg or filling the bladder with 600 mL of saline through a Foley catheter in the bladder. However, these steps may carry the cervix cephalad and away from the operating field. Instead, membranes can be pushed inward by a wide, moist sponge stick. A Foley catheter can instead be inserted through the cervix, and inflation of the 30-mL balloon can deflect the amnionic sac inward. The balloon is gradually deflated as the cerclage suture is tightened around the catheter tubing, which is then removed. With any of these, simultaneous gentle outward traction created by ring forceps placed on the cervical edges may be helpful.

For uncomplicated pregnancies without labor, the cerclage is usually snipped and removed at 37 weeks' gestation. This balances the risk of preterm birth against that of cervical laceration from a cerclage in place with labor contractions. Transvaginally placed cerclages are typically removed even with cesarean delivery to avoid rare long-term foreign-body complications (Hawkins, 2014). With scheduled cesarean delivery, the cerclage may be removed at 37 weeks or deferred until the time of regional analgesia and delivery. Again, the risk of labor ensuing before delivery must be considered. During extraction, particularly with a Shirodkar cerclage or a cerclage using Mersilene tape, analgesia aids patient comfort and adequate visualization.

Transabdominal Cerclage

At times, suture at the uterine isthmus is placed abdominally. Performed less often than transvaginal methods, selected indications include prior transvaginal cerclage failure or severe cervical anatomical defects. The cerclage is left until childbearing completion, and thus cesarean delivery is required. With the cerclage in place, conception rates still approximate 75 percent (Moawad, 2018). If needed for a fetal loss, dilation and evacuation can be performed with the suture in place (Dethier, 2020).

With the procedure, after abdomen entry, sharp dissection in the vesicocervical space allows the bladder to be pushed caudally. At the level of the internal os, a window is made in free space *medial* to the uterine vessels. This avoids vessel compression by the tightened cerclage. The nearby ureter is identified and avoided. One end of the ligating suture is passed into the right window, and the other is threaded into the left. Per surgeon preference, the knot is tied either in the front or back. The vesicouterine peritoneum is closed with absorbable suture in a running fashion.

In the MAVRIC trial, 111 women with a prior failed vaginal cerclage were randomly assigned to transabdominal, McDonald, or Shirodkar methods. Almost half of the transabdominal ones were placed prior to conception. The preterm birth rate before 32 weeks was 8 percent in the transabdominal group and 38 percent in each of the transvaginal cerclage groups (Shennan, 2020).

Of morbidity, rates of bleeding, adjacent organ injury, uterine perforation, and infection can be greater with transabdominal compared with transvaginal methods. Transabdominal cerclage performs suitably whether laparotomy or laparoscopy is used to place the sutures (Moawad, 2018).

Complications

With cerclage in general, PPROM, preterm labor, hemorrhage, or infection is a potential risk. All are uncommon with prophylactic cerclage. In the trial by MacNaughton and associates (1993), membrane rupture complicated only 1 of more than 600 procedures done before 19 weeks. In our view, clinical infection mandates immediate removal of the suture with labor induced or augmented. Similarly, with imminent abortion or delivery, the suture should be removed to avoid cervical laceration.

Following cerclage, sonographic surveillance does not improve outcomes (Dijkstra, 2000). Evidence does not support a subsequent reinforcing cerclage procedure (Baxter, 2005). Membrane rupture during suture placement or within the first 48 hours after surgery is considered by some to be an indication for cerclage removal to avoid serious fetal or maternal infection (Kuhn, 1977). In those with later PPROM but without infection or labor, options include observation alone or cerclage removal and observation. In these cases, data are contradictory regarding prolonged gestational latency and infection rates with retention or removal (Jenkins, 2000; Pergialiotis, 2015). In the absence of infection or labor, we allow cerclage retention with close clinical surveillance.

INDUCED ABORTION

Definitions

The term *induced abortion* is defined as termination of pregnancy with medication or surgery before fetal viability. The *abortion ratio* is the number of abortions per 1000 live births, and *abortion rate* is the number per 1000 women aged 15 to 44 years. For 2018, approximately 620,000 elective abortions were reported (Kortsmit, 2020). Of these, 78 percent were pregnancies aged ≤9 weeks' gestation, and 92 percent of abortions were completed before ≤13 weeks. The abortion ratio was 189 per 1000 live births, and the abortion rate was 11.3.

Therapeutic abortion refers to pregnancy termination for medical reasons, and suitable maternal or fetal indications are described in respective chapters. In cases of rape or incest, many consider termination. The most frequent therapeutic indication currently is to prevent birth of a fetus with a significant anatomical, metabolic, or mental deformity.

The term *elective abortion* or *voluntary abortion* describes the interruption of pregnancy before viability at the request of the woman, but not for medical reasons. Most abortions done today are elective.

Legal Influence

The legality of elective abortion was established by the United States Supreme Court in the case of *Roe v. Wade*. The Court defined the extent to which states might regulate abortion and ruled that first-trimester procedures must be left to the medical judgment of the physician. After this, the state could regulate abortion procedures in ways reasonably related to maternal health. Last, subsequent to viability, the state could promote its interest in the potential of human life and regulate abortion, except for preservation of the mother's health.

Other legislation followed. The 1976 Hyde Amendment forbids use of federal funds to provide abortion services except in cases of rape, incest, or life-threatening circumstances. The Supreme Court in 1992 reviewed *Planned Parenthood v. Casey* and upheld the fundamental right to abortion, but established that regulations are constitutional as long as they do not impose an "undue burden" on the woman. Subsequently, many states introduced counseling requirements, waiting periods, parental consent for minors, facility requirements, and funding restrictions. Such limits are often called targeted regulation of abortion providers (TRAP) laws. One major choice-limiting decision was the 2007 Supreme Court decision that reviewed *Gonzales v. Carhart* and upheld the 2003 Partial-Birth Abortion Ban Act. In 2016, some TRAP laws were dialed back by the Supreme Court ruling in the case of *Whole Woman's Health v. Hellerstedt*. With this, the justices noted that abortion laws must confer health safety benefits that outweigh burdens on access.

Provider Availability

Major women's health organizations support the legal right of women to obtain an abortion (Espey, 2019). The Accreditation Council for Graduate Medical Education mandates that obstetrics and gynecology residency education must include access to experience with induced abortion. The Kenneth J. Ryan Residency Training Program was established in 1999 to work with residency programs to improve abortion and contraceptive training. Moreover, postresidency training in these techniques is available in formal 2-year Family Planning fellowships. Other residency programs have a less-codified abortion curriculum. Instead, residents learn technical aspects through their management of miscarriage and pregnancy interruption for medical indications.

The American College of Obstetricians and Gynecologists (2019g) respects the need and responsibility of health-care providers to determine their individual positions on induced abortion. It also advocates for counseling and timely referral if providers have individual beliefs that preclude pregnancy termination. Knowledgeable and compassionate counseling objectively describes and provides information to the woman to permit informed decision-making.

FIRST-TRIMESTER METHODS

Abortions can be completed with either medication or surgery. In the absence of serious maternal disorders, abortion procedures do not require hospitalization (Guiahi, 2012). However, outpatient facilities should be able to provide emergency resuscitation and immediate transfer to a hospital (Levy, 2019).

■ Surgical Abortion

Preoperative Preparation

Surgical evacuation is performed transvaginally through an appropriately dilated cervix. For this, preoperative cervical ripening is typically associated with easier intraoperative cervical dilation, less pain, a technically easier procedure, and shorter operative times (Kapp, 2010; Webber, 2015). On balance, this preparation adds a surgical delay and potential side effects. Thus, cervical priming in the first trimester may be reserved for those with anticipated challenges to dilation. Examples are those with cervical stenosis or adolescents, who overall may experience higher associated pain (Allen, 2016). Surgical steps presented here apply to both induced abortion and miscarriage.

For ripening, hygroscopic dilators, also called osmotic dilators, are devices that draw water from surrounding tissues and expand gradually to dilate the endocervical canal. One type is derived from various species of *Laminaria* algae that are harvested from the ocean floor (Fig. 11-5). These come in different diameters, which allow the number and diameters of inserted devices, also called tents, to be customized to a given cervix. Another device is *Dilapan-S,* which is composed of an acrylic-based gel. Each type expands to an ultimate diameter three to four times that of its dry state.

With hygroscopic dilators, shallow insertion yields insufficient dilation or tent expulsion. Overly deep placement risks dislodgement into the uterine cavity. Once tents are inserted, several gauze sponges placed at the external os help prevent spontaneous tent expulsion. Patients can ambulate, void, or stool without limitation. The numbers of sponges and dilators inserted are carefully counted and recorded in the chart.

Schneider and coworkers (1991) described 21 cases in which women who had a hygroscopic dilator placed changed their minds. Of 17 women who chose to continue their pregnancy, 14 delivered at term, two delivered preterm, and one miscarried 2 weeks later. None suffered infection-related morbidity, including three untreated women with cervical cultures positive for *Chlamydia trachomatis*.

Instead, misoprostol is often used for cervical ripening. The typical dose is 400 μg administered sublingually, buccally, or

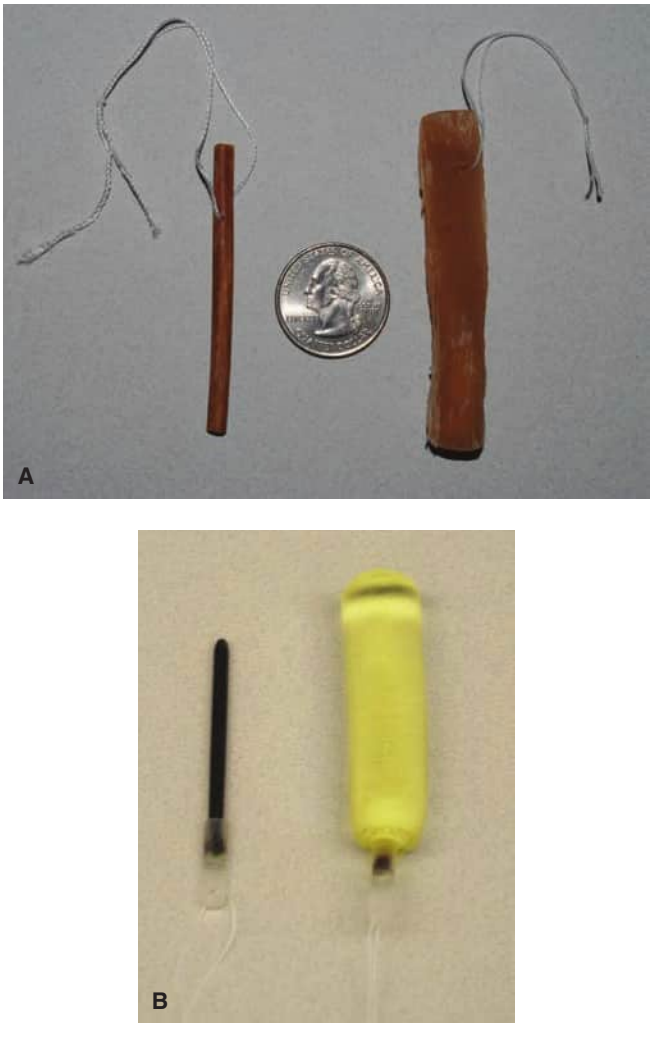


FIGURE 11-5 Hygroscopic dilators. With each type, the dry unit (*left*) expands exponentially when exposed to water (*right*) as in the endocervical canal. **A.** Laminaria. **B.** Dilapan-S.

placed into the posterior vaginal fornix at least 3 to 4 hours prior to surgery. Oral ingestion is less effective (Allen, 2016). Another option is a 200-mg oral mifepristone dose given 24 to 48 hours before surgery (Ashok, 2000). However, misoprostol is typically favored, because of mifepristone's greater delay to the procedure, cost, and limited access within the FDA's REMS program (p. 202).

Of options, hygroscopic dilators provide equal or slightly greater dilation than misoprostol. Other surgical parameters do not vary significantly (Bartz, 2013; MacIsaac, 1999). On balance, the ripening time required for hygroscopic dilators extends the total procedure time and can be uncomfortable, whereas misoprostol can cause fever, bleeding, and gastrointestinal side effects.

If not done as part of early prenatal care, hemoglobin level and Rh status are assessed prior to abortion. Screening for gonorrhea, for syphilis, and for human immunodeficiency virus, hepatitis B, and chlamydial infections also is completed. Obvious cervical infections are treated and resolved before elective procedures. To prevent postabortal infection after a first- or second-trimester surgical evacuation, a 200-mg oral prophylactic dose

of doxycycline is given 1 hour before. For those electing local anesthesia, evidence also supports adding an oral or intramuscular dose of a nonsteroidal antiinflammatory drug 30 to 60 minutes prior to surgery (Allen, 2018). Prophylaxis specifically for infective endocarditis prevention in those with valvular heart disease is not required in the absence of active infection (American College of Obstetricians and Gynecologists, 2020g,i). No recommendations specifically address venous thromboembolism prophylaxis for suction curettage in low-risk gravidas. At our hospital, we encourage early ambulation.

Vacuum Aspiration

Also called *suction curettage* or *suction dilation and curettage*, vacuum aspiration is a transcervical approach, in which the cervix is first dilated and tissue is then evacuated. For this, a rigid cannula is attached either to an electric-powered vacuum source or to a handheld 60-mL syringe for its vacuum source. These are *electric vacuum aspiration (EVA)* or *manual vacuum aspiration (MVA)*, respectively. *Sharp dilation and curettage (D & C)* in which contents are mechanically scraped out *solely* by a sharp curette is currently not recommended for pregnancy evacuation due to greater blood loss, pain, and procedural time (National Abortion Federation, 2020; World Health Organization, 2012). Importantly, this practice is distinguished from brief final sharp curettage following initial aspiration.

To begin, the surgeon performs a bimanual examination to confirm uterine size and orientation. A speculum is inserted, and the cervix is swabbed with povidone-iodine or equivalent solution. The anterior cervical lip is grasped with a toothed tenaculum. The cervix, vagina, and uterus are richly supplied by nerves of the Frankenhäuser plexus, which lies within connective tissue lateral to the uterosacral and cardinal ligaments. Thus, vacuum aspiration at minimum requires intravenously or orally administered sedatives or analgesics, and some add a paracervical or intracervical block (Allen, 2009; Renner, 2012). For a pudendal block, 5 mL of 1- or 2-percent lidocaine is injected into the uterosacral ligaments at their insertion into the uterus at 4 and 8 o'clock. Instead, an intracervical block with 5-mL aliquots of 1-percent lidocaine injected at 12, 3, 6, and 9 o'clock was reported to be equally effective (Mankowski, 2009). General or regional anesthesia may instead be elected.

First, a Sims uterine sound is passed into the uterus to measure the depth and inclination of the cavity. This provides parameters for subsequent instrument insertion. If required, the cervix is further dilated with Hegar, Hank, or Pratt dilators until a suction cannula can be inserted. As a rough rule, the degree of required cervical dilation in millimeters approximates gestational age. Hegar sizes reflect their diameter in millimeters. Pratt and Hank dilators are sized in French units, which can be converted to millimeters by dividing the French value by three.

With dilation, the fourth and fifth fingers of the introducing hand should rest on the perineum and buttocks as the instrument is guided through the internal os (Fig. 11-6). This technique minimizes forceful insertion and helps prevent uterine perforation.

Following dilation, for most first-trimester aspiration procedures, an 8- to 12-mm Karman cannula is appropriate. Small cannulas carry the risks of a longer surgery and of missed

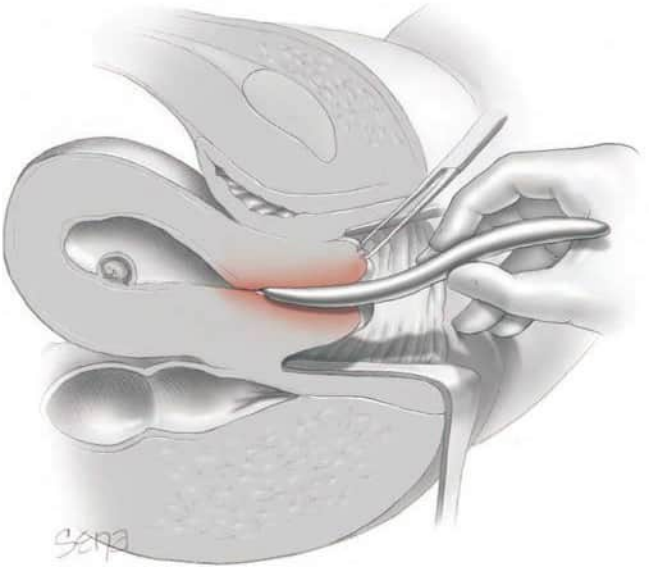


FIGURE 11-6 Dilation of cervix with a Hegar dilator. Note that the fourth and fifth fingers rest against the perineum and buttocks, lateral to the vagina. This maneuver is an important safety measure because if the cervix relaxes abruptly, these fingers prevent a sudden and uncontrolled thrust of the dilator, a common cause of uterine perforation.

intrauterine tissue. Large cannulas risk cervical injury and more discomfort. For evacuation, the cannula is slowly moved toward the fundus until resistance is met. Suction is then activated. The cannula is gradually pulled back toward the os and is simultaneously slowly turned circumferentially to cover the entire uterine cavity surface (Fig. 11-7). This is repeated until no more tissue is aspirated. A gentle sharp curettage can follow to remove any remaining tissue fragments (Fig. 11-8). Strong and consistent evidence supports the high efficacy, safety, and patient acceptability for both MVA and EVA (Lichtenberg, 2013).

For abortion done at ≤6 weeks' gestation, a distinct drawback is that the pregnancy may be small and missed by the curette. To identify placenta, the aspirated contents are rinsed in a strainer to remove blood, and then placed in a clear plastic container with saline and examined with back lighting (MacIsaac, 2000). Placental tissue macroscopically appears feathery. A magnifying lens, colposcope, or microscope can augment viewing. With gestations <6 weeks, the failed abortion rate approximates 2 percent (Paul, 2002). Thus, if products are not clearly identified, serial serum β-hCG levels can be informative (Dean, 2015).

Abortion Complications

Legally induced abortion in the United States has a low associated mortality rate, and from 2013 to 2017, the rate was 0.4 deaths in 100,000 procedures (Kortsmit, 2020). Early abortions are safer. The mortality rate was 0.3 deaths in 100,000 procedures performed ≤8 weeks' gestation but rose to 2.5 at 14 to 17 weeks and to 6.7 at ≥18 weeks (Zane, 2015). Notably, maternal mortality rates are 14-fold greater for pregnancies that are continued (Raymond, 2012).

Uterine perforation and lower-genital-tract laceration are uncommon but potentially serious, and rates also rise with

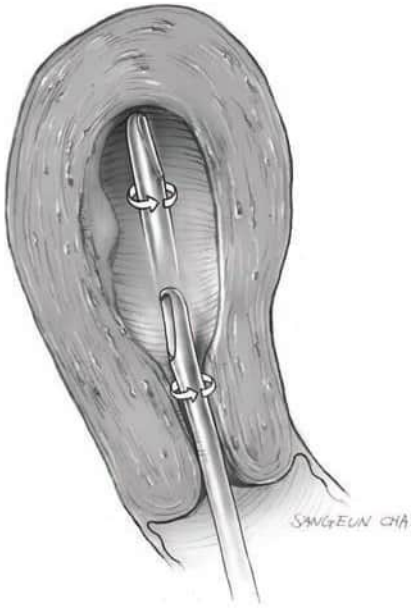


FIGURE 11-7 A suction curette has been placed through the cervix into the uterus. The figure shows the rotary motion used to aspirate the contents. (Figures 11-7 and 11-8: Reproduced with permission from Hoffman BL, Hamid CA, Corton MM: Surgeries for benign gynecologic disorders. In Hoffman BL, Schorge JO, Halvorson LM, et al (eds): Williams Gynecology, 4th ed. New York, McGraw Hill Education, 2020.)

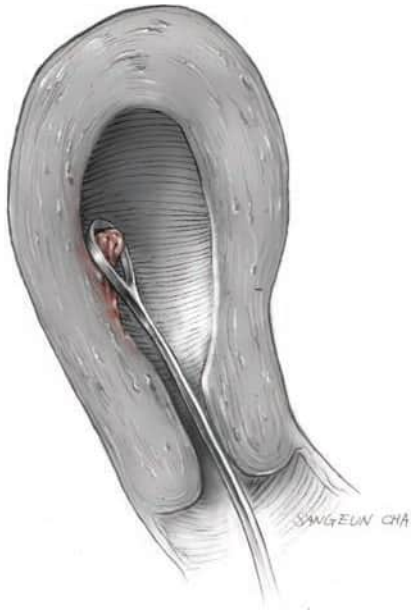


FIGURE 11-8 A sharp curette is advanced into the uterine cavity while the instrument is held with the thumb and forefinger as shown in Figure 11-6. Upon reaching the fundus, the curette is placed flush against the uterine wall. Firm pressure against the wall as the instrument is dragged out will scrape away adhered tissue fragments. With movement of the curette, only the strength of these two fingers should be used to help avoid perforation.

gestational age. In one systematic review of first-trimester abortion, the uterine perforation and laceration rates were each ≤1 percent (White, 2015). Perforation is usually recognized when the instrument passes without resistance deep into the pelvis. Risk factors include operator inexperience, prior cervical surgery or anomaly, adolescence, multiparity, and advanced gestational age (Allen, 2016; Grimes, 1984). If the uterine perforation is small and fundal, as when produced by a uterine sound or narrow dilator, observation for vital sign changes or uterine bleeding is usually sufficient.

If a suction cannula or sharp curette passes into the peritoneal cavity, considerable intraabdominal damage can ensue. Laparotomy or laparoscopy to thoroughly examine the abdominal contents is often the safest course. After potential injuries are resolved, intraoperatively, curettage can be completed under the direct guidance provided by laparoscopy or laparotomy (Owen, 2017).

Following curettage, uterine synechiae may form, and the risk of synechiae increases with procedure number. Most cases are mild and of unclear reproductive significance (Hooker, 2014). However, of Asherman syndrome cases, one series found that two thirds were linked to first-trimester curettage (Schenker, 1982).

Other first-trimester abortion complications are germane to both surgical and medication abortion techniques. First, hemorrhage with abortion is variably defined. One supported by the Society for Family Planning is bleeding that prompts a clinical response or bleeding in excess of 500 mL (Kerns, 2013). For first-trimester surgical abortions, hemorrhage complicates ≤1 percent (White, 2015). Atony, abnormal placentation, and coagulopathy are frequent sources, whereas surgical trauma is a rare cause. With medication abortion, bleeding is more common. In one study of more than 42,000 Finnish women undergoing pregnancy termination with pregnancies less 63 days, hemorrhage complicated 15 percent of medication abortion but only 2 percent of surgical cases (Niinimäki, 2009).

Infection is another risk. One review found a cumulative rate of 0.5 percent in those given prophylaxis compared with 2.6 percent in those given placebo (Achilles, 2011). In another review, the postoperative infection rate was <0.3 percent for either surgical or medication abortion (Upadhyay, 2015).

Incomplete abortion may require reevacuation. For medication abortion, this neared 5 percent in one systematic review (Raymond, 2013). Reaspiration rates following surgical abortion are typically <2 percent (Ireland, 2015; Niinimaki, 2009).

In sum, surgical abortion offers higher efficacy rates (96 to 100 percent) than medication abortion (83 to 98 percent) in the first trimester. Medication abortion also carries a greater cumulative risk of complications, although differences are small (Lichtenberg, 2013). These are balanced against the greater privacy of medication abortion and the more invasive steps of curettage.

■ Medication Abortion

Agents Used

For many women, outpatient medication abortion is an acceptable option for pregnancies with a menstrual age ≤70 days. Although suitable at later gestational ages, successful evacuation rates are lower.

Among abortions performed at ≤9 weeks' gestation, 39 percent were completed with medication in the United States

in 2018 (Kortsmit, 2020). One regimen provides mifepristone plus misoprostol, but another provides misoprostol alone. Of actions, mifepristone augments uterine contractility by reversing progesterone-induced myometrial quiescence. Misoprostol directly stimulates the myometrium. Both also ripen the cervix (Mahajan, 1997; Tang, 2007).

Contraindications have evolved from exclusion criteria that were used in clinical trials. Cautions include suspected ectopic pregnancy; in-situ intrauterine device; severe anemia, coagulopathy, or anticoagulant use; long-term systemic corticosteroid therapy; chronic adrenal failure; inherited porphyria; or allergy to agents used (American College of Obstetricians and Gynecologists, 2020c). Of note, misoprostol is suitable for early pregnancy failure in those with prior uterine surgery (Chen, 2008).

Misoprostol is a teratogen that is associated with transverse limb reduction or with the Mobius sequence, which is manifest by cranial nerve palsy. *Thus, a commitment to abortion completion is essential once this drug is given* (Vauzelle, 2013). With mifepristone, for women who choose to continue their pregnancies after exposure, the ongoing pregnancy rate ranges from 10 to 46 percent (Grossman, 2015). The associated major malformation rate was 5 percent in one series of 46 exposed pregnancies (Bernard, 2013).

Administration

Several dosing schemes are effective (Table 11-6). Because of its greater efficacy, mifepristone plus misoprostol combinations are favored. For gestations ≤70 days, the most widely accepted regimen is mifepristone, 200 mg given orally on day 0. This is followed in 24 to 48 hours by an 800-μg misoprostol dose that is administered vaginally, buccally, or sublingually (American College of Obstetricians and Gynecologists, 2020c). Oral ingestion has lower efficacy rates. If desired, mifepristone and misoprostol may be self-administered at home (Gambir, 2020). Associated infection rates approximate 0.3 percent, and antibiotic prophylaxis is not currently recommended (Achilles, 2011).

Symptoms following misoprostol are common within 3 hours and include vomiting, diarrhea, fever, and chills. Bleeding and cramping with medication abortion typically is significantly worse than that with menses. Thus, oral analgesics are provided. If bleeding soaks two or more pads in an hour for at least 2 hours, the woman is instructed to contact her provider.

Reappointment is 1 to 2 weeks following drug administration, and bimanual pelvic examination is recommended. Abortion completion may be assessed with β-hCG levels. Expected rates of decline at 1 week can be extrapolated from Table 11-1 and can guide care. However, specific β-hCG values lack suitable sensitivity (Rørbye, 2004). Moreover, routine postabortal sonographic examination is typically unnecessary (Clark, 2010). If done, it performs comparably to β-hCG level assessment (Dayananda, 2013). If sonography is done due to concern for failed abortion or for bleeding, unnecessary surgery can be avoided if scans are interpreted appropriately. If no gestational sac is seen and no heavy bleeding is noted, intervention is unnecessary. This is true even when, as is common, the uterus contains sonographically evident debris (Reeves, 2008).

TABLE 11-6. Various Regimens for Medical Termination of Pregnancy

First Trimester
Mifepristone/Misoprostol Mifepristone, 200 mg orally, and after 24 hr provide misoprostol[a] 800 μg
Misoprostol[a] Alone 800 μg and then may repeat every 3 hr for 3 total doses
Second Trimester
Mifepristone/Misoprostol Mifepristone, 200 mg orally, and after 24 hr provide misoprostol[a] 400 μg every 3 hr up to 5 total doses[b]
Misoprostol[a] Alone 400 μg every 3 hr up to 5 total doses[b]
Dinoprostone 20 mg vaginal suppository every 4 hr
Concentrated Oxytocin 50 units oxytocin in 500 mL of normal saline and infuse during 3 hr; then 1-hr diuresis (no oxytocin); then escalate sequentially in a similar fashion through 150, 200, 250, and finally 300 units oxytocin, each in 500 mL normal saline

[a]With misoprostol, efficacy is similar for vaginal, buccal, and sublingual routes, whereas oral ingestion is less effective.
[b]If abortion not completed by fifth dose, the cycle may be repeated following a 24-hour rest period.
American College of Obstetricians and Gynecologists, 2019f, 2020c; Raymond, 2019; Schreiber, 2018; Whitehouse, 2020; World Health Organization, 2018.

SECOND-TRIMESTER METHODS

In the second trimester, fetal anomaly or death, maternal health complications, inevitable abortion, or desired termination may be indications for uterine evacuation. As in the first trimester, medication or surgery is an option. In the second trimester, *dilation and evacuation (D & E)* rather than suction D & C is needed because of larger fetal size and bones.

Of options, D & E is a common means in the United States. Of all induced abortions in 2018, nearly 8 percent were performed by D & E at gestational ages >13 weeks (Kortsmit, 2020). Many of the surgical and medication steps for second-trimester abortion mirror those in the first trimester, and differences are emphasized here.

■ Dilation and Evacuation

Preparation

With D & E, wide mechanical cervical dilation is needed for evacuation of fetal parts. The degree needed rises with fetal gestational age, and inadequate dilation risks cervical trauma, uterine perforation, or tissue retention (Peterson, 1983). Thus, presurgical cervical preparation is advised, and main options include hygroscopic dilators or misoprostol (p. 209).

With laminaria, overnight preparation offers optimal cervical dilation (Fox, 2014). Uncommonly, laminaria may fail to adequately dilate the cervix, and serial insertions over several days with an increasing number of tents is an option. Dilapan-S also is suitable. It may be preferable for same-day procedures, as this device achieves its maximal effect in 4 to 6 hours (Newmann, 2014). Supplementing laminaria with mifepristone can aid procedures for gestations >19 weeks (Diedrich, 2020; Goldberg, 2015). In contrast, misoprostol supplementation to hygroscopic dilators failed to add benefits in one metaanalysis (Cahill, 2020).

If a patient changes abortion plans after hygroscopic dilator removal, preterm delivery and PPROM rates are substantial. In one series of 12 such cases, 50 percent ended with miscarriage or perinatal death (Mark, 2019).

Misoprostol alone can be used for cervical preparation. The typical dose is 400 μg given vaginally or buccally 3 to 4 hours prior to D & E. Randomized trial results vary regarding the ability of misoprostol to achieve results equal to that with hydroscopic dilators (Bartz, 2013; Goldberg, 2005; Sagiv, 2015). In women with one prior hysterotomy, the risk of uterine rupture was not elevated by misoprostol cervical ripening in one review but rose to 2.5 percent in those with ≥2 cesarean deliveries (Andrikopoulou, 2016).

With mifepristone alone for cervical ripening, fewer studies provide data. In one, mifepristone alone provided less dilation than hydroscopic dilators (Borgatta, 2012). In another trial, mifepristone given 48 hours before misoprostol created greater cervical dilation compared with misoprostol alone (Carbonell, 2007).

In sum, hygroscopic dilators soften and dilate the cervix before D & E. Sequential insertions or layering agents may be most helpful for later gestations or for an inadequate response to initial hygroscopic dilators alone. Yet, layering adds cost and potential side effects.

With elective abortion, some choose to induce fetal demise prior to D & E to avert a live birth. For this, an intracardiac potassium chloride or lidocaine injection or an intraamnionic or intrafetal digoxin injection is used prior to cervical ripening (Tufa, 2020).

Technique

During D & E, sonography can be used as an adjunct in all cases or selectively in more challenging ones. Perioperative antibiotic prophylaxis mirrors that for first-trimester procedures (p. 209). To reduce postprocedure bleeding, dilute vasopressin can be injected intracervically or as part of a paracervical block (Kerns, 2013; Schulz, 1985). Once adequate cervical dilation is achieved, the initial surgical step drains amnionic fluid with an 11- to 16-mm suction cannula or with amniotomy. This reduces the risk of amnionic fluid embolism and brings the fetus into the lower uterine segment for removal (Owen, 2017; Prager, 2009).

For pregnancies >16 weeks' gestation, the fetus is extracted, often in parts, using Sopher forceps or other destructive instruments. With complete removal of the fetus, a large-bore vacuum curette is used to remove the placenta.

Major complications are infrequent with D & E, and rates range from 1 to 2 percent in large series (Lederle, 2015; Peterson, 1983). These include uterine perforation, cervical laceration, uterine bleeding, and postabortal infection. Prior *cesarean delivery* is not a contraindication for D & E and may be preferred over prostaglandins for those with multiple prior hysterotomies (Ben-Ami, 2009).

Other Surgical Considerations

Placenta previa or the placenta accreta syndrome (PAS) can raise D & E risks. Once diagnosed, PAS typically prompts hysterectomy (Matsuzaki, 2015). For *placenta previa,* D & E is preferred to quickly evacuate the placenta, but the ability to transfuse blood products and perform possible hysterectomy must be available (American College of Obstetricians and Gynecologists, 2019f; Perriera, 2017). Medication abortion may be elected, but the risk for transfusion is greater than with D & E (Nakayama, 2007). Data are conflicting regarding the value of predelivery uterine artery embolization to lessen bleeding risks (Wang, 2019).

In some cases of failed second-trimester medication abortion, hysterotomy may be considered. In other cases, if comorbid uterine pathology is significant, such as numerous large myomas, hysterectomy may provide ideal treatment. Some women with second-trimester pregnancies desire sterilization following evacuation. Because the contracted uterine fundus will lie lower, any laparotomy incision must be placed to allow fallopian tube access.

■ Medication Abortion

Principal among noninvasive methods is a mifepristone plus misoprostol regimen or misoprostol alone (see Table 11-6). Of these two options, the combined regimen yields a shorter termination duration (Kapp, 2007; Ngoc, 2011). Hygroscopic dilators may speed the time to delivery with this combined regimen

(Mazouni, 2009; Vincienne, 2018). In selecting misoprostol routes, oral administration leads to a longer time to delivery compared with vaginal or sublingual routes (Dickinson, 2014). Prophylactic antibiotics are not typically given, and infection surveillance during labor is instead applied (Achilles, 2011).

Another induction agent, PGE_2, shows similar efficacy and side effects compared with misoprostol (Jain, 1994; Jansen, 2008). Simultaneous administration of an antiemetic such as metoclopramide (Reglan), an antipyretic such as acetaminophen, and an antidiarrheal such as diphenoxylate/atropine (Lomotil) will help prevent or treat symptoms. Dinoprostone (Prostin) is an available PGE_2 in the United States. However, its greater cost and poor pharmacologic stability at room temperature may make it less attractive than misoprostol.

During medication abortion, the uterine rupture rate is 0.4 percent with misoprostol and one prior low transverse cesarean delivery (Berghella, 2009). Both misoprostol and PGE_2 appear to pose similar risk (le Roux, 2001; Reichman, 2007). Few data guide their use for medication abortion in those with ≥2 prior cesarean deliveries.

Of other agents, high-dose intravenous oxytocin in saline will result in second-trimester abortion in 80 to 90 percent of cases (see Table 11-6). However, by comparison, misoprostol leads to higher successful induction rates and faster delivery times (Alavi, 2013).

Rarely used in the United States, ethacridine lactate is an organic antiseptic that activates myometrial mast cells to release prostaglandins (Olund, 1980). The solution is instilled either intraamnionically or extraovularly, that is, into the potential space between the uterine wall and amnion. Compared with misoprostol, it is associated with longer times to delivery and lower success rates (Hou, 2011).

Fetal and Placental Evaluation

For second-trimester pregnancies being terminated for maternal health or fetal indications, either D & E or medication abortion is suitable. Thus, patient input and clinical indication both guide selection. Perinatal palliative care can be instituted (p. 203) (Marc-Aurele, 2020).

Evaluation of a stillborn fetus is described in Chapter 35 (p. 626). One component is autopsy, which can also be valuable for second-trimester terminations due to anomalies (Hauerberg, 2012; Man, 2016). Fragmented D & E specimens may provide less information than intact fetuses (Lal, 2014).

ELECTIVE ABORTION CONSEQUENCES

Data relating abortion to overall maternal health and to subsequent pregnancy outcome are limited. Rates of infertility or ectopic pregnancy are not increased (Burkman, 1988; Frank, 1993). Exceptions may stem from postabortal infections, especially those caused by *C trachomatis*. Of subsequent adverse pregnancy outcomes, several studies note an approximate 1.5-fold greater incidence of preterm delivery following surgical evacuation (Lemmers, 2016; Saccone, 2016). This risk accrues with the number of terminations (Klemetti, 2012). Subsequent pregnancy outcomes are similar if a prior induced abortion was completed with medication or by surgery (Männistö, 2013; Virk, 2007).

POSTABORTAL CONTRACEPTION

After early abortion, woman may ovulate after 8 days, but the average is 3 weeks (Lahteenmaki, 1978; Stoddard, 2011). Unless another pregnancy is imminently desired, contraception, either hormonal or nonhormonal, can be started immediately after abortion (Curtis, 2016). In candidates, defined in Chapter 38 (p. 667), an intrauterine device can be inserted immediately after surgery or medication abortion is completed (Bednarek, 2011; Korjamo, 2017).

For women who desire another pregnancy, conception need not be delayed. From studies, groups conceiving within 3 months of a first-trimester loss had lower subsequent miscarriage rates compared with groups with later conceptions (Schliep, 2016).

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CHAPTER 12

Ectopic Pregnancy

Following fertilization and fallopian tube transit, the blastocyst normally implants in the endometrial lining of the uterine cavity. Implantation elsewhere is considered ectopic. In the United States, numbers from an insurance database and from Medicaid claims showed ectopic pregnancy rates of 1.54 percent and 1.38 percent, respectively, in 2013 (Tao, 2017). Ectopic implantation accounts for 3 percent of all pregnancy-related deaths (Creanga, 2017). Fortunately, beta-human chorionic gonadotropin (β-hCG) assays and transvaginal sonography (TVS) aid earlier diagnosis, maternal survival, and fertility conservation.

TUBAL PREGNANCY

Classification

Of ectopic pregnancies, nearly 95 percent implant in the fallopian tube's various segments (Fig. 2-13, p. 26). The ampulla (70 percent) is the most frequent site (Fig. 12-1). The rate for isthmic implantation is 12 percent; fimbrial, 11 percent; and interstitial, 2 percent (Bouyer, 2002). Nontubal ectopic pregnancies compose the remaining 5 percent and implant in the ovary, peritoneal cavity, cervix, or prior cesarean scar. Occasionally, a multifetal pregnancy contains one conceptus with normal uterine implantation and the other implanted ectopically. This is termed a *heterotopic pregnancy* (p. 231).

For all ectopic pregnancy sites, management is influenced by pregnancy viability, gestational age, maternal health, desires for

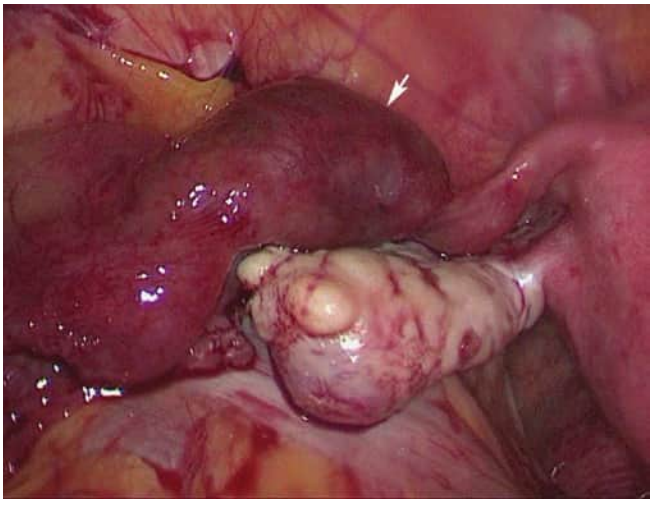


FIGURE 12-1 Ampullary tubal pregnancy (*arrow*) seen during laparoscopy. (Reproduced with permission from Dr. Lisa Chao.)

the index pregnancy and for future fertility, physician skill, and available resources. Regardless of location, D-negative women with an ectopic pregnancy are given anti-D immunoglobulin. In first-trimester pregnancies, a single intramuscular 50- or 120-μg dose is appropriate. Later gestations are given 300 μg (American College of Obstetricians and Gynecologists, 2019b).

Risks

Abnormal fallopian tube anatomy underlies most cases of tubal ectopic pregnancy. Surgeries for a prior tubal pregnancy, for fertility restoration, or for sterilization confer the highest risk. After one prior ectopic pregnancy, the chance of another nears 10 percent (de Bennetot, 2012). Previous tubal infection, which can distort normal tubal anatomy, is another risk. Specifically, one episode of salpingitis can be followed by a subsequent ectopic pregnancy in up to 9 percent of women (Westrom, 1992). Peritubal adhesions that form from salpingitis, appendicitis, or endometriosis also raise chances.

Infertility and the use of assisted reproductive technologies (ART) to overcome it are linked to increased ectopic pregnancy rates (Li, 2015; Perkins, 2015). Newer techniques aim to lower this rate with ART (Londra, 2015; Zhang, 2017). Smoking is another known association, although the underlying mechanism is unclear (Hyland, 2015). Last, with any form of contraception, the absolute number of ectopic pregnancies declines because pregnancy is effectively prevented. However, some methods more efficiently prevent intracavity implantation and with their failure, ectopic implantation is favored. These methods are tubal sterilization, intrauterine devices (IUDs), and progestin-only contraceptives.

Pathogenesis and Potential Outcomes

With tubal pregnancy, because the fallopian tube lacks a submucosal layer, the fertilized ovum promptly burrows through the epithelium. The zygote comes to lie near or within the muscularis, which is invaded by rapidly proliferating trophoblast. Potential outcomes from this include tubal rupture, tubal abortion, or pregnancy failure with resolution.

With rupture, the invading and expanding conceptus can tear the fallopian tube. Tubal ectopic pregnancies usually rupture spontaneously but may occasionally burst following coitus or bimanual examination. Hemorrhage usually persists and can become life threatening.

Tubal abortion describes the pregnancy's passage out the fallopian tube's distal end. Subsequently, hemorrhage may cease, and symptoms eventually disappear. However, bleeding instead can progress to induce symptoms as long as products remain in the tube. Blood slowly issues from the tubal fimbria into the peritoneal cavity and pools in the rectouterine cul-de-sac. If the fimbriated extremity is occluded, the fallopian tube may gradually distend with blood to form a hematosalpinx. Rarely, an aborted fetus will secondarily implant on a peritoneal surface and become an abdominal pregnancy (p. 231).

Last, *spontaneous failure* reflects ectopic pregnancy death and subsequent reabsorption. These are now more regularly identified by current sensitive β-hCG assays and surveillance.

Distinctions between *acute* ectopic pregnancy, just described, and *chronic* ectopic pregnancy also can be drawn. Acute ectopic pregnancies are more common, produce a high serum β-hCG level, and grow rapidly, leading to a timely diagnosis. These carry a greater risk of rupture (Barnhart, 2003c). With chronic ectopic pregnancy, abnormal trophoblasts die early, and thus serum β-hCG levels are negative or are low and static. Chronic ectopic pregnancies typically rupture late, if at all, but commonly form a persistent complex pelvic mass. This sonographic finding, rather than patient symptoms, often is the reason that prompts diagnostic surgery (Tempfer, 2019).

Clinical Manifestations

Sources of abdominal pain during pregnancy are extensive. Uterine conditions include miscarriage, infection, degenerating or enlarging leiomyomas, or round-ligament pain. Adnexal pain may reflect ectopic pregnancy or ovarian masses that are hemorrhagic, ruptured, or torsed. Appendicitis, renal stone, cystitis, and gastroenteritis are some nongynecological reasons for lower abdominal pain in early pregnancy. Thus, an initial urine β-hCG assay, urinalysis, and measure of hemoglobin or hematocrit are routine. A complete blood count (CBC) to assess the white blood cell count may be preferred if serious infection is a possible diagnosis. A positive urine pregnancy test result should prompt a serum β-hCG assay for those with pain or bleeding.

Before rupture, symptoms and signs of ectopic pregnancy are often subtle or absent. The classic triad is amenorrhea that is followed by pain and vaginal bleeding. With tubal rupture, lower abdominal and pelvic pain is usually severe and frequently described as sharp, stabbing, or tearing. Some degree of vaginal spotting or bleeding is reported by most women with tubal pregnancy. Although profuse vaginal bleeding suggests an incomplete abortion, such bleeding occasionally is seen with tubal gestations. Moreover, tubal pregnancy can lead to significant intraabdominal hemorrhage. Neck or shoulder pain, especially on inspiration, develops in women with diaphragmatic irritation from a sizable hemoperitoneum. Vertigo and syncope may reflect hemorrhage-related hypovolemia.

Of physical findings, abdominal palpation elicits tenderness. Bimanual pelvic examination may reveal a mass and tenderness, but this examination should be limited and gentle to avoid iatrogenic rupture. The uterus itself can be slightly enlarged due to hormonal stimulation. Responses to moderate bleeding include no change in vital signs, a slight rise in blood pressure, or a vasovagal response with bradycardia and hypotension. Blood pressure will fall and pulse will rise only if bleeding continues and hypovolemia becomes significant.

Of laboratory findings, hemoglobin or hematocrit readings may at first show only a slight reduction, even after substantive hemorrhage. Thus, after acute hemorrhage, a trending decline in hemoglobin or hematocrit levels over several hours is a more valuable index of blood loss than is the initial level. In approximately half of women with a ruptured ectopic pregnancy, varying degrees of leukocytosis may reach 30,000/μL.

Decidua is endometrium that is hormonally prepared for pregnancy. The degree to which the endometrium is converted with ectopic pregnancy varies. Thus, in addition to bleeding,

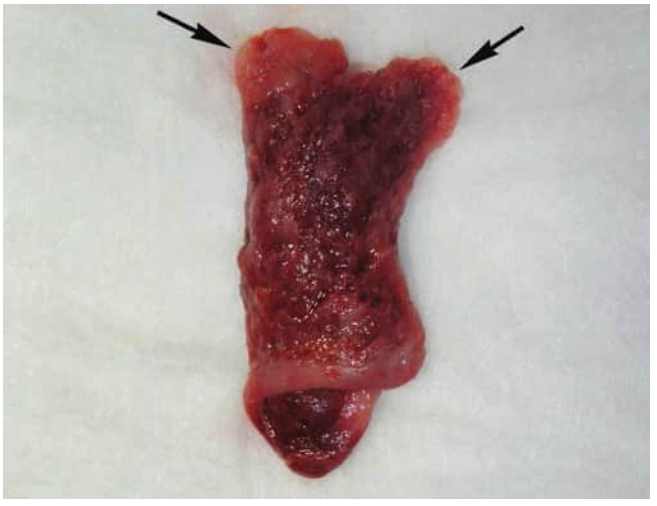


FIGURE 12-2 This 7-cm decidual cast was passed by a patient with a tubal ectopic pregnancy. The cast mirrors the shape of the endometrial cavity, and each arrow marks the portion of decidua that lined the cornua.

women with ectopic tubal pregnancy may pass a *decidual cast.* This is the entire sloughed endometrium that takes the form of the endometrial cavity (Fig. 12-2). Importantly, decidual sloughing may also occur with miscarriage. Thus, tissue is carefully examined by the provider and then submitted to evaluate for histological evidence of a conceptus. If no clear gestational sac is seen by inspection or if no villi are identified histologically, the possibility of ectopic pregnancy must still be considered.

TUBAL PREGNANCY DIAGNOSIS

For ectopic pregnancy, physical findings, serum β-hCG level measurement, TVS, and at times diagnostic surgery are tools for diagnosis. Women with evidence of tubal rupture undergo prompt surgery. For all other hemodynamically stable women without a clearly identified pregnancy, diagnostic strategies use these tools to identify ectopic pregnancy.

Strategies involve trade-offs. Those that maximize ectopic pregnancy detection may terminate a normal intrauterine pregnancy (IUP). Conversely, those that reduce the potential interruption of a normal IUP can delay ectopic pregnancy diagnosis. Patient desires for the index pregnancy are sought and influence these trade-offs.

■ Beta-Human Chorionic Gonadotropin

Rapid and accurate determination of pregnancy is a fundamental step. hCG is a glycoprotein produced by placental trophoblast and can be detected in serum in early pregnancy. Current pregnancy tests are immunoassays that seek the beta subunit of hCG. Lower limits of detection are 20 to 25 mIU/mL for urine and ≤5 mIU/mL for serum (Greene, 2015). Different assays can have results that vary by 5 to 10 percent. Thus, serial values are more reliable when performed by the same laboratory (Desai, 2014).

For women with a positive pregnancy test result plus bleeding or pain, an initial TVS is typically performed to locate the gestation. The initial β-hCG level sets expectations for anticipated TVS finding. With values above a discriminatory threshold, a normal IUP is expected to be seen within the uterus. Some institutions set their discriminatory threshold at ≥1500 mIU/mL, whereas others use ≥2000 mIU/mL. Connolly and associates (2013) suggested an even higher threshold. They noted that with live IUPs, a gestational sac was seen 99 percent of the time in those with a discriminatory level >3510 mIU/mL.

■ Transvaginal Sonography

Pregnancy of Unknown Location

If a yolk sac, embryo, or fetus is found within the uterus or within the adnexa, a diagnosis is made. However, if no evidence of an IUP is seen with TVS, the diagnosis is a *pregnancy of unknown location (PUL).* Most PULs reflect: (1) a failing IUP, (2) recent completed abortion, (3) early IUP, or (4) ectopic pregnancy.

Without clear evidence for ectopic pregnancy, serial β-hCG level assessment is reasonable, and a second level is obtained 48 hours after the first. This practice averts unnecessary methotrexate therapy and avoids harming an early, normal IUP.

With early, normal IUPs, Barnhart and coworkers (2004b) reported a 53-percent minimum rise over 48 hours. Seeber and colleagues (2006) found an even more conservative minimal 35-percent rise in normal IUPs. With multifetal gestation, this same anticipated rate of rise is expected (Chung, 2006).

With a PUL ultimately diagnosed as a failed IUP, a pattern of β-hCG level decline also can be anticipated, and levels drop rapidly (Table 11-1, p. 202) (Barnhart, 2004a). Sometimes, PULs fail before their location is identified. With failing PULs, Butts and coworkers (2013) found rates of decline that ranged from 35 to 50 percent at 48 hours and 66 to 87 percent at 7 days for starting hCG values between 250 and 5000 mIU/mL.

Despite these benchmarks, a third of women with an ectopic pregnancy can also have a 53-percent rise at 48 hours (Silva, 2006). Overall, approximately half of ectopic pregnancies show declining β-hCG levels, whereas the other half have rising levels. Importantly, despite a declining β-hCG level, a resolving ectopic pregnancy may rupture. Rupture at low values likely reflects partial disruption of the vascular connection between trophoblast and maternal vessels. Here, although β-hCG is produced, it is unable to enter circulation and be detected.

After the initial two β-hCG tests during PUL assessment, additional levels are drawn every 2 to 7 days. In general, testing is typically more frequent if symptoms or β-hCG level trends reflect a higher ectopic pregnancy risk (American College of Obstetricians and Gynecologists, 2019c). TVS also may be repeated. This serial assessment to reach a diagnosis is balanced against the rupture risk if the pregnancy is indeed ectopic. Dilation and curettage (D & C) is an option (Barnhart, 2021). It may give a faster diagnosis but may interrupt a normal IUP. Before curettage, a second TVS examination may be indicated and may display new informative findings.

As noted, ectopic pregnancies can rupture even at low β-hCG levels. Thus, serum β-hCG values are usually followed until they lie below the negative-result threshold for the given assay.

Endometrial Findings

In a woman in whom ectopic pregnancy is suspected, TVS is performed to look for findings indicative of an IUP or ectopic

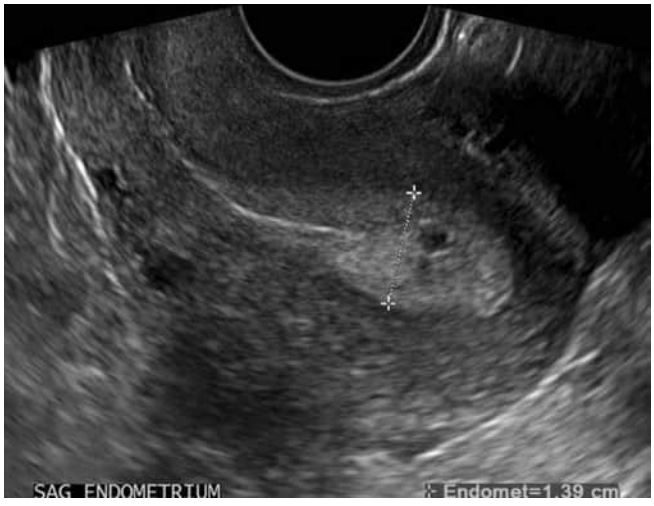


FIGURE 12-3 Transvaginal sonography of a pseudogestational sac within the endometrial cavity. Its central location is characteristic of these anechoic fluid collections. The endometrium is marked by calipers, and distal to this fluid, the endometrial thickness has a trilaminar pattern. This pattern is common with ectopic pregnancy. (Reproduced with permission from Jason McWhirt, ARDMS.)

pregnancy. During endometrial cavity evaluation, an intrauterine gestational sac is usually visible between 4½ and 5 weeks. The yolk sac appears between 5 and 6 weeks, and a fetal pole with cardiac activity is first detected at 5½ to 6 weeks (Fig. 14-1, p. 248). With transabdominal sonography, these structures are visualized slightly later.

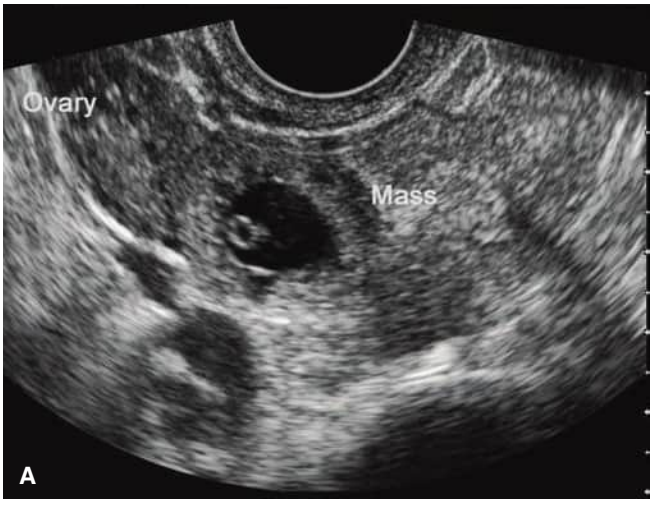
In contrast, with ectopic pregnancy, a trilaminar endometrial pattern is characteristic (Fig. 12-3). Its specificity is 94 percent, but with a sensitivity of only 38 percent (Hammoud, 2005). In addition, Moschos and Twickler (2008) determined in women with a PUL at presentation that no normal IUPs had an endometrial stripe thickness <8 mm.

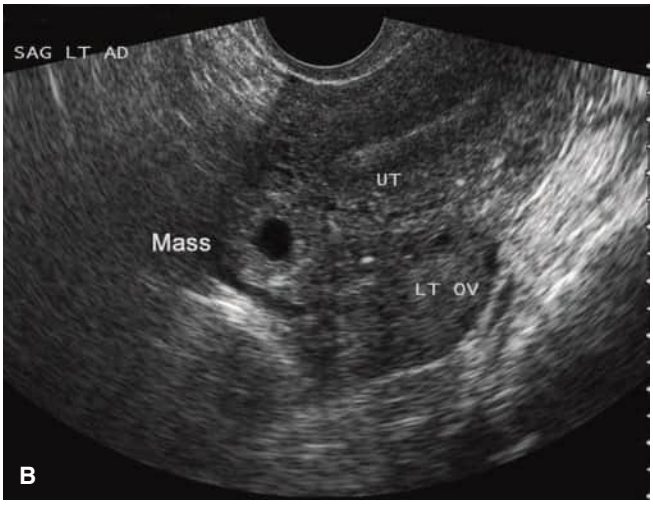
Anechoic fluid collections, which might normally suggest an early intrauterine gestational sac, may also be seen with ectopic pregnancy. These include pseudogestational sac and decidual cyst. First, a pseudosac is a fluid collection between the endometrial layers and conforms to the cavity shape (see Fig. 12-3). If a pseudosac is noted, the risk of ectopic pregnancy is increased (Hill, 1990). Second, a decidual cyst is identified as an anechoic area lying within the endometrium but remote from the canal and often at the endometrial–myometrial border. This may represent early decidual breakdown that precedes cast formation (Ackerman, 1993b).

These two findings contrast with the intradecidual sign seen with IUPs. With this sign, the early gestational sac is an anechoic sac eccentrically located within one of the endometrial stripe layers (Dashefsky, 1988). The American College of Obstetricians and Gynecologists (2020) advises caution in diagnosing an IUP if a definite yolk sac or embryo is not seen.

Adnexal Findings

The sonographic diagnosis of ectopic pregnancy rests on seeing an adnexal mass separate from the ovary (Fig. 12-4). If an extrauterine yolk sac, embryo, or fetus is identified, ectopic





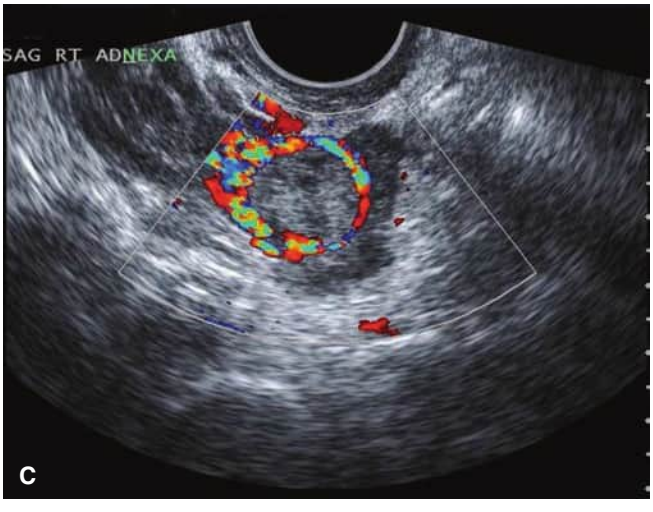


FIGURE 12-4 Various transvaginal sonographic findings with ectopic tubal pregnancies. For sonographic diagnosis, an ectopic mass should be seen in the adnexa separate from the ovary and may be seen as: **(A)** a yolk sac (shown here) and/or fetal pole with or without cardiac activity within an extrauterine sac, **(B)** an empty extrauterine sac with a hyperechoic ring, or **(C)** an inhomogeneous adnexal mass. In this last image, color Doppler shows a classic "ring of fire," which reflects increased vascularity typical of ectopic pregnancies. LT OV = left ovary; SAG LT AD = sagittal left adnexal; UT = uterus.

pregnancy is clearly confirmed. In other cases, a hyperechoic halo or tubal ring surrounding an anechoic gestational sac is seen. Alternatively, hemorrhage within the ectopic pregnancy can form a solid, complex adnexal mass. Overall, 60 percent of ectopic pregnancies are a complex mass; 20 percent are a hyperechoic ring; and 13 percent have an obvious gestational sac with a yolk sac or embryo (Condous, 2005). Importantly, not all adnexal masses represent an ectopic pregnancy. In this case, integration of sonographic findings with other clinical information is necessary.

Placental blood flow within the periphery of the complex adnexal mass—the *ring of fire*—can be seen with application of color Doppler. A corpus luteum cyst often displays a similar vascular pattern, and differentiation can be challenging.

Hemoperitoneum

In affected women, blood in the peritoneal cavity is most often identified using TVS (Fig. 12-5). A small amount of peritoneal fluid is physiologically normal. However, with hemoperitoneum, anechoic or hypoechoic fluid initially collects in the dependent retrouterine cul-de-sac. It then additionally surrounds the uterus as blood fills the pelvis. With significant intraabdominal hemorrhage, blood will track up the pericolic gutters to fill Morison pouch near the liver. Free fluid in this pouch typically is not seen until accumulated volumes reach 400 to 600 mL (Branney, 1995; Rodgerson, 2001). Diagnostically, peritoneal fluid in conjunction with an adnexal mass and a positive pregnancy test result are highly predictive of ectopic pregnancy (Nyberg, 1991). Ascites from cancer is a notable mimic.

If sonography is unavailable, culdocentesis is a simple technique and was used commonly in the past. The cervix is pulled outward and upward toward the symphysis with a tenaculum, and a long, 18-gauge needle is inserted through the posterior vaginal fornix into the retrouterine cul-de-sac. If present, fluid can be aspirated. However, no fluid is interpreted only as unsatisfactory entry into the cul-de-sac. Bloody fluid or fluid with old clot fragments suggests hemoperitoneum. If the blood sample clots, it may reflect an adjacent blood vessel puncture or brisk bleeding from ectopic pregnancy rupture.

Serum Progesterone

Although not our practice, this hormone is used by some to aid ectopic pregnancy diagnosis when serum β-hCG levels and TVS findings are inconclusive (Stovall, 1992). A single value is sufficient. From studies, a serum progesterone level <6 ng/mL (<20 nmol/L) has a pooled specificity of 98 percent to predict a nonviable pregnancy in women with a PUL (Verhaegen, 2012). A value >25 ng/mL suggests a live IUP and excludes ectopic pregnancy with 97-percent sensitivity (Carson, 1993). With most ectopic pregnancies, progesterone levels range between 10 and 25 ng/mL and thus have limited diagnostic utility (American College of Obstetricians and Gynecologists, 2019c). Serum progesterone levels can be used to buttress a clinical impression, but again they cannot reliably identify location (Guha, 2014).

Endometrial Sampling

Several endometrial changes accompany ectopic pregnancy, and all lack coexistent chorionic villi. Decidual reaction is found in 42 percent of samples, secretory endometrium in 22 percent, and proliferative endometrium in 12 percent (Lopez, 1994). Some recommend that lack of chorionic villi be confirmed by D & C before methotrexate treatment is given. Chung and associates (2011) found that the presumptive diagnosis of ectopic pregnancy is inaccurate in 27 percent of cases without histological exclusion of a spontaneous pregnancy loss. Nevertheless, the risks of D & C are weighed against the limited maternal risks of methotrexate.

Endometrial biopsy with a Pipelle catheter or endometrial aspiration was studied as an alternative to surgical curettage and found inferior (Barnhart, 2003b; Insogna, 2017). Instead, frozen section of curettage fragments to identify products of conception is accurate in 95 percent of cases (Li, 2014).

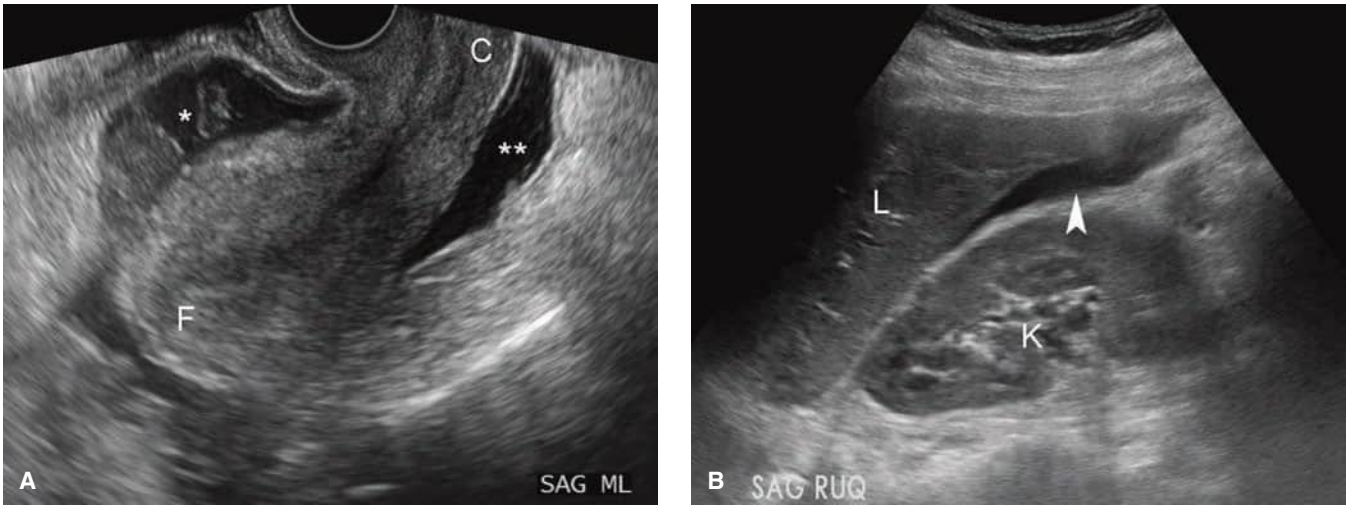


FIGURE 12-5 Hemoperitoneum. **A.** This transvaginal sagittal view of the pelvis shows anechoic fluid initially pooling in the retrouterine cul-de-sac (**). Large accumulations will also extend into the anterior cul-de-sac (*). **B.** In this right upper quadrant sonogram, anechoic fluid is seen in Morison pouch (*arrowhead*). C = cervix; F = fundus; K = kidney; L = liver. (Reproduced with permission from Dr. Devin Macias.)

Laparoscopy

Direct visualization of the fallopian tubes and pelvis by laparoscopy offers a reliable diagnosis in most cases of suspected ectopic pregnancy. This also permits a ready transition to definitive operative therapy, which is discussed subsequently.

MEDICAL MANAGEMENT

Regimen Options

For most ectopic pregnancies, medical therapy is preferred, if feasible, to avoid surgical risks. Disqualifying criteria are a ruptured fallopian tube and drug contraindications. Other considerations include reasonably close access to emergency care and a commitment to surveillance laboratory testing.

Medical therapy traditionally involves the antimetabolite methotrexate (MTX). This drug is a folic acid antagonist. It tightly binds to dihydrofolate reductase, blocking the reduction of dihydrofolate to tetrahydrofolate, which is the active form of folic acid. As a result, de novo purine and pyrimidine production is halted, which then arrests DNA, RNA, and protein synthesis. Thus, MTX is highly effective against rapidly proliferating trophoblast. However, gastrointestinal mucosa, bone marrow, and respiratory epithelium also can be harmed.

To help select suitable candidates, laboratory tests are obtained. First, MTX is renally cleared, and significant renal dysfunction, reflected by an elevated serum creatinine level, precludes its use. Second, MTX can be hepato- and myelotoxic, and CBC and liver function tests (LFTs) help establish a baseline. Last, blood type and Rh status are determined. All except blood typing are considered surveillance laboratory tests and are repeated prior to additional MTX doses.

With administration, women are counseled to avoid several aggravating agents until treatment is completed. These are: (1) folic acid-containing supplements, which can competitively reduce MTX binding to dihydrofolate reductase; (2) nonsteroidal antiinflammatory drugs, which reduce renal blood flow and delay drug excretion; (3) alcohol, which can predispose to concurrent hepatic enzyme elevation; (4) sunlight, which can provoke MTX-related dermatitis; and (5) sexual activity, which can rupture the ectopic pregnancy (American College of Obstetricians and Gynecologists, 2019c).

MTX is a potent teratogen, and MTX embryopathy is notable for craniofacial and skeletal abnormalities and fetal-growth restriction (Nurmohamed, 2011). MTX is excreted into breast milk and may accumulate in neonatal tissues and interfere with neonatal cellular metabolism (American Academy of Pediatrics, 2001; Briggs, 2017). Based on all these findings, a list of contraindications and pretherapy laboratory testing is found in Table 12-1.

For ease and efficacy, intramuscular MTX administration is used most often for ectopic pregnancy treatment, and single-dose and multidose MTX protocols are available. With single-dose therapy, the dose is 50 mg/m^2 body surface area (BSA), and BSA can be derived using various Internet-based BSA calculators. At our institution, patients are observed for 30 minutes following MTX injection to exclude an adverse reaction.

With the multidose regimen, leucovorin is added to blunt MTX toxicity. Leucovorin is *folinic acid* and has folic acid activity. Thus, it allows some purine and pyrimidine synthesis to buffer side effects.

Comparing these two protocols, trade-offs are recognized. Single-dose therapy offers simplicity, less expense, and less intensive posttherapy monitoring. However, some but not all studies report a higher success rate for the multidose regimen (Barnhart, 2003a; Lipscomb, 2005; Tabatabaii, 2012). Overall, ectopic tubal pregnancy resolution rates approximate 90 percent with MTX use. At our institution, we use single-dose MTX.

TABLE 12-1. Medical Treatment Protocols for Ectopic Pregnancy

	Single Dose	Multidose
Dosing	One dose; repeat if necessary	Up to four doses of both drugs until serum β-hCG declines by 15%
Medication Dosage		
Methotrexate	50 mg/m^2 BSA (day 1)	1 mg/kg, days 1, 3, 5, and 7
Leucovorin	NA	0.1 mg/kg days 2, 4, 6, and 8
Serum β-hCG level	Days 1 (baseline), 4, and 7	Days 1 (baseline), 3, 5, and 7
Indication for additional dose	If serum β-hCG level does not decline by 15% from day 4 to day 7 Less than 15% decline during weekly surveillance	If serum β-hCG level declines <15%, give additional dose; repeat serum β-hCG in 48 hours and compare with previous value; maximum four doses
Surveillance	Once 15% decline achieved, then weekly serum β-hCG levels until undetectable	
Methotrexate Contraindications		
MTX sensitivity	Intrauterine pregnancy	Immunodeficiency
Tubal rupture	Peptic ulcer disease	Hepatic, renal, or hematologic dysfunction
Breastfeeding	Active pulmonary disease	

BSA = body surface area; β-hCG = β-human chorionic gonadotropin; MTX = methotrexate; NA = not applicable.
From American College of Obstetricians and Gynecologists, 2019c; American Society for Reproductive Medicine, 2013.

Patient Selection

The best candidate for medical therapy is the woman who is asymptomatic, motivated, and compliant. With medical therapy, some classic predictors of success include a low initial serum β-hCG level, small ectopic pregnancy size, and absent fetal cardiac activity. Of these, initial serum β-hCG level is the best prognostic indicator with single-dose MTX. Reported failure rates are 1.5 percent if the initial serum β-hCG concentration is <1000 mIU/mL; 5.6 percent at 1000 to 2000 mIU/mL; 3.8 percent at 2000 to 5000 mIU/mL; and 14.3 percent for levels between 5000 and 10,000 mIU/mL (Menon, 2007).

Many early trials also used large size as an exclusion criterion. Lipscomb and colleagues (1998) reported a 93-percent success rate with single-dose MTX when the ectopic mass was ≤3.5 cm. This compared with success rates between 87 and 90 percent when the mass was >3.5 cm. These authors also found ectopic pregnancies measuring ≤4 cm and lacking cardiac activity to be suitable candidates. Failure rates rise if cardiac activity is seen, with an 87-percent success rate in such cases.

Side Effects

These regimens are associated with minimal laboratory changes and symptoms, but rarely toxicity may be severe. Kooi and Kock (1992) reviewed 16 studies and reported that adverse effects were resolved by 3 to 4 days after MTX was discontinued. The most frequent were liver involvement—12 percent; stomatitis—6 percent; and gastroenteritis—1 percent. One woman had bone marrow depression. More commonly, 65 to 75 percent of women given MTX will have increasing pain beginning several days after therapy. Thought to reflect separation of the ectopic pregnancy from the tubal wall, this pain generally is mild and relieved by analgesics. In a series of 258 women treated with MTX by Lipscomb and colleagues (1999), 20 percent had pain that merited evaluation in a clinic or emergency department to exclude tubal rupture.

Long term, MTX treatment does not diminish ovarian reserve (Ohannessian, 2014). However, after successful MTX therapy, pregnancy is ideally delayed for at least 3 months, because this drug may persist in human tissues for months after a single dose (Hackmon, 2011). Although data are very limited, conception before this waiting period appears reassuring. In one study, 45 women who conceived <6 months after MTX had similar pregnancy outcomes compared with 80 women who conceived >6 months after MTX (Svirsky, 2009).

Surveillance

As shown in Table 12-1, monitoring single-dose therapy calls for serum β-hCG determinations at days 4 and 7 following initial MTX injection on day 1. After single-dose MTX, mean serum β-hCG levels may rise or fall during the first 4 days and then should gradually decline. If the level fails to drop by ≥15 percent between days 4 and 7, a second MTX dose is recommended. This is necessary in 20 percent of women treated with single-dose therapy (Cohen, 2014). In such cases, a CBC, creatinine level, and LFTs are rechecked. If these surveillance tests are normal, a second equivalent dose is administered. The date of this second injection will become the new day 1, and the protocol is restarted.

Multidose therapy provides MTX (1 mg/kg) treatment with leucovorin (0.1 mg/kg) therapy on alternating days. After this first pair of injections, a serum β-hCG concentration is obtained. Values between days 1 and 3 are anticipated to drop by ≥15 percent. If not and if surveillance tests are normal, an additional MTX/leucovorin pair is given. A serum β-hCG level is repeated 2 days later. Up to four doses may be given if required (Stovall, 1991).

With either dosing regimen, once a decline ≥15 percent is achieved, weekly serum β-hCG level testing then begins until values are undetectable. Lipscomb and colleagues (1998) used single-dose MTX to successfully treat 287 women and reported that the average time to resolution—defined as a serum β-hCG level <15 mIU/mL—was 34 days. The longest time was 109 days.

SURGICAL MANAGEMENT

Options

Before surgery, future fertility desires are discussed. In women desiring sterilization, the unaffected tube can be ligated or removed. This is done concurrently with salpingectomy for the ectopic-containing tube.

Laparoscopy is the preferred surgical approach for ectopic pregnancy unless a woman is hemodynamically unstable. This is supported first by comparable subsequent uterine pregnancy rates and tubal patency rates in those undergoing salpingostomy completed either by laparoscopy or by laparotomy (Hajenius, 2007). Second, laparoscopy has lower infection, adhesion, and thromboembolism risks and faster recovery times than laparotomy. Moreover, as experience has accrued, cases previously managed by laparotomy—for example, those with hemoperitoneum—can safely be managed laparoscopically by those with suitable expertise. However, the lowered venous return and cardiac output associated with pneumoperitoneum must be factored into the selection of minimally invasive surgery for a hypovolemic woman.

Two procedures—salpingostomy or salpingectomy—are options. In the past, some favored salpingostomy to preserve future fertility. However, two randomized trials compared laparoscopic outcomes between the two procedures in women with a normal contralateral fallopian tube. The European Surgery in Ectopic Pregnancy (ESEP) study randomized 231 women to salpingectomy and 215 to salpingostomy. After surgery, the subsequent cumulative rates of ongoing pregnancy by natural conception did not differ significantly between groups—56 versus 61 percent, respectively (Mol, 2014). Again, in the DEMETER trial, the subsequent 2-year rate for achieving an IUP did not differ between groups—64 versus 70 percent, respectively (Fernandez, 2013). However, for women with an *abnormal-appearing* contralateral tube, salpingostomy of the ectopic-containing tube may be preferred if feasible to help preserve fertility.

Of the two procedures, salpingectomy may be used for both ruptured and unruptured ectopic pregnancies. With one

laparoscopic technique, the affected fallopian tube is lifted and held with atraumatic grasping forceps. One of several suitable bipolar grasping devices is placed across the fallopian tube at the uterotubal junction. Once desiccated, the tube is cut from its uterine attachment. The bipolar device is then advanced across the mesosalpinx to free the entire tube.

Salpingostomy is typically used to remove a small unruptured pregnancy. A 10- to 15-mm linear incision is made on the antimesenteric border of the fallopian tube and over the pregnancy. The products usually will extrude from the incision. These can be carefully extracted or can be flushed out using high-pressure irrigation that more thoroughly removes the trophoblastic tissue. Small bleeding sites are controlled with needlepoint electrosurgical coagulation, and the incision is left unsutured to heal by secondary intention (Tulandi, 1991). With either procedure and after specimen removal, the pelvis and abdomen are irrigated and suctioned free of blood and tissue debris to remove all trophoblastic tissue.

■ Persistent Trophoblast

After trophoblast removal during surgery, β-hCG levels usually fall quickly. Persistent trophoblast is rare following salpingectomy but complicates 5 to 15 percent of salpingostomy cases (Pouly, 1986; Seifer, 1993). Incomplete trophoblast removal can be identified by stable or rising β-hCG levels (Hajenius, 1995). Monitoring approaches are not codified. Weekly measures are reasonable following salpingostomy (Mol, 2008). Following uncomplicated salpingectomy, we do not repeat β-hCG levels in women without pain or symptoms of hemoperitoneum.

With stable or increasing β-hCG levels, additional surgical or medical therapy is necessary. In those without evidence for tubal rupture, standard therapy for persistent trophoblast is single-dose MTX, 50 mg/m^2 × BSA. Tubal rupture and bleeding require a second surgery.

■ Medical versus Surgical Therapy

Of options, multidose MTX treatment and laparoscopic salpingostomy have been compared in one randomized trial of 100 patients. The authors found no differences for rates of tubal preservation, primary treatment success, and subsequent fertility (Dias Pereira, 1999; Hajenius, 1997).

For single-dose MTX, its efficacy compared with laparoscopic salpingostomy shows conflicting results. In one randomized trial, single-dose MTX was less successful in pregnancy resolution, whereas in the other, single-dose MTX was equally effective (Saraj, 1998; Sowter, 2001). Krag Moeller and associates (2009) reported during a median surveillance period of 8.6 years that ectopic-resolution success rates and cumulative spontaneous IUP rates were not significantly different between those managed by laparoscopic salpingostomy and those treated with single-dose MTX.

Salpingectomy effectively removes the entire conceptus and yields high resolution rates. It thus outperforms MTX in this regard. Yet, when future fertility and ectopic pregnancy recurrence rates are analyzed, both salpingectomy and MTX therapy show comparable results (de Bennetot, 2012; Irani, 2017). In another study, surgery, MTX, or expectant management all yielded statistically similar subsequent spontaneous IUP rates (Demirdag, 2017).

In sum, medical or surgical management offer similar outcomes in women who are hemodynamically stable, have serum β-hCG concentrations <5000 mIU/mL, and have a small pregnancy with no cardiac activity. Despite lower success rates with medical therapy for women with larger tubal size, higher serum β-hCG levels, and fetal cardiac activity, medical management can be offered to the motivated woman who understands the risks of emergency surgery in the event of treatment failure.

■ Expectant Management

In select asymptomatic women, observation of a very early tubal pregnancy that is associated with stable or falling serum β-hCG levels is reasonable. A commitment to surveillance visits and relative proximity to emergency care are other safeguards. Importantly, this differs from expectant management of a PUL during its evaluation.

Predictive factors for success include a low initial serum β-hCG concentration, a significant drop in levels over 48 hours, and a sonographic inhomogeneous mass rather than a tubal halo or other gestational structures. For example, initial values <175 mIU/mL predict spontaneous resolution in 88 to 96 percent of attempts (Elson, 2004; Kirk, 2011). Initial values <1000 mIU/mL have success rates ranging from 71 to 92 percent (Jurkovic, 2017; Mavrelos, 2013; Silva, 2015).

With expectant management, subsequent rates of tubal patency and intrauterine pregnancy are comparable with surgery (Helmy, 2007). That said, compared with the established safety of medical or surgical therapy, the prolonged surveillance and risks of tubal rupture support the practice of expectant therapy only in appropriately selected and counseled women.

INTERSTITIAL PREGNANCY

■ Diagnosis

An interstitial pregnancy is one that implants within the tubal segment that lies within the muscular uterine wall (Fig. 12-6). Incorrectly, they may be called cornual pregnancies, but this term describes a conception that develops in the rudimentary horn of a uterus with a müllerian anomaly. Risk factors are similar to others discussed for tubal ectopic pregnancy, although previous ipsilateral salpingectomy is a specific one for interstitial pregnancy (Lau, 1999). Undiagnosed interstitial pregnancies usually rupture following 8 to 16 weeks of amenorrhea, which is later than for more distal tubal pregnancies. The myometrium covering the interstitial fallopian tube segment permits greater distention before rupture. Because of the proximity of these pregnancies to the uterine and ovarian arteries, hemorrhage can be severe and associated with mortality rates as high as 2.5 percent (Tulandi, 2004).

In many cases, these pregnancies are identified early, but diagnosis can still be challenging. These pregnancies sonographically

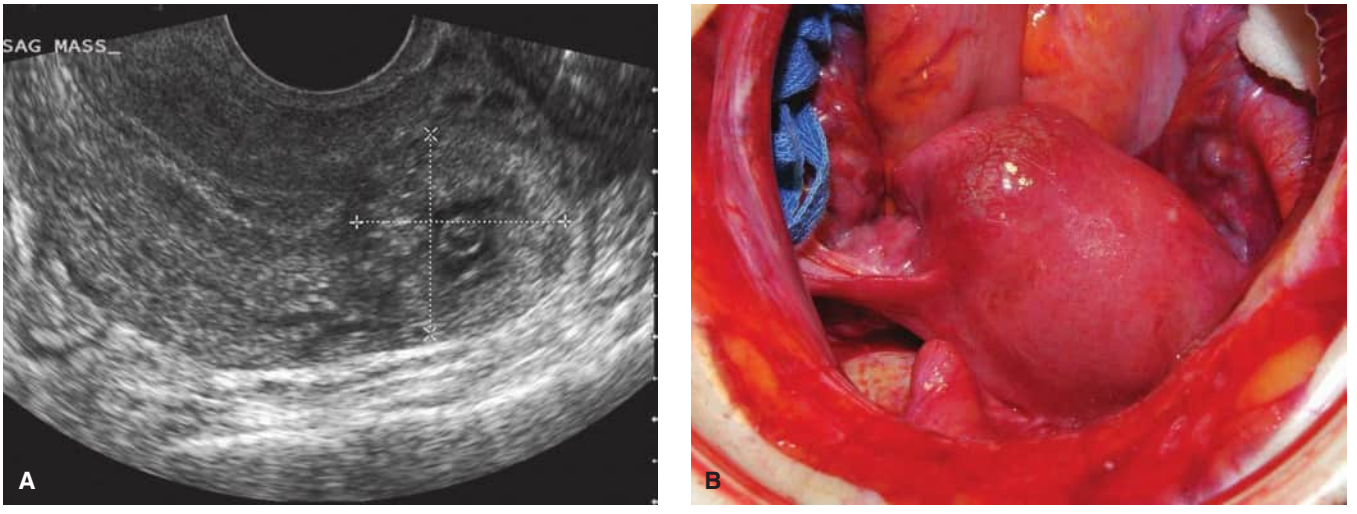


FIGURE 12-6 Interstitial ectopic pregnancy. **A.** This parasagittal view using transvaginal sonography shows an empty uterine cavity and a mass that is cephalad and lateral to the uterine fundus (*calipers*). **B.** Intraoperative photograph during laparotomy and before cornual resection of the same ectopic pregnancy. In this frontal view, the bulging right-sided interstitial ectopic pregnancy is lateral to the round ligament insertion and medial to the isthmic portion of the fallopian tube. (Reproduced with permission from Drs. David Rogers and Elaine Duryea.)

can appear similar to an eccentrically implanted IUP, especially in a uterus with a müllerian anomaly. Criteria that may aid differentiation include: an empty uterus, a gestational sac seen separate from the endometrium and >1 cm away from the most lateral edge of the uterine cavity, and a thin, <5-mm myometrial mantle surrounding the sac (Timor-Tritsch, 1992). Moreover, an echogenic line, known as the *interstitial line sign*, extending from the gestational sac to the endometrial cavity most likely represents the interstitial portion of the fallopian tube and is highly sensitive and specific (Ackerman, 1993a). In unclear cases, three-dimensional (3-D) sonography, magnetic resonance (MR) imaging, or diagnostic laparoscopy can help clarify anatomy. Laparoscopically, a myometrial protuberance is seen to lie lateral to the round ligament and coexists with normal distal tubes and ovaries.

■ Management

Surgically, either cornual resection or cornuostomy may be performed via laparotomy or laparoscopy, depending on patient hemodynamic stability and surgeon expertise. With either approach, intraoperative intramyometrial vasopressin injection may limit surgical blood loss. Cornual resection removes the gestational sac and surrounding cornual myometrium by means of a wedge excision (Fig. 12-7). Alternatively, cornuostomy involves incision of the cornual myometrium and suction or instrument extraction of the pregnancy. Both instances require layered myometrial closure. β-hCG levels are monitored postoperatively to exclude remnant trophoblast.

With early diagnosis, medical management may be considered. However, consensus regarding MTX regimens is lacking because of small study numbers. Jermy and coworkers (2004) reported a 94-percent success with systemic MTX using a dose of 50 mg/m^2 × BSA. Others employ a traditional multidose MTX regimen (Hiersch, 2014). Direct MTX injection into the gestational sac also offers comparable success (Framarino-dei-Malatesta, 2014). Last, a uterine artery MTX infusion followed by uterine artery embolization (UAE) is termed *chemoembolization* by some. This combined with systemic MTX has shown promise (Krissi, 2014).

The risk of uterine rupture with subsequent pregnancies following either medical or surgical management is undefined. Thus, elective cesarean delivery after $37^{0/7}$ weeks' gestation, which is timed similarly to those with prior at-risk myomectomy, is reasonable (American College of Obstetricians and Gynecologists, 2021).

Distinct from interstitial pregnancy, the term *angular pregnancy* is used by some to describe eccentric implantation near

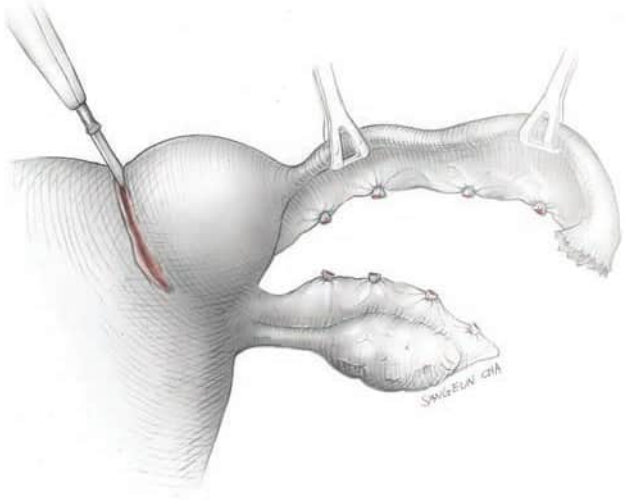


FIGURE 12-7 During cornual resection, the pregnancy, surrounding myometrium, and ipsilateral fallopian tube are excised en bloc. The incision is angled inward as it is deepened. This creates a wedge shape into the myometrium, which is then closed in layers with delayed-absorbable suture. The serosa is closed with subcuticular style suturing. (Reproduced with permission from Hoffman BL, Hamid CA, Corton MM: Surgeries for benign gynecologic conditions. In Hoffman BL, Schorge JO, Halvorson LM, et al: Williams Gynecology, 4th ed. New York, NY: McGraw Hill; 2020.)

one cornu but within the endometrial cavity. In one prospective case series of 42 such pregnancies, 80 percent progressed to a viable age, and abnormal placentation or uterine rupture did not develop (Bollig, 2020). These eccentrically implanted early IUPs are managed as normal pregnancies at our institution.

CESAREAN SCAR PREGNANCY

Diagnosis

This term describes implantation within the myometrium of a prior cesarean delivery scar. Its incidence approximates 1 case in 2000 normal pregnancies and has increased along with the cesarean delivery rate (Rotas, 2006).

Women with symptomatic cesarean scar pregnancy (CSP) usually present early, and pain and bleeding are common. Still, up to 40 percent of women are asymptomatic, and the diagnosis is made during routine sonographic examination (Rotas, 2006). Sonographic criteria are described in Figure 12-8 (Timor-Tritsch, 2012). Further, CSP implantation can be divided into *endogenic* and *exogenic* patterns. Endogenic CSPs implant on the scar and expand toward the uterine cavity, whereas exogenic ones implant deeply within the scar niche and grow toward the bladder or abdominal cavity. In one small study of CSPs that continued to viability, endogenic CSPs yielded variable obstetric outcomes, whereas all exogenic CSPs underwent hysterectomy with placenta accreta spectrum (PAS) at delivery (Kaelin Agten, 2017).

Sonographically, differentiating between an IUP implanted at the cervicoisthmic junction and a CSP can be difficult. Investigators in one study marked the midpoint of the uterine length (cervix to fundus) in sagittal views. If the center of the gestational sac lay distal to this midpoint, a CSP was diagnosed (Timor-Tritsch, 2016). A spontaneous expelling abortus is another mimic. Color Doppler will show the intense placental vascularity around a CSP, whereas as the aborting sac is avascular. Moreover, gentle pressure applied to the cervix by the vaginal probe will fail to move an implanted gestation—a negative sliding sign. Instead, an aborted sac will slide against the endocervical canal (Jurkovic, 2003). TVS is the typical first-line imaging tool, but MR imaging is useful for inconclusive cases.

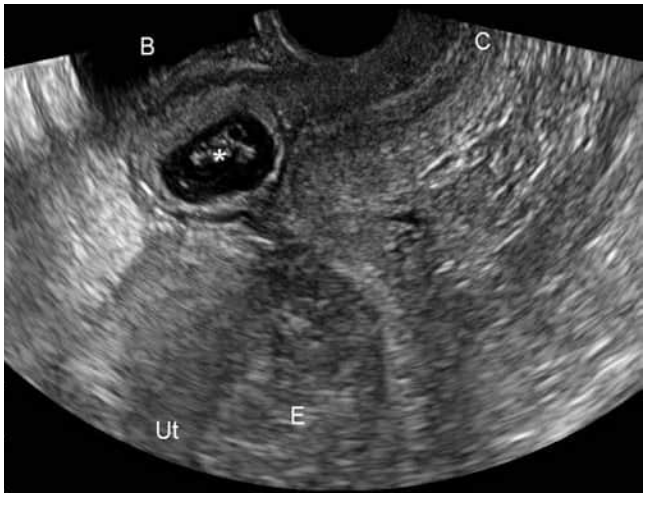


FIGURE 12-8 Transvaginal sonogram of a uterus with a cesarean scar pregnancy in a sagittal plane. Diagnostic criteria include: (1) an empty uterine cavity (*E*) and empty endocervical canal, (2) placenta or gestational sac (*asterisk*) embedded in the hysterotomy scar niche, (3) a thin myometrial mantle between the gestational sac and bladder (*B*), and (4) a prominent vascular pattern at the scar. C = cervix; Ut = anterior uterine wall.

Management

Insights into the pathogenesis of CSPs are expanding management options. Namely, growing evidence suggests that some of these pregnancies will not behave as a typical ectopic pregnancy, and rupture rates are lower. CSPs are thought by some to be a precursor of PAS (Timor-Tritsch, 2014). As such, a significant percentage of affected pregnancies will progress to a viable-aged neonate, albeit with the complications associated with PAS (Calì, 2018; Timor-Tritsch, 2015b).

Patients may prefer to avoid rupture and PAS risks and seek pregnancy termination. From one literature review, the most successful operations include: (1) laparoscopic uterine isthmic resection; (2) transvaginal isthmic resection through an anterior colpotomy, created similarly to anterior entry during vaginal hysterectomy; (3) UAE, followed by D & C with or without hysteroscopy; and (4) hysteroscopic resection (Birch Petersen, 2016; Wang, 2014). The Society for Maternal-Fetal Medicine (SMFM) (2020) considers sonography-guided vacuum aspiration alone, but not sharp curettage, to be suitable. In some instances, hysterectomy is required or may be elected in those not desiring future fertility.

Medical management is an option for those hoping to avoid surgery. However, compared with surgery, pregnancy resolution rates are more varied and lengthier. In one review, local MTX injection into the gestational sac alone provided a success rate of 60 percent, and systemic plus local MTX raised the rate to nearly 80 percent (Maheux-Lacroix, 2017). The SMFM (2020) recommends against systemic MTX alone.

With local MTX, doses of 1 mg/kg or 50-mg doses have been described. Prior to local MTX, fetal death can be induced in more advanced gestations by potassium chloride (KCL) injection into the sac (Grechukhina, 2018). One option is 1 mL of 2 mEq/mL KCL. Also, if associated bleeding complicates medical management, a Foley balloon catheter can be placed and expanded (Timor-Tritsch, 2015a). Recently, a novel double-balloon catheter, in which the balloons lie in tandem, has been used with MTX to resolve CSPs (Monteagudo, 2019). The cephalad balloon is filled within the endometrial cavity to prevent device expulsion. The lower balloon is tightly inflated to interrupt the CSP via mechanical pressure and tamponades potential bleeding.

Following conservative treatment, subsequent pregnancies have good outcomes, but PAS and recurrent CSP are risks (Gao, 2016; Wang, 2015). In one series of 30 CSPs, five subsequent pregnancies developed normally, whereas four were recurrent CSPs (Grechukhina, 2018). Uterine arteriovenous malformations are a potential long-term complication (Timor-Tritsch, 2015b).

CSPs have also been expectantly managed. The Society for Maternal–Fetal Medicine (2020) recommends against this practice. Exceptions may be early CSPs with evidence of pregnancy failure. One review of 69 patients continuing their gestation found that uterine rupture or dehiscence complicated 10 percent of all

cases (Calì, 2018). During the first or second trimester, hysterectomy was performed in 15 percent. For the 40 patients progressing to the third trimester, 17 had placenta percreta, 23 patients underwent hysterectomy, and two patients had uterine rupture or dehiscence. For all trimesters, 60 percent of cases ultimately underwent hysterectomy. More reassuringly, in early pregnancies without cardiac activity, 70 percent had uncomplicated miscarriage, whereas 30 percent required surgical or medical intervention. Of these early demises, none required hysterectomy.

Women accepting expectant care are ideally well counseled on these potential obstetric complications. If not prompted by earlier complications, repeat cesarean delivery is recommended at $34^{0/7}$ and $35^{6/7}$ weeks' gestation, and this timing recognizes the PAS and uterine rupture risks associated with CSP. Betamethasone to hasten lung maturity is recommended prior to delivery (Society for Maternal–Fetal Medicine, 2020).

CERVICAL PREGNANCY

Diagnosis

This rare ectopic pregnancy is defined first by cervical glands noted histologically opposite the placental attachment site. Second, all or part of the placenta lies at a level below the entrance of the uterine vessels or below the peritoneal reflection on the anterior uterus. Trophoblast invades the endocervix, and the pregnancy develops in the fibrous cervical wall. Risk factors include ART and prior uterine curettage (Ginsburg, 1994).

Painless vaginal bleeding is reported by 90 percent of women with a cervical pregnancy, and it can be severe (Ushakov, 1997). As pregnancy progresses, a distended, thin-walled cervix with a partially dilated external os may be evident. Above the cervical mass, a slightly enlarged uterine fundus is felt. Typical sonographic findings are shown and described in Figure 12-9. In some cases, MR imaging and 3-D TVS can aid diagnosis.

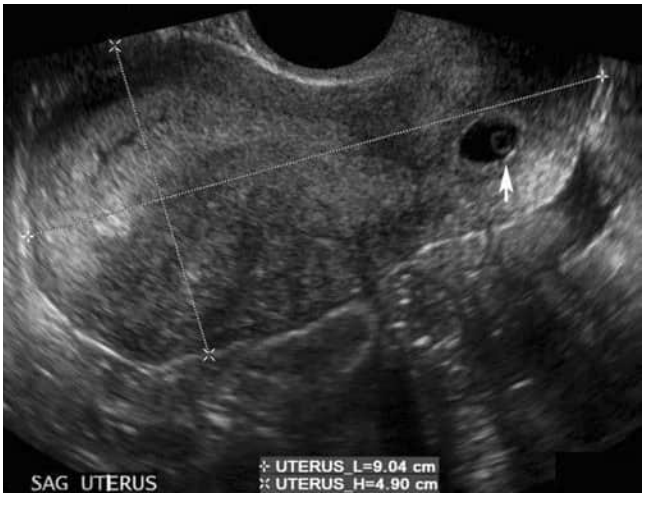


FIGURE 12-9 Cervical pregnancy. Transvaginal sonographic findings may include: (1) an hourglass uterine shape and ballooned cervix; (2) gestational tissue at the level of the cervix (*arrow*); (3) absent intrauterine gestational tissue; and (4) a portion of the endocervical canal seen interposed between the gestation and the endometrial canal. (Reproduced with permission from Dr. Angela Seasely.)

At times, cervical ectopic pregnancy can mimic a miscarriage in transit through the cervix. Similar to CSPs and described in that section, color Doppler will show the intense vascularity of cervical implantation, and gentle pressure applied to the cervix by the vaginal probe will fail to move an implanted gestation—a negative sliding sign.

Management

Cervical pregnancy may be treated medically or surgically. In many centers, including ours, MTX is first-line therapy in hemodynamically stable women. Of options, single- or multidose systemic MTX and dosing found in Table 12-1 are suitable (Murji, 2015). Alternatively, 50 mg of MTX can be injected directly into the gestational sac (Jeng, 2007; Yamaguchi, 2017). Others describe chemoembolization with MTX and UAE, as described for interstitial pregnancy (p. 228).

With MTX regimens, resolution and uterine preservation are achieved for gestations <12 weeks in 91 percent of cases (Kung, 1997). To select appropriate candidates, Hung and colleagues (1996) noted higher risks of systemic MTX treatment failure in those with a gestational age >9 weeks, β-hCG levels >10,000 mIU/mL, crown-rump length >10 mm, and fetal cardiac activity. For this reason, feticidal KCL can be injected into the fetus or gestational sac (Verma, 2009). Notably, during posttherapy surveillance, sonographic resolution lags far behind serum β-hCG level regression (Song, 2009).

Although conservative management is feasible for many women with cervical pregnancies, suction evacuation or hysterectomy may be selected. Moreover, hysterectomy may be required with bleeding uncontrolled by conservative methods (Fowler, 2021). *During hysterectomy, because of the close proximity of the ureters to the ballooned cervix, urinary tract injury rates are a concern.*

If suction evacuation of the cervix is planned, intraoperative bleeding may be lessened by preoperative UAE, by intracervical vasopressin injection, or by a cerclage placed at the internal cervical os to compress feeding vessels (Chen, 2015; Fylstra, 2014; Wang, 2011). Cervical branches of the uterine artery can effectively be ligated with vaginal placement of hemostatic cervical sutures on the lateral aspects of the cervix at 3 and 9 o'clock (Bianchi, 2011).

As an adjunct to medical or surgical therapy, UAE has been described either as a response to bleeding or as a preprocedural prevention (Hirakawa, 2009; Zakaria, 2011). Also, in the event of hemorrhage, a 26F Foley catheter with a 30-mL balloon can be placed intracervically and inflated to effect hemostasis by vessel tamponade and to monitor bloody drainage. The balloon remains inflated for 24 to 48 hours and is gradually decompressed over a few days (Ushakov, 1997).

ABDOMINAL PREGNANCY

Diagnosis

These rare ectopic pregnancies are defined as an implantation in the peritoneal cavity exclusive of tubal, ovarian, or

intraligamentous implantations. Most are thought to follow early tubal rupture or tubal abortion with reimplantation.

Clinically, symptoms may be absent or vague. Laboratory tests are typically uninformative, although maternal serum alpha-fetoprotein levels can be elevated. With later gestations, abnormal fetal positions may be palpated, or the cervix is displaced (Zeck, 2007). Sonographically, clues are a fetus or placenta seen eccentrically positioned within the pelvis or separate from the uterus; lack of myometrium between the fetus and the maternal anterior abdominal wall or bladder; or bowel loops surrounding the gestational sac (Allibone, 1981; Chukus, 2015). Oligohydramnios is common but nonspecific. Often needed, MR imaging can aid diagnosis and provide placental information.

Management

Abdominal pregnancy treatment depends on the gestational age at diagnosis. Conservative expectant management carries a maternal risk for sudden, dangerous hemorrhage. Moreover, Stevens (1993) reported fetal malformations and deformations in 20 percent. Thus, we believe that termination generally is indicated once the diagnosis is made. Certainly, before 24 weeks' gestation, conservative treatment rarely is justified. Despite this, some describe waiting until fetal viability with close surveillance (Harirah, 2016).

Principal surgical objectives are delivery of the fetus and careful assessment of placental implantation without provoking hemorrhage. Unnecessary exploration is avoided because the anatomy is commonly distorted and surrounding areas are extremely vascular. Importantly, placental removal may precipitate torrential hemorrhage because the normal hemostatic mechanism of myometrial contraction to constrict hypertrophied blood vessels is lacking. If it is obvious that the placenta can be safely removed or if the implantation site is already bleeding, then removal begins immediately. Blood vessels supplying the placenta are ideally ligated first. For early gestations, locally injected dilute vasopressin also can be employed.

Some advocate leaving the placenta in place as the lesser of two evils. It decreases the chance of immediate life-threatening hemorrhage, but at the expense of long-term sequelae. Placental embolization may play a role prior to or following fetal extraction (Frischhertz, 2019; Marcelin, 2018). If left in the abdominal cavity, the placenta can form abscesses, adhesions, intestinal or ureteral obstruction, and wound dehiscence (Bergstrom, 1998; Martin, 1988). In many of these cases, surgical removal becomes inevitable. If the placenta is left, its involution can be monitored using serum β-hCG levels and color Doppler sonography or MR imaging (France, 1980; Martin, 1990). Placental function usually declines rapidly. The placenta is eventually resorbed, but this can take months or years with advanced gestations (Valenzano, 2003).

If the placenta is left, postoperative MTX is often given to hasten involution. Accelerated placental destruction with accumulation of necrotic tissue follows (Deng, 2017). Infection with abscess formation can be a complication (Rahman, 1982). Similar to persistent trophoblastic tissue, early gestations may benefit most (Ansong, 2019).

OVARIAN PREGNANCY

Ectopic implantation of the fertilized egg in the ovary is rare and is diagnosed if four clinical criteria are met. These were outlined by Spiegelberg (1878): (1) the ipsilateral tube is intact and distinct from the ovary; (2) the ectopic pregnancy occupies the ovary; (3) the ectopic pregnancy is connected by the uteroovarian ligament to the uterus; and (4) ovarian tissue can be demonstrated histologically amid the placental tissue. Risk factors are similar to those for tubal pregnancies, but ART or IUD failure are prominent (Zhu, 2014). Presenting complaints and findings mirror those for tubal ectopic pregnancy. Although the ovary can accommodate the expanding pregnancy more easily than the fallopian tube, rupture at an early stage is the usual consequence (Melcer, 2016).

Sonographically, an internal anechoic area is surrounded by a wide echogenic ring, which in turn is surrounded by ovarian cortex (Comstock, 2005). In one review of 49 cases, the diagnosis was not be made until surgery, and many cases were presumed to be a tubal ectopic pregnancy (Choi, 2011). Moreover, at surgery, an early, unrecognized ovarian pregnancy may instead be considered and managed as a hemorrhagic corpus luteum.

Evidence-based management accrues mainly from case reports (Hassan, 2012). Classically, management for ovarian pregnancies has been surgical. Selection of laparoscopy or laparotomy are influenced by gestational age, hemoperitoneum, and hemodynamic status. Small lesions can be managed by ovarian wedge resection or cystectomy, whereas larger lesions require oophorectomy (Elwell, 2015; Melcer, 2015). With conservative surgery, β-hCG levels should be monitored to exclude remnant trophoblast.

HETEROTOPIC PREGNANCY

This pairing of an IUP and an ectopically located pregnancy is rare, and the most common dyad is an IUP and an ampullary tubal pregnancy. The natural incidence of these *heterotopic pregnancies* approximates 1 case per 30,000 pregnancies (Reece, 1983). However, with ART, their incidence is higher and is 9 cases in 10,000 pregnancies (Perkins, 2015). Initial clinical symptoms usually reflect those from the ectopic. Because an IUP is seen sonographically and the ectopic pregnancy may not be visualized, rates of rupture are higher in heterotopic pregnancy (Dendas, 2017).

In patients wishing to preserve the IUP, management initially is dictated by bleeding. In those with hemorrhage, treatment of the ectopic pregnancy is surgical. Depending on the ectopic location, resection or suction aspiration is the most common method (Wu, 2018). Of note, adjunctive UAE and vasopressin and their effects on uterine blood flow are less desirable for the ongoing IUP. With a rare comorbid ovarian ectopic pregnancy, early excision of the corpus luteum merits progesterone supplementation (Chap. 66, p. 1170).

In those without significant bleeding, medical steps to disrupt the ectopic pregnancy typically involve gestational-sac injection of KCl or of hyperosmolar glucose. This may be followed by later aspiration evacuation of the ectopic gestation. Because of toxicity to the IUP, MTX is avoided.

With ongoing pregnancy, adverse neonatal outcome rates are not appreciably elevated (Clayton, 2007). However, initial sonographic surveillance of fetal growth seems reasonable. Route of ultimate delivery is influenced mainly by myometrial integrity following ectopic treatment (Dendas, 2017; OuYang, 2014).

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CHAPTER 13

Gestational Trophoblastic Disease

Gestational trophoblastic disease (GTD) is the term used to encompass a group of tumors typified by abnormal trophoblast proliferation. Trophoblast produces human chorionic gonadotropin (hCG). Thus, the measurement of this peptide hormone in serum is essential for GTD diagnosis, management, and surveillance. GTD histologically is divided into hydatidiform moles, which are characterized by the presence of villi, and nonmolar trophoblastic malignant neoplasms, which lack villi.

Hydatidiform moles are excessively edematous immature placentas (Benirschke, 2012). These include the benign *complete hydatidiform mole* and *partial hydatidiform mole* (Table 13-1). The third member is the malignant *invasive mole* (Hui, 2014b). Invasive mole is deemed malignant because of its marked penetration into and destruction of the myometrium and its ability to metastasize.

Nonmolar trophoblastic neoplasms include choriocarcinoma, placental site trophoblastic tumor, and epithelioid trophoblastic tumor (Hui, 2014a). These three are differentiated by the trophoblast type that they contain.

Under the GTD umbrella term, the malignant forms of GTD are termed *gestational trophoblastic neoplasia (GTN).* These include invasive mole, choriocarcinoma, placental site trophoblastic tumor, and epithelioid trophoblastic tumor. These malignancies develop weeks or years following any type of pregnancy, but more frequently follow hydatidiform mole.

Each GTN malignancy type is histologically distinct and varies in its propensity to invade and metastasize. However, these diagnoses are infrequently identified from an actual histological specimen. Instead, measurement of serum hCG levels and clinical findings are more often used to diagnose and treat this malignancy. Accordingly, GTN is often managed as a single composite clinical entity. With chemotherapy, most tumors currently are highly curable.

TABLE 13-1. Modified WHO Classification of GTD

Molar Pregnancies
Hydatidiform mole
Complete
Partial
Invasive mole
Trophoblastic Tumors
Choriocarcinoma
Placental site trophoblastic tumor
Epithelioid trophoblastic tumor

GTD = gestational trophoblastic disease; WHO = World Health Organization.
From Hui, 2014a,b.

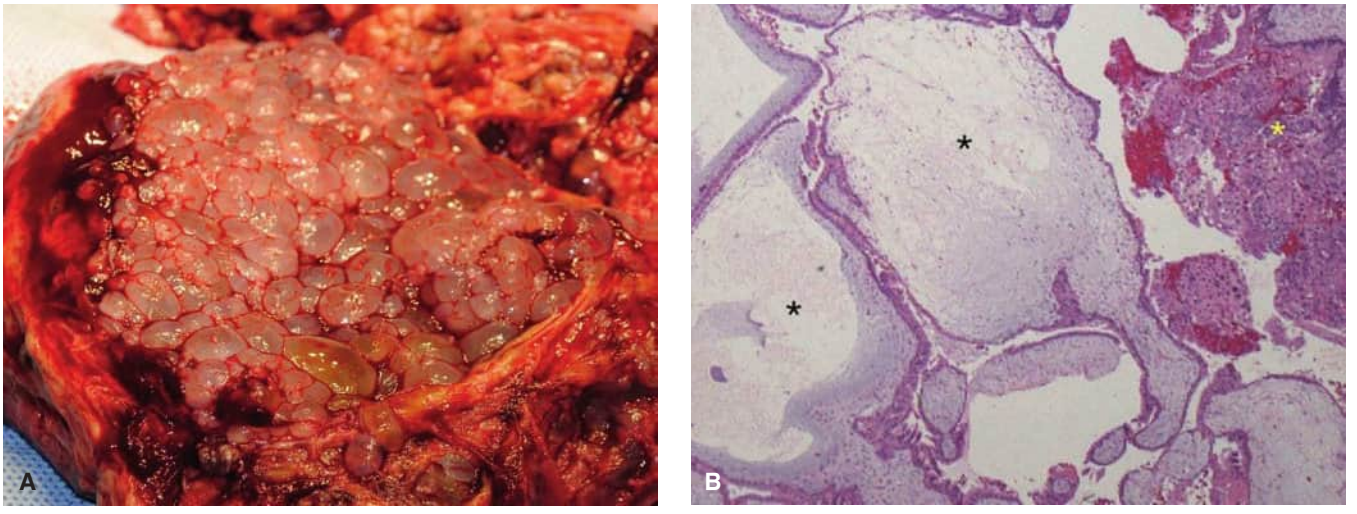


FIGURE 13-1 Complete hydatidiform mole. **A.** Gross specimen with characteristic vesicles of variable size. (Photograph contributed by Dr. Sasha Andrews. Reproduced with permission from Patel S, Roberts S, Rogers V, et al [eds]: Williams Obstetrics Study Guide, 25th ed. New York, NY: McGraw Hill; 2019.) **B.** Low-magnification photomicrograph shows generalized edema and cistern formation (*black asterisks*) within avascular villi. Haphazard trophoblastic hyperplasia is marked by a yellow asterisk on the right. (Reproduced with permission from Dr. Erika Fong.)

HYDATIDIFORM MOLE

Classic histological findings of molar pregnancy include trophoblast proliferation and villi with stromal edema (Fig. 13-1). The degree of histological changes, karyotype and immunostaining differences, and the absence or presence of embryonic elements are used to classify them as either *complete* or *partial hydatidiform moles* (Table 13-2). These two also vary in their associated risks for developing medical comorbidities and postevacuation GTN. Of the two, GTN more frequently follows complete hydatidiform mole.

Grossly, complete moles have abnormal chorionic villi that appear as a mass of clear vesicles. These vary in size and often hang in clusters from thin pedicles. In contrast, partial molar pregnancies have focal and less advanced hydatidiform changes and contain some fetal tissue. Both forms of moles usually fill the uterine cavity, but they rarely may be ectopic (Sebire, 2005; Yamada, 2016).

TABLE 13-2. Features of Partial and Complete Hydatidiform Moles

Feature	Partial Mole	Complete Mole
Karyotype[a]	69,XXX or 69,XXY	46,XX
Clinical presentation		
Diagnosis	Missed abortion	Molar gestation
Uterine size	Small for dates	Large for dates
Theca-lutein cysts	Rare	25–30% of cases
Initial hCG levels	<100,000 mIU/mL	>100,000 mIU/mL
Medical complications[b]	Rare	Uncommon
Rate of subsequent GTN	1–5% of cases	15–20% of cases
Pathology		
Embryo-fetus	Often present	Absent
Amnion, fetal erythrocytes	Often present	Absent
Villous edema	Focal	Widespread
Trophoblastic proliferation	Focal, slight to moderate	Slight to severe
Trophoblast atypia	Mild	Marked
$p57^{KIP2}$ immunostaining	Positive	Negative

[a]Typical karyotypes.
[b]These include anemia, hyperthyroidism, hyperemesis gravidarum, preeclampsia, and infection.
GTN = gestational trophoblastic neoplasia; hCG = human chorionic gonadotropin.

Epidemiology and Risk Factors

Ethnic predisposition is seen with hydatidiform mole, and prevalences are higher in Asians, Hispanics, and American Indians (Choi, 2015; Drake, 2006). The incidence in the United States and Europe has been relatively constant at 1 per 1000 deliveries (Eysbouts, 2016; Melamed, 2016).

The strongest risk factors are age and a prior hydatidiform mole. Women at both extremes of reproductive age are most vulnerable (Savage, 2013; Sebire, 2002a). With a prior complete mole, the risk of another mole is 0.9 percent, and with a previous partial mole, the rate is 0.3 percent. After two prior complete moles, approximately 20 percent of women have a third mole (Eagles, 2015).

Pathogenesis

Molar pregnancies typically arise from chromosomally abnormal fertilizations. Complete moles most often have a diploid chromosomal composition. These usually are 46,XX and result from *androgenesis,* meaning both sets of chromosomes are paternal. The chromosomes of the ovum are either absent or inactivated. As shown in Figure 13-2A, an ovum is fertilized by a haploid sperm, which then duplicates its own chromosomes after meiosis. Less commonly, the chromosomal pattern may be 46,XY or 46,XX and due to fertilization by two sperm, that is, *dispermic fertilization* or *dispermy* (Lawler, 1991; Ohama, 1981).

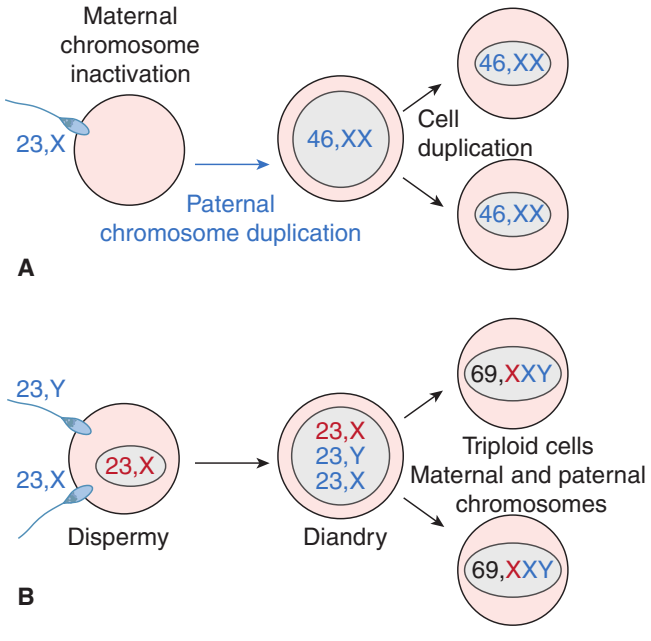


FIGURE 13-2 Typical pathogenesis of complete and partial moles. **A.** A 46,XX complete mole may be formed if a 23,X-bearing haploid sperm penetrates a 23,X-containing haploid egg whose genes have been "inactivated." Paternal chromosomes then duplicate to create a 46,XX diploid complement solely of paternal origin. **B.** A partial mole may be formed if two sperm—either 23,X- or 23,Y-bearing—both fertilize (*dispermy*) a 23,X-containing haploid egg whose genes have not been inactivated. The resulting fertilized egg is triploid with two chromosome sets being donated by the father (*diandry*).

Partial moles have a triploid karyotype, which is 69,XXX, 69,XXY, or much less commonly, 69,XYY. These are each composed of two paternal haploid sets of chromosomes contributed by dispermy and one maternal haploid set (see Fig. 13-2B). Less frequently, a similar haploid egg may be fertilized by an unreduced diploid 46,XY sperm. These triploid zygotes result in some embryonic development, however, it ultimately is a lethal fetal condition (Joergensen, 2014; Lakovschek, 2011). Fetuses that reach advanced ages have severe growth restriction, multiple congenital anomalies, or both.

Twin Pregnancy

Rarely, in some twin pregnancies, one chromosomally normal fetus is paired with a complete diploid molar pregnancy. Importantly, these cases must be distinguished from a single partial molar pregnancy with its associated abnormal fetus. Other potential diagnoses include placental mesenchymal dysplasia, subchorionic hematoma, or chorioangioma (Chap. 6, p. 112) (Cavoretto, 2020). To help distinguish among these, chorionic villus sampling, amniocentesis, or fetal cord blood sampling coupled with fetal karyotyping aid confirmation (Lee, 2010).

Several unique pregnancy problems complicate such twin pregnancies. Thyrotoxicosis is common, but the most worrisome are preeclampsia or hemorrhage. These frequently necessitate preterm delivery. Thus, many women may choose to terminate the gestation, if diagnosed early. In those with continuing pregnancy, survival of the normal fetus varies and depends on associated comorbidity from the molar component. Wee and Jauniaux (2005) reviewed outcomes in 174 women, of whom 82 chose termination. Of the remaining 92 pregnancies, 42 percent either miscarried or had a perinatal death; approximately 60 percent delivered preterm; and 40 percent delivered at term.

Another concern for those continuing their pregnancy is the risk for developing subsequent GTN. Most evidence indicates no significant difference between women who continue or terminate their pregnancy (Lin, 2017; Sebire 2002b).

Clinical Findings

Molar pregnancy is diagnosed sooner than in the past because prenatal care is sought much earlier and sonography is virtually universal. For example, in 194 women with a complete mole, evacuation was completed at a median gestational age of 9 weeks and at 12 weeks for 172 patients with a partial mole (Sun, 2015). As a result, most molar pregnancies are treated before complications ensue.

Typically, 1 to 2 months of amenorrhea precede the diagnosis. As gestation advances, symptoms tend to be more pronounced with complete compared with partial moles (Niemann, 2007). Untreated molar pregnancies will almost always cause uterine bleeding that varies from spotting to profuse hemorrhage. Bleeding may presage spontaneous molar abortion, but more often, it follows an intermittent course for weeks to months.

In more advanced moles with considerable concealed uterine hemorrhage, moderate iron-deficiency anemia develops. Nausea and vomiting also may be significant. Of physical findings, many women have uterine growth exceeding that expected, and the enlarged uterus is comparatively softer. Fetal heart motion is absent with complete moles. The ovaries can be fuller and cystic

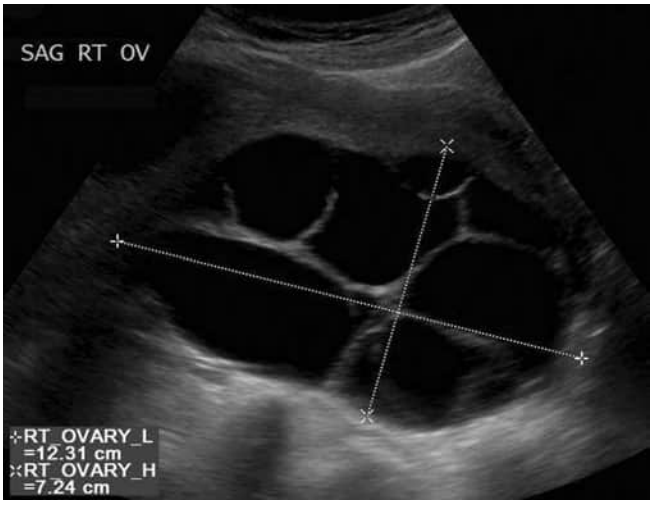


FIGURE 13-3 Sonogram of an ovary with multiple theca-lutein cysts in a woman with a complete hydatidiform mole.

from multiple theca-lutein cysts (Fig. 13-3). These are more common with a complete mole and likely result from ovarian overstimulation by excessive hCG levels. Remember that hCG and luteinizing hormone share the same receptor, and both can stimulate the theca layer that surrounds follicles. Because theca-lutein cysts regress following pregnancy evacuation and subsequent hCG level decline, expectant management is preferred. Occasionally, a larger cyst may undergo torsion, infarction, and hemorrhage. However, oophorectomy is not performed unless extensive infarction persists after untwisting.

The thyrotropin-like effects of hCG frequently cause serum free thyroxine (fT_4) levels to be elevated and thyroid-stimulating hormone (TSH) levels to be decreased (Chap. 61, p. 1089). Despite this, clinically apparent thyrotoxicosis is unusual and in our experience can be mimicked by bleeding and sepsis from infected products. Moreover, the serum free T_4 levels rapidly normalize after uterine evacuation. Despite this, cases of presumed "thyroid storm" have been reported (Kofinas, 2015).

Severe preeclampsia and eclampsia are relatively common with advanced molar pregnancies. However, these are seldom seen today because of early diagnosis and evacuation. An exception is the case of a normal fetus coexisting with a complete mole, described earlier. In continuing twin gestations, severe preeclampsia frequently mandates preterm delivery.

Diagnosis

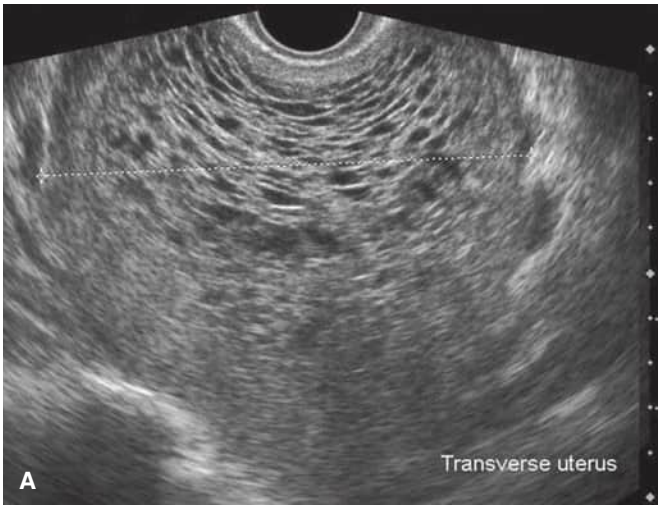
Serum β-HCG Measurements

Most women initially have irregular bleeding that almost always prompts pregnancy testing and sonography. Less often, women will spontaneously pass molar tissue.

With a complete molar pregnancy, serum β-hCG levels are commonly elevated above those expected for gestational age. With more advanced moles, values in the millions are not unusual. Importantly, these high values can lead to erroneous false-negative *urine* pregnancy test results. Termed a *hook effect*, excessive β-hCG hormone levels oversaturate the assay's targeting antibody and create a false-negative reading (Cormano, 2016). In these cases, *serum* β-hCG determinations with or without sample dilution will yield a positive result. With a partial mole, β-hCG levels may also be significantly elevated, but more commonly concentrations are in ranges expected for gestational age.

Sonography

Although this is the mainstay of trophoblastic disease diagnosis, not all cases are confirmed initially. In a large series of more than 1000 patients with molar pregnancy, sonography's sensitivity was 44 percent, and its specificity was 74 percent (Fowler, 2006). With grayscale sonography, a complete mole appears as an echogenic uterine mass filling the endometrial cavity and is surrounded by normal myometrium. The mass is composed of numerous anechoic cystic spaces of different sizes and shapes, but without a fetus or amnionic sac. The appearance is often described as a "snowstorm" (Fig. 13-4). Application of color Doppler displays marked surrounding myometrial vascularity.



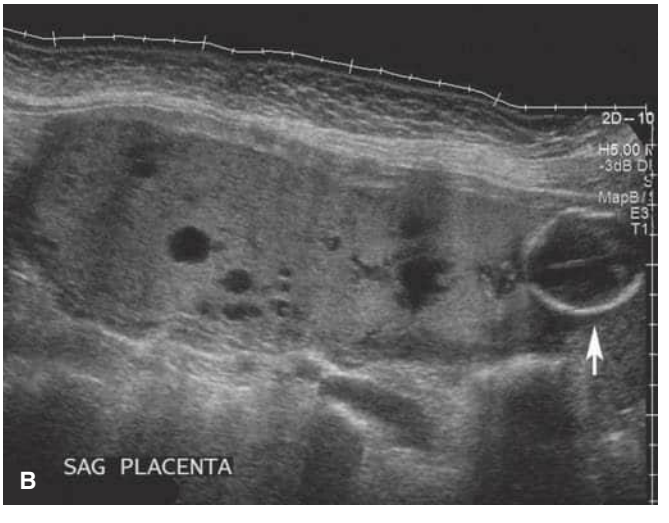


FIGURE 13-4 Sonograms of hydatidiform moles. **A.** Transverse view of a uterus with a complete hydatidiform mole. The characteristic "snowstorm" appearance reflects an echogenic uterine mass, marked by calipers, that has numerous anechoic cystic spaces. Notably, a fetus or amnionic sac is absent. **B.** In this sagittal image of a partial hydatidiform mole, the fetal head (*arrow*) lies adjacent to an enlarged, multicystic placenta.

However, absent internal flow reflects the avascular villi of complete moles.

A partial mole has features that include a thick, multicystic placenta plus a fetus or fetal tissue. Thin septa can be found within the gestational sac (Savage, 2017). Affected fetuses usually die in the first trimester. Those advancing further often show growth restriction, oligohydramnios, and limb or CNS defects (Cavoretto, 2020).

In early pregnancy, however, these sonographic characteristics are seen in fewer than half of hydatidiform moles. At earlier gestations, a complete mole may appear as a polypoid hyperechoic mass that lacks internal cysts and is surrounded by anechoic fluid (Jauniaux, 2018).

The most common mimics are incomplete or missed abortion. In these cases, histological evaluation, described next, ultimately is diagnostic. Occasionally, molar pregnancy may be confused for a multifetal pregnancy or a uterine leiomyoma with cystic degeneration.

Pathology

Because of the risk for subsequent GTN following molar pregnancy, postevacuation surveillance is indicated. Thus, moles must be distinguished from other pregnancy types that are not molar but that have hydropic placental degeneration. Most often, these are hydropic abortuses formed by the traditional union of one haploid egg and one haploid sperm but are pregnancies that have failed. Their placentas display hydropic degeneration, in which villi are edematous and swollen, and thus mimic some villous features of hydatidiform moles. These mimics do not require postevacuation surveillance. Some distinguishing histological characteristics are shown in Table 13-2.

In pregnancies before 10 weeks, classic molar histological changes may not be apparent. Villi may not be enlarged, and molar stroma may not yet be edematous and avascular. Histopathologic evaluation can be enhanced by immunohistochemical staining for p57 expression and by molecular genotyping (Banet, 2014). $p57^{KIP2}$ is a nuclear protein whose gene is paternally imprinted and maternally expressed. This means that the gene product is produced only in tissues containing a maternal allele. Because complete moles contain only paternal genes, the $p57^{KIP2}$ protein is absent in complete moles, and tissues do not pick up this stain (Merchant, 2005). In contrast, this nuclear protein is strongly expressed in normal placentas, in spontaneous pregnancy losses with hydropic degeneration, and in partial hydatidiform moles (Castrillon, 2001). Accordingly, immunostaining for $p57^{KIP2}$ is an effective means to isolate complete mole from the diagnostic list. For distinction of a partial mole from a nonmolar hydropic abortus, both of which express $p57^{KIP2}$, molecular genotyping can be used (Ronnett, 2018). Molecular genotyping determines the parental source of alleles. Thereby, it can distinguish among a diploid diandric genome (complete mole), a triploid diandric-monogynic genome (partial mole), or biparental diploidy (nonmolar abortus) (Xing, 2021).

■ Management

Maternal deaths from molar pregnancies are rare because of early diagnosis, timely evacuation, and vigilant postevacuation surveillance for GTN (Sun, 2016). Preoperative evaluation strives to identify potential complications, such as preeclampsia, hyperthyroidism, anemia, electrolyte depletions from hyperemesis, and metastatic disease (Table 13-3). Most recommend chest radiography, whereas computed tomography (CT) and magnetic resonance (MR) imaging are not routinely done unless a chest radiograph shows lung lesions or unless other extrauterine disease is suspected.

Molar Pregnancy Termination

Regardless of uterine size, molar evacuation by suction curettage usually is the preferred treatment. Preoperative cervical dilation with an osmotic dilator is recommended if the cervix is minimally dilated. Intraoperative bleeding can be greater with molar pregnancy than with a comparably sized uterus containing nonmolar products. Thus with large moles, adequate anesthesia, sufficient intravenous access, and blood-banking support is imperative.

A step by step description of dilation and curettage is found in Chapter 11 (p. 213). For molar evacuation, the cervix is mechanically dilated to preferably allow insertion of a large Karman suction cannula. Depending on uterine size, a 10- to 14-mm diameter is typical. As evacuation is begun, oxytocin is infused to limit bleeding. Intraoperative sonography is often recommended to help ensure complete uterine cavity emptying and minimize perforation risk. When the myometrium has contracted, a thorough but gentle curettage with a sharp large-loop Sims curette may be performed. If bleeding continues despite uterine evacuation and oxytocin infusion, other uterotonic agents are given (see Table 13-3). Uncommonly, pelvic arterial embolization, uterine packing, or hysterectomy may be necessary (Chap. 44, p. 779) (Tse, 2007).

Some volume of trophoblast is deported into the pelvic venous system during molar evacuation (Hankins, 1987). With large moles, the amount of tissue may be sufficient to produce clinically apparent respiratory insufficiency, pulmonary edema, or even embolism (Delmis, 2000). In our earlier experiences with substantial moles, these and their chest radiographic manifestations clear rapidly without specific treatment.

Following curettage, anti-D immunoglobulin (Rhogam) is given to Rh D-negative women because fetal tissues with a partial mole may include red cells with D-antigen (Chap. 18, p. 356). Those with suspected complete mole are similarly treated because a definitive diagnosis of complete versus partial mole may not be confirmed until histological evaluation of the evacuated products.

Following evacuation, the long-term prognosis for women with a hydatidiform mole is not improved with prophylactic chemotherapy. Moreover, chemotherapy toxicity can be significant, and thus it is not recommended routinely (Gueye, 2014; Wang, 2017).

Methods other than suction curettage can be considered for select cases. Hysterectomy with ovarian preservation may be preferable for women who have finished childbearing and who carry complete moles with high-risk features. Of women aged 40 to 49 years, up to 50 percent will subsequently develop GTN, and hysterectomy markedly reduces this likelihood (Elias, 2012; Zhao, 2019). During hysterectomy, theca-lutein cysts do not require removal, and they spontaneously regress following molar termination. Last, labor induction or hysterotomy is seldom

TABLE 13-3. Some Considerations for Management of Hydatidiform Mole

Preoperative
Laboratory
Hemogram; serum β-hCG, creatinine, and hepatic aminotransferase levels
TSH, free T_4 levels
Type and Rh; group & screen or crossmatch depending on uterine size
Chest radiograph
Consider hygroscopic dilators
Intraoperative
Large-bore intravenous catheter(s)
Regional or general anesthesia
Oxytocin (Pitocin): 20 units in 1000 mL Ringer lactate for continuous infusion
One or more other uterotonic agents may be added as needed:
Methylergonovine (Methergine): 0.2 mg = 1 mL = 1 ampule IM every 2 h prn
Carboprost tromethamine ($PGF_{2\alpha}$) (Hemabate): 250 μg = 1 mL = 1 ampule IM every 15–90 min prn
Misoprostol (PGE_1) (Cytotec): 200 mg tablets for rectal administration, 800–1000 mg once
Karman cannula: size 10 or 14 mm
Consider sonography machine
Postevacuation
Anti-D immune globulin (Rhogam) if Rh D-negative
Initiate effective contraception[a]
Review pathology report
Serum hCG levels: within 48 h of evacuation, weekly until undetectable, then monthly for 6 months

[a]Intrauterine devices are not suitable during surveillance.
hCG = human chorionic gonadotropin; IM = intramuscular; PG = prostaglandin; T_4 = thyroxine; TSH = thyroid-stimulating hormone.

used for molar evacuation in the United States. Both will likely increase blood loss and theoretically may raise the incidence of persistent trophoblastic disease (Tidy, 2000).

Postevacuation Surveillance

Close biochemical surveillance for persistent gestational neoplasia follows each hydatidiform mole evacuation. Serial measurement of serum β-hCG levels aim to detect persistent or renewed trophoblastic proliferation. As a glycoprotein, hCG shows structural heterogeneity and exists in different isoforms. Thus, for surveillance, an hCG assay that can detect all forms of hCG should be used (Harvey, 2010; Ngan, 2018). These are different from those used for routine pregnancy testing (de Medeiros, 2009). The initial β-hCG level is obtained within 48 hours after evacuation. This serves as the baseline, which is compared with β-hCG quantification done thereafter every 1 to 2 weeks. Levels are followed until they become undetectable.

The median time for such resolution is 6 weeks for partial moles and 7 weeks for complete moles. Of patients, 95 percent have normal β-hCG levels by 14 weeks postevacuation and 99 percent by 25 weeks (Eysbouts, 2017a). Once β-hCG is undetectable, this is confirmed with monthly determinations for another 6 months (Lurain, 2010; Sebire, 2007).

Concurrently, reliable contraception is imperative to avoid confusion caused by rising β-hCG levels from a new pregnancy. Most recommend combination hormonal contraception, injectable depot medroxyprogesterone acetate, or progestin implant. The latter two are particularly useful if poor patient compliance is anticipated. Intrauterine devices are not used until β-hCG levels are undetectable because of the risk of uterine perforation if an invasive mole is present. After these 6 months, monitoring is discontinued and pregnancy allowed. Although not recommended, if a woman conceives during surveillance, live-birth and congenital anomalies rates appear to mirror general population rates (Tuncer, 1999b).

During β-hCG levels surveillance, increasing or persistently plateaued levels mandate evaluation for GTN. If the woman has not become pregnant, these levels signify trophoblast proliferation that is most likely malignant. Several factors predispose a patient to GTN following molar evacuation. Complete moles have a 15 to 20 percent incidence of malignant sequelae, compared with 1 to 5 percent following partial moles. Surprisingly, with much earlier recognition and evacuation of molar pregnancies, the risk for GTN has not dropped (Sun, 2015). Other GTN risk factors are older maternal age, preevacuation β-hCG levels >100,000 mIU/mL, uterine size that is large-for-gestational age, theca-lutein cysts >6 cm, and a slow decline in β-hCG levels (Berkowitz, 2009; Kang, 2012; Wolfberg, 2005).

GESTATIONAL TROPHOBLASTIC NEOPLASIA

This group includes invasive mole, choriocarcinoma, placental site trophoblastic tumor, and epithelioid trophoblastic tumor. These tumors almost always develop with or after some form

TABLE 13-4. Criteria for Diagnosis of Gestational Trophoblastic Neoplasia

1. Plateau of β-hCG level (± 10 percent) for four measurements during a period of 3 weeks or longer—days 1, 7, 14, 21
2. Rise of serum β-hCG level >10 percent during three weekly consecutive measurements or longer, during a period of 2 weeks or more—days 1, 7, 14
3. Serum β-hCG level remains detectable for 6 months or more
4. Histological criteria for choriocarcinoma

of recognized pregnancy. Half follow hydatidiform mole, a fourth follow miscarriage or tubal pregnancy, and another fourth develop after a preterm or term pregnancy (Goldstein, 2012). These four tumor types are histologically distinct but are usually diagnosed solely by persistently elevated serum β-hCG levels because tissue is infrequently available for study. Criteria to diagnose postmolar GTN are shown in Table 13-4.

Diagnosis, Staging, and Prognostic Scoring

Clinically, these placental tumors are characterized by their aggressive invasion into the myometrium and propensity to metastasize. The most common finding with GTN is irregular bleeding associated with uterine subinvolution. The bleeding may be continuous or intermittent and sometimes may be sudden and massive. Myometrial perforation from trophoblastic growth can cause intraperitoneal hemorrhage. In some women, lower genital tract metastases are evident. In others, only distant metastases, with no trace of uterine tumor, are found.

Consideration for the possibility of GTN is the most important factor in its recognition. Unusually persistent bleeding after any type of pregnancy should prompt serum β-hCG level measurement. Uterine size is assessed, and careful examination seeks lower genital tract metastases, which usually are bluish vascular masses (Cagayan, 2010). Tissue biopsy of such masses is unnecessary and may cause significant bleeding.

Once the diagnosis is verified, a baseline serum β-hCG level and hemogram are obtained. A search for local disease and metastases includes tests of liver and renal function, transvaginal sonography, chest CT or radiography, and brain and abdominopelvic CT scan or MR imaging. Less often, positron-emission tomographic (PET) scanning and cerebrospinal fluid β-hCG level determination are used to identify metastases (Lurain, 2011).

If no extrauterine disease is found, a second curettage or hysterectomy may be considered. After either, β-hCG levels are then measured every 2 weeks until three consecutively lie in undetectable range. Levels are subsequently repeated monthly for 6 months. In contrast, if β-hCG levels persist after curettage or hysterectomy or if initial extrauterine disease is found, patients undergo staging and chemotherapy is instituted (Koh, 2018; Osborne, 2016).

GTN is staged clinically using the system of the International Federation of Gynecology and Obstetrics (FIGO) (2009). This includes a modification of the World Health Organization (WHO) (1983) prognostic index score, with which scores of 0 to 4 are given for each of the categories shown in Table 13-5. Women with WHO scores of 0 to 6 are considered to have

TABLE 13-5. International Federation of Gynecology and Obstetrics (FIGO) Staging and Diagnostic Scoring System for Gestational Trophoblastic Neoplasia

Anatomical Staging	
Stage I	Disease confined to the uterus
Stage II	GTN extends outside of the uterus but is limited to the genital structures (adnexa, vagina, broad ligament)
Stage III	GTN extends to the lungs, with or without known genital tract involvement
Stage IV	All other metastatic sites

Modified World Health Organization (WHO) Prognostic Scoring System[a]

Scores[b]	0	1	2	4
Age (years)	<40	≥40	—	—
Antecedent pregnancy	Mole	Abortion	Term	—
Interval after index pregnancy (mo)	<4	4–6	7–12	>12
Pretreatment serum β-hCG (mIU/mL)	$<10^3$	10^3 to 10^4	10^4 to 10^5	$\geq 10^5$
Largest tumor size (including uterus)	<3 cm	3–4 cm	≥5 cm	—
Site of metastases		Spleen, kidney	GI	Liver, brain
Number of metastases	—	1–4	5–8	>8
Previous failed chemotherapy drugs	—	—	1	≥2

[a]Adapted by FIGO.
[b]Low risk = WHO score of 0 to 6; high risk = WHO score of ≥7.
β-hCG = beta human chorionic gonadotropin; GI = gastrointestinal; GTN = gestational trophoblastic neoplasia.

low-risk disease, whereas those with scores ≥7 are considered in the high-risk group.

Histological Classification

Clinical staging is assigned without regard to histological findings, even if available. Still, distinct histological types are recognized.

Invasive Mole

These are a common trophoblastic neoplasm, and almost all invasive moles arise from partial or complete moles. Previously known as *chorioadenoma destruens*, invasive mole is characterized by extensive tissue invasion by trophoblast and whole villi. Trophoblastic cells penetrate deep into the myometrium and sometimes involve the peritoneum, adjacent parametrium, or vaginal vault. Although locally aggressive, invasive moles are less prone to metastasize.

Gestational Choriocarcinoma

This is the most common trophoblastic neoplasm to follow a term pregnancy or a miscarriage, and only a fourth of cases follow a molar gestation (Soper, 2021). Choriocarcinoma is composed of cells reminiscent of early cytotrophoblast and syncytiotrophoblast, however, it contains no villi. This rapidly growing tumor invades both myometrium and blood vessels to create hemorrhage and necrosis. Myometrial tumor may spread outward and become visible on the uterine surface as dark, irregular nodules. Metastases often develop early and are generally blood-borne. The most common sites are the lungs and vagina, but tumor may travel to the vulva, kidneys, liver, brain, ovaries, and bowel. With choriocarcinomas, ovarian theca-lutein cysts commonly coexist.

Placental Site Trophoblastic Tumor

This uncommon tumor arises from *intermediate trophoblasts* at the placental site. These tumors have associated serum β-hCG levels that may be only modestly elevated (Gadducci, 2019). However, they produce variant forms of hCG, and identifying a high proportion of free β-hCG favors this diagnosis (Horowitz, 2017). Treatment of placental site trophoblastic tumor by hysterectomy is preferred because these locally invasive tumors are usually resistant to chemotherapy. For higher-risk stage I and for later stages, adjuvant multidrug chemotherapy also is given (Koh, 2018; Schmid, 2009).

Epithelioid Trophoblastic Tumor

This rare tumor develops from *chorionic-type intermediate trophoblast*. The uterus is mainly involved, and bleeding but low hCG levels are typical findings (Gadducci, 2019). Primary treatment is hysterectomy because this tumor is relatively resistant to chemotherapy. Metastatic disease is common, and combination chemotherapy is employed (Frijstein, 2019; Koh, 2018).

Treatment

Women with GTN are best managed by oncologists, and some evidence supports treatment in centers specializing in GTN (Kohorn, 2014). Chemotherapy alone is usually the primary treatment. In some GTN cases without extrauterine disease, a second uterine evacuation may be an adjuvant therapeutic option to avoid or minimize chemotherapy (Hemida, 2019; Koh, 2018; Pezeshki, 2004). In other cases, suction curettage may infrequently be needed to resolve bleeding or remove a substantial amount of retained molar tissue. In specific cases, hysterectomy may be primary or adjuvant treatment (Bolze, 2018; Eysbouts, 2017b).

Single-agent chemotherapy protocols are usually sufficient for nonmetastatic or low-risk metastatic neoplasia (Lawrie, 2016; Koh, 2018). In their review of 108 women with low-risk disease, Abrão and colleagues (2008) reported that monotherapy protocols with either methotrexate or actinomycin D were equally effective compared with a regimen containing both. In general, methotrexate is less toxic than actinomycin D (Chan, 2006; Seckl, 2010). Regimens are repeated until serum β-hCG levels are undetectable.

Combination chemotherapy is given for high-risk disease, and reported cure rates approximate 90 percent (Lurain, 2011). Several regimens are successful. One is *EMA-CO,* which includes etoposide, methotrexate, actinomycin D, cyclophosphamide, and vincristine (Oncovin). In selected cases, adjuvant surgical and radiotherapy also may be employed (Hanna, 2010). Despite chemotherapy successes in general, frequent causes of death include hemorrhage from metastatic sites, respiratory failure, sepsis, and multiorgan failure due to widespread chemoresistant disease (Lybol, 2012; Neubauer, 2015).

With either low- or high-risk disease, once serum β-hCG levels are undetectable, serosurveillance is continued for 1 year. During this time, effective contraception is crucial to avoid teratogenic effects of chemotherapy to the fetus and to mitigate confusion from rising β-hCG levels caused by superimposed pregnancy.

A few women during surveillance, despite no evidence of metastases, will be found to have very low β-hCG levels that plateau. This phenomenon is called *quiescent hCG* and presumably stems from dormant trophoblast. Close observation without therapy is recommended, but 20 percent will eventually have recurrent active and progressive GTN (Ngu, 2014).

SUBSEQUENT PREGNANCY

Women with prior hydatidiform mole generally do not have impaired fertility, and their pregnancy outcomes are usually normal (Joneborg, 2014; Matsui, 2001; Sebire, 2003). One concern is the 1-percent risk for developing trophoblastic disease in a subsequent pregnancy (p. 237). Sonographic evaluation is recommended in early pregnancy, and subsequently as needed.

Women with GTN who have successfully completed chemotherapy are advised to delay pregnancy for 1 year. Most relapses develop within this time period (Tranoulis, 2019). Also, methotrexate may persist in human tissues for months (Hackmon, 2011). Despite this, women who become pregnant within 1 year postchemotherapy for GTN can be reassured of a likely favorable outcome (Woolas, 1998). Risk of miscarriage or GTN relapse is not increased compared with women conceiving after the suggested 1-year surveillance (Williams, 2014). However, these gravidas are advised that the diagnosis

of a tumor relapse may be delayed during pregnancy (Blagden, 2002; Tuncer, 1999a).

In general, fertility and pregnancy outcomes following GTN treatment are typically normal, and congenital anomaly rates are not increased (Berkowitz, 2000; Tse, 2012). One exception is a higher stillbirth rate of 1.5 percent compared with a background rate of 0.8 percent (Vargas, 2014).

For those with prior hydatidiform mole or GTN treatment, the placenta or products of conception in a subsequent pregnancy are sent for pathological evaluation at delivery. A serum β-hCG level also is measured 6 weeks postpartum (Lurain, 2010; Royal College of Obstetricians and Gynaecologists, 2010). This assay may be less valuable for those solely with a prior mole compared with those previously treated for GTN (Earp, 2019).

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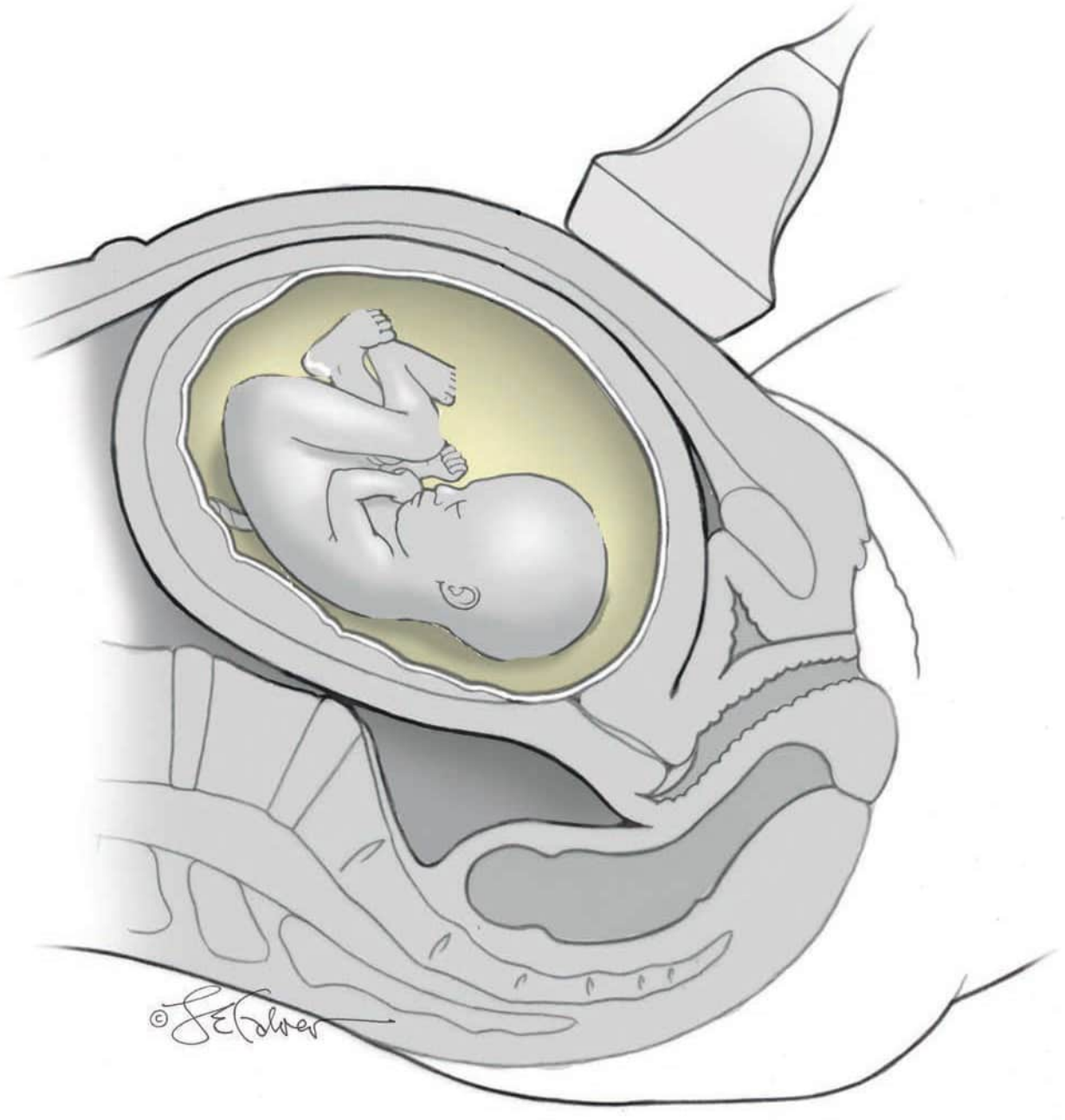
SECTION 6

THE FETAL PATIENT



CHAPTER 14

Obstetrical Imaging

Obstetrical ultrasound is fundamental to prenatal care. It is used to confirm gestational age and viability; to detect and characterize abnormalities of the fetus, amnionic fluid, and placenta; and to assist with diagnostic and therapeutic procedures.

Ultrasound practice continues to evolve. The number of components included in the second-trimester standard and detailed fetal anatomical surveys has expanded. With improved image resolution, fetal abnormalities are increasingly identified in the late first trimester. This has prompted the requirement for a limited anatomical survey during the standard first-trimester examination and has led to the development of a new detailed first-trimester examination. Detailed placental evaluation is a new specialized examination to aid detection and characterization of placenta accreta spectrum.

Across the United States, pregnant women receive ultrasound examinations in various practice settings staffed by obstetrician–gynecologists, maternal–fetal medicine specialists, and radiologists. Ideally, examinations are performed by registered diagnostic medical sonographers or physicians with certification in their area(s) of practice and in units accredited by the American Institute of Ultrasound in Medicine (AIUM) or American College of Radiology. Components of accreditation include evidence of physician training, sonographer credentialing, continuing medical education, and protocols and procedures to ensure proper and safe ultrasound practice. One important component is independent review of submitted images.

To standardize ultrasound education for residents in obstetrics and gynecology and fellows in maternal-fetal medicine, the American College of Obstetricians and Gynecologists, the Society for Maternal-Fetal Medicine, and the AIUM have developed consensus documents (Abuhamad, 2018; Benacerraf, 2018). A focus of training—and of ultrasound practice—is standardization of an ultrasound curriculum and provision of competency assessment tools for image acquisition.

TECHNOLOGY AND SAFETY

The image on the ultrasound screen is produced by sound waves that are reflected back from fluid and tissue interfaces of the fetus, amnionic fluid, and placenta. Ultrasound transducers contain groups of piezoelectric crystals that convert electrical energy into sound waves and convert returning sound waves back into electrical energy. The sound waves are emitted in synchronized pulses. As these pulses pass through tissue layers, dense tissue such as bone produces high-velocity reflected waves. With routine gray-scale imaging, which is also known as brightness-mode (B-mode), these reflected waves are displayed as bright echoes on the screen. Conversely, fluid generates few reflected waves and appears dark. Digital images generated at

50 to more than 100 frames per second undergo postprocessing that yields the appearance of real-time imaging.

Ultrasound refers to sound waves traveling at a frequency above 20,000 hertz (Hz [cycles per second]). Transducers use wide-bandwidth technology to perform within a range of frequencies. Higher-frequency transducers yield better image resolution, whereas lower frequencies penetrate tissue more effectively. In early pregnancy, a 5- to 12-megahertz (MHz) transvaginal transducer usually provides excellent resolution, because the early fetus lies close to the transducer. In the first and second trimesters, a 4- to 6-MHz transabdominal transducer is similarly sufficiently close to the fetus to yield precise images. By the third trimester, however, a lower-frequency 2- to 5-MHz transducer may be needed for tissue penetration—particularly in obese patients—and this can lead to compromised image resolution.

Embryo and Fetal Safety

Sonography should be performed only for a valid medical indication and use the lowest possible exposure setting to gain necessary information. This is the *ALARA* principle—as low as reasonably achievable. Examinations are performed only by those trained to recognize fetal abnormalities and artifacts that may mimic pathology and with techniques to avoid ultrasound exposure beyond what is considered safe for the fetus (American College of Obstetricians and Gynecologists, 2020; American Institute of Ultrasound in Medicine, 2018a). No causal relationship has been demonstrated between diagnostic ultrasound and any recognized adverse effect in human pregnancy. The International Society of Ultrasound in Obstetrics and Gynecology (2016) further concludes that there is no scientifically proven association between ultrasound exposure in the first or second trimesters and autism spectrum disorder or its severity.

All ultrasound machines are required to display two indices: the *thermal index* and the *mechanical index*. The thermal index measures the relative probability that the examination may raise the temperature enough to induce injury. However, fetal damage resulting from commercially available ultrasound equipment in routine practice is extremely unlikely. The potential for temperature elevation is higher with longer examination time and is greater near bone than in soft tissue. Theoretical risks are higher during organogenesis than later in gestation. The thermal index for soft tissue, *Tis*, should be used before 10 weeks' gestation, and that for bone, *Tib*, at or beyond 10 weeks (American Institute of Ultrasound in Medicine, 2018a).

The thermal index is higher with pulsed Doppler applications than with routine B-mode scanning. In the first trimester, if pulsed Doppler is clinically indicated, the thermal index should be ≤ 0.7, and the exposure time should be as brief as possible (American Institute of Ultrasound in Medicine, 2020b). This is an important consideration when pulsed Doppler is applied to assist with identification or characterization of suspected abnormalities at 11 to 14 weeks' gestation. To document the embryonic or fetal heart rate, motion-mode (M-mode) scanning is used instead of pulsed Doppler imaging.

The mechanical index is a measure of the likelihood of adverse effects related to rarefactional pressure, such as cavitation, which is relevant only in tissues that contain air. Microbubble ultrasound contrast agents are not used in pregnancy for this reason. In mammalian tissues that do not contain gas bodies, no adverse effects have been reported over the range of diagnostically relevant exposures. Fetuses cannot contain gas bodies and thus are not considered at risk.

The use of ultrasound for any nonmedical purpose, such as "keepsake fetal imaging," is considered *contrary to responsible medical practice* and is not condoned by the Food and Drug Administration (FDA) (2019), the American Institute of Ultrasound in Medicine (2020b), or the American College of Obstetricians and Gynecologists (2020b). However, images or video clips from medically indicated ultrasound examinations may be shared with patients.

Operator Safety

The reported prevalence of work-related musculoskeletal discomfort or injury among sonographers approximates 70 percent (Janga, 2012; Roll, 2012). The most common injuries are capsulitis and tendonitis of the shoulder, epicondylitis of the elbow, carpal and cubital tunnel syndrome, and neck or back strain (Murphey, 2018). The main risk factors for injury during transabdominal ultrasound examinations are awkward posture, sustained static forces, and various pinch grips used to maneuver the transducer (Centers for Disease Control and Prevention, 2006). Excessive flexion, extension, or abduction while scanning places stress on joints and muscles. Task repetition without adequate recovery time may compound risks. Maternal habitus can be contributory because more force is often needed when imaging obese patients.

The following guidelines may help avert injury:

1. Position the patient close to you on the examination table. As a result, your elbow is close to your body, shoulder abduction is <30 degrees, and your thumb is facing up.
2. Adjust the table or chair height so that your forearm is parallel to the floor.
3. Use a chair with back support, if seated. Avoid leaning toward the patient or monitor. Support your feet, and keep ankles in neutral position.
4. Face the monitor squarely and position it so that it is viewed at a neutral angle from the horizon, such as 15 degrees downward.
5. Avoid reaching, bending, or twisting while scanning.
6. Take frequent breaks to help prevent muscle strain. Stretching and strengthening exercises can be helpful.

GESTATIONAL AGE ASSESSMENT

Gestational age is based on two things: the certainty of the woman's last menstrual period (LMP) date and measurements of the embryo or fetus at the initial ultrasound examination. Gestational sac measurement is not suitable for gestational age assignment. If the LMP is certain, the estimated due date (EDD) is based on LMP unless the date–measurement discrepancy exceeds thresholds listed in Table 14-1 (American College of Obstetricians and Gynecologists, 2019b,c). If the

TABLE 14-1. Assessment of Gestational Age

Gestational Age[a]	Parameter(s)	Threshold Value to Redate[b]
<9 wks	CRL	>5 d
9 to <14 wks	CRL	>7 d
14 to <16 wks	BPD, HC, AC, FL	>7 d
16 to <22 wks	BPD, HC, AC, FL	>10 d
22 to <28 wks	BPD, HC, AC, FL	>14 d
≥28 wks	BPD, HC, AC, FL	>21 d

[a]Based on last menstrual period (LMP).
[b]Ultrasound gestational age should be used if it differs from the LMP-derived gestational age by more than the threshold value.
AC = abdominal circumference; BPD = biparietal diameter; CRL = crown-rump length; FL = femur length; HC = head circumference.

discrepancy exceeds these thresholds, or if the LMP is uncertain or unknown, ultrasound measurements establish the EDD.

Ultrasound measurement of the crown-rump length (CRL) is the most accurate method to establish or confirm gestational age (Appendix, p. 1234). Transvaginal imaging yields higher resolution images. The CRL is measured in the midsagittal plane with the embryo or fetus in a neutral, nonflexed position. This allows its length to be measured in a straight line (Fig. 14-1). The mean of three discrete measurements is used. Before 14 weeks' gestation, the CRL is accurate to within 5 to 7 days (American College of Obstetricians and Gynecologists, 2019c).

Starting at $14^{0/7}$ weeks' gestation, the biparietal diameter, head circumference, abdominal circumference, and femur length should be measured. Equipment software formulas calculate estimated gestational age and fetal weight from these four biometric parameters. The accuracy of the fetal weight estimate is assumed to be within 15 percent of the actual weight (American Institute of Ultrasound in Medicine, 2018a). Measurement criteria are discussed in Chapter 15 (p. 272).

Before 22 weeks, gestational age assessment using these four biometric parameters is accurate to within 7 to 10 days (American College of Obstetricians and Gynecologists, 2019c). Various nomograms are available for other structural measurements, including the transverse cerebellar diameter, orbital distances, thoracic circumference, and length of the ear, kidney, long bones, and feet. These may be used to address specific questions regarding organ system abnormalities or syndromes (Appendix, pp. 1238–1241).

If the initial ultrasound examination is performed at or beyond 22 weeks' gestation, the pregnancy is *suboptimally dated* (American College of Obstetricians and Gynecologists, 2019b). In such cases, subsequent ultrasound evaluation in 3 to 4 weeks may be considered. This is especially true if the ultrasound measurements are smaller than expected for gestational age based on LMP and thus poor fetal growth is a possibility.

Fertilization is presumed to occur 2 weeks after a confident LMP. Therefore, for pregnancies achieved with in vitro fertilization and fresh transfer, 266 days are added to the egg-retrieval/fertilization date to calculate the EDD. Similarly, if using a day-3 frozen embryo, adding 263 days accounts for the days of embryo culture. For pregnancies conceived with intrauterine insemination, LMP is used.

FIRST-TRIMESTER ULTRASOUND

The three types of first-trimester examinations include standard ultrasound; nuchal translucency evaluation—between 11 and 14 weeks' gestation; and detailed first-trimester anatomy evaluation between 12 and 14 weeks' gestation.

Indications for the standard first-trimester examination are listed in Table 14-2 (American College of Obstetricians and Gynecologists, 2020; American Institute of Ultrasound in Medicine, 2018a). Early pregnancy can be evaluated with transabdominal or transvaginal sonography, or both. The components listed in Table 14-3 should be assessed (American

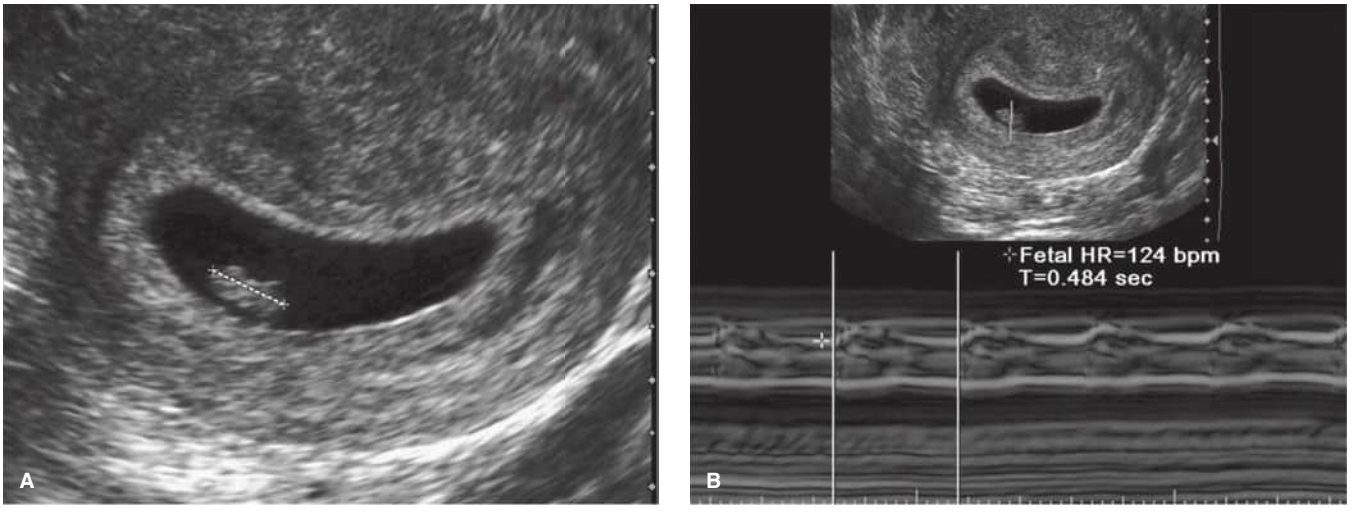


FIGURE 14-1 A. The measured crown-rump length is approximately 7 mm in this 6-week embryo. **B.** M-mode demonstrates embryonic cardiac activity and a heart rate of 124 beats per minute.

TABLE 14-2. Indications for First-Trimester Ultrasound Examination

Confirm an intrauterine pregnancy
Estimate gestational age
Confirm cardiac activity
Diagnose/evaluate a multifetal gestation, including chorionicity and amnionicity
Assess for certain fetal anomalies, such as anencephaly
Measure fetal nuchal translucency, when part of an aneuploidy screening program
Evaluate for uterine abnormalities or pelvic masses
Evaluate for suspected ectopic pregnancy
Evaluate for suspected gestational trophoblastic disease
Evaluate for the cause of vaginal bleeding
Evaluate for the cause of pelvic pain
Serve as adjunct to embryo transfer, chorionic villus sampling, and intrauterine device localization and removal

College of Obstetricians and Gynecologists, 2020; American Institute of Ultrasound in Medicine, 2018a). The first trimester is the ideal time to evaluate the uterus, adnexa, and cul-de-sac. Ultrasound interrogation at this time can reliably diagnose anembryonic gestation, embryonic demise, ectopic pregnancy, and gestational trophoblastic disease. In a multifetal gestation, determination of chorionicity is most accurate in the first trimester (Chap. 48, p. 841). Gestational sac implantation in a prior cesarean scar is increasingly detected in the first trimester as well.

An intrauterine gestational sac may be consistently visualized with transvaginal sonography by 5 weeks' gestation, and an embryo with cardiac activity by 6 weeks. The embryo should be visible transvaginally once the mean sac diameter has reached 25 mm—otherwise the gestation is *anembryonic*. Whenever an embryo or fetus is identified, it should be measured, and cardiac motion should be documented with either video clip or M-mode scanning (see Fig. 14-1B). Cardiac motion may be visible with transvaginal imaging when the length of the embryo is 2 mm and should be visible at 7 mm in a live embryo (American College of Obstetricians and Gynecologists, 2020). If an embryo measures <7 mm and has no visible cardiac activity, subsequent examination is recommended in 1 week (American Institute of Ultrasound in Medicine, 2018a). At Parkland Hospital, first-trimester demise is diagnosed with transvaginal ultrasound if the embryo has reached 10 mm and lacks cardiac motion, taking measurement error into consideration. Criteria to diagnose first-trimester demise are found in Table 11-2 (p. 202).

A recent addition to the standard first-trimester examination is an assessment of selected anatomical components when fetal size permits. These include the calvarium, umbilical cord insertion into the ventral wall, and presence of extremities (American Institute of Ultrasound in Medicine, 2018a).

Nuchal Translucency

This represents the maximum thickness of the subcutaneous translucent area between the skin and soft tissue overlying the fetal spine at the back of the neck. The nuchal translucency (NT) is measured in the sagittal plane between 11 and 14 weeks' gestation using precise criteria (Table 14-4) (American Institute of Ultrasound in Medicine, 2018a; International Society of Ultrasound in Obstetrics and Gynecology, 2016). When the NT measurement is increased, the risk for fetal aneuploidy and various structural anomalies—in particular heart defects—is significantly elevated. It is a component of first-trimester

TABLE 14-3. Components of Standard Ultrasound Examination by Trimester

First Trimester[a]	Second and Third Trimester
Gestational sac size, location, and number	Gestational age assessment
Embryo and/or yolk sac identification	Fetal number, including amnionicity and chorionicity of multifetal gestations
Crown-rump length	Fetal weight estimation
Gestational age assessment	Fetal anatomical survey, including documentation of technical limitations
Fetal number, including amnionicity and chorionicity of multifetal gestations	Fetal cardiac activity, documented with M-mode or 2-dimensional video clip
Embryonic/fetal cardiac activity, documented with M-mode or 2-dimensional video clip	Fetal presentation
Fetal anatomy assessment including calvarium, nuchal region, ventral wall cord insertion, and presence of limbs (depending on gestational age and fetal size)	Amnionic fluid measurement (single deepest pocket, amniotic fluid index, or qualitative assessment)
Fetal nuchal translucency assessment	Placental location, appearance, and relationship to internal cervical os[a]
Maternal uterus, adnexa, and cul-de-sac evaluation	Placental cord insertion site documentation when technically possible
	Evaluation of the maternal uterus, adnexa, and cervix[a]

[a]If a transabdominal examination is not definitive, transvaginal (or transperineal) evaluation is recommended.

TABLE 14-4. Guidelines for Nuchal Translucency (NT) Measurement

Angle of insonation is perpendicular to NT line
Fetus is measured in midsagittal plane, with nasal tip, palate, and diencephalon visible
Margins of NT edges are visible
Majority of image is filled by the fetal head, neck, and upper thorax
Fetal neck lies in a neutral position, not flexed or hyperextended
Amnion line must be separate from the NT line
+ calipers are placed perpendicular to the fetal long axis, on the inner borders of the nuchal membranes, with none of the horizontal crossbar protruding into the space
Measurement should be obtained at the widest NT space
Largest of 3 NT measurements should be used

aneuploidy screening, which is discussed in Chapter 17 (p. 337). The aneuploidy risk calculation depends on the crown-rump length. However, an NT measurement ≥3 mm is associated with increased risk for fetal structural or genetic abnormalities and is an indication for a detailed fetal anatomical survey.

Detailed First-Trimester Ultrasound Examination

Assessment for fetal abnormalities in an at-risk pregnancy may include a detailed survey of fetal anatomy at 12 to 14 weeks' gestation. Such examinations are a recent addition and limited to specialized centers with advanced imaging skills, although use may be expected to expand. *Despite improvements in imaging technology, it is not realistic to expect that all major abnormalities detectable in the second trimester may be visualized in the first trimester.* Abnormalities may change in appearance as the fetus develops, and new findings may become evident. If an abnormality is identified in the first trimester, detailed second-trimester sonography will be important to further characterize the findings or identify associated abnormalities. In an at-risk pregnancy, a normal first-trimester examination does not obviate the recommendation for a detailed second-trimester fetal anatomical survey.

In a systematic review of more than 118,000 pregnancies undergoing fetal NT assessment, 46 percent of major abnormalities were detected in low-risk or unselected pregnancies (Karim, 2017). In high-risk pregnancies, anomaly detection exceeded 60 percent. Detection rates are high for fetal anencephaly, alobar holoprosencephaly, and ventral wall defects. However, in one series of 40,000 pregnancies with fetal anatomical evaluation at the time of NT assessment, only a third of major cardiac anomalies were identified. No cases of microcephaly, agenesis of the corpus callosum, cerebellar abnormalities, congenital pulmonary airway malformations, or bowel obstruction were detected (Syngelaki, 2011). Some of these abnormalities had not yet developed by the end of the first trimester, and this is an important caveat for counseling.

SECOND- AND THIRD-TRIMESTER ULTRASOUND

Ultrasound should be routinely offered to all pregnant women between 18 and 22 weeks' gestation (American College of Obstetricians and Gynecologists, 2020). Recognizing that the gestational age at which an abnormality is identified may affect pregnancy management options, providers often opt to perform the examination before 20 weeks. Indications for second- and third-trimester sonograms are listed in Table 14-5 (American College of Obstetricians and Gynecologists, 2020; American Institute of Ultrasound in Medicine, 2018a). Based on data from large insurance providers, pregnant women typically receive at least 4 to 5 sonograms per pregnancy (O'Keeffe, 2013). Examinations are classified as standard, specialized, or limited. Specialized examination types include the detailed fetal anatomy examination, detailed evaluation for placenta accreta spectrum (p. 253), fetal echocardiography, Doppler velocimetry (p. 262), and the biophysical profile (Chap. 20, p. 389).

Standard Second- and Third-Trimester Ultrasound Examinations

The standard examination includes evaluation of fetal number and presentation, cardiac activity, fetal biometry, amnionic fluid volume, placental location, cervical length, and a survey of fetal anatomy (see Table 14-3). Anatomical components are listed in Table 15-1 (p. 273). With twins or other multiples, documentation should also include the number of chorions

TABLE 14-5. Indications for Standard Second- and Third-trimester Ultrasound Examinations

Routine evaluation of gestational age and fetal anatomy[a]
Fetal growth evaluation or size-date discrepancy
Fetal abnormality (follow-up evaluation)
Amniocentesis or other procedure
Cervical length assessment
Multifetal gestation
Vaginal bleeding
Placenta previa or low-lying placenta[b]
Vasa previa[b]
Placenta accreta spectrum[b]
Placental abruption[b]
Uterine or adnexal abnormality[b]
Gestational trophoblastic disease[b]
Amnionic fluid volume abnormality[b]
Preterm rupture of membranes or preterm labor
Inability to document fetal heart tones
Assessment of fetal well-being
Assessment of fetal presentation
Adjunct to external cephalic version

[a]Standard ultrasound examination should be offered in all pregnancies, ideally at 18–20 weeks' gestation.
[b]Includes evaluation of suspected cases.

and amnions, comparison of fetal sizes, estimation of amnionic fluid volume within each sac, and fetal phenotypic gender.

The American Institute of Ultrasound in Medicine (2018a) revised its prior 2013 standard ultrasound practice parameter to include the following updates:

1. Components added to the standard fetal anatomical survey are presence of the hands and feet, and when feasible, the three-vessel view and three-vessel trachea views of the heart (Fig. 15-37, p. 290).
2. If the relationship between placenta and cervix cannot be assessed transabdominally, transvaginal evaluation should be performed. Transperineal evaluation remains an option but in our experience is rarely used.
3. If the cervix appears abnormal or is not adequately visualized transabdominally, transvaginal (or transperineal) examination is recommended. If cervical length assessment is requested, measurement should be based on a transvaginal image.
4. In the setting of velamentous cord insertion, color and pulsed Doppler ultrasound should be used to evaluate for vasa previa (Figs. 6-6 and 6-7, p. 115).

Detailed Second- and Third-Trimester Ultrasound Examinations

The *detailed fetal anatomy* examination is also known as a targeted or 76811 examination. It is performed when the risk for a fetal structural or genetic abnormality is elevated because of history, screening test result, or abnormal finding during standard examination (Table 14-6) (American Institute of Ultrasound in Medicine, 2019). The detailed ultrasound examination is intended to be indication-driven and is not repeated without an extenuating circumstance, such as a new risk factor (American Institute of Ultrasound in Medicine, 2019). Physicians who perform or interpret these ultrasound examinations should have gained expertise in fetal imaging through both training and ongoing experience (American College of Obstetricians and Gynecologists, 2020).

Components of the detailed examination are intended to be determined on a case-by-case basis. Table 15-1 (p. 273) lists nearly 70 anatomical components that may be included. When practices apply for adjunct accreditation in performance of the detailed fetal anatomic survey, the American Institute of Ultrasound in Medicine specifies 50 components that must be included when submitting normal cases for review. At Parkland Hospital, we attempt to image these components in all detailed anatomic surveys. When performing a given detailed examination, one challenge is determining which components are needed for a given indication, as these have not been codified. The most prevalent risk factors and thus indications for detailed ultrasound examinations are maternal obesity and maternal age ≥35 years. In a systematic review of more than 16,000 pregnancies affected by anomalies, obesity conferred modestly

TABLE 14-6. American Institute for Ultrasound in Medicine Indications for Detailed Second- and Third-trimester Ultrasound Examinations

Prior fetus or infant with a structural or genetic abnormality
Current pregnancy with known or suspected fetal abnormality or growth restriction
Increased risk for fetal structural abnormality in current pregnancy
Teratogen exposure (Chap. 8)
Diabetes diagnosed before 24 weeks' gestation
Nuchal translucency ≥3.0 mm
Abnormal serum analyte levels (e.g., elevated alpha fetoprotein)
Assisted reproductive technology used to achieve conception
Prepregnancy body mass index ≥30 kg/m^2
Multifetal gestation
Increased risk for fetal genetic abnormality in current pregnancy
Woman or her partner carries a genetic abnormality
Maternal age ≥35 years at delivery
Nuchal translucency ≥3.0 mm
Abnormal aneuploidy screening test result (Chap. 17, p. 333)
Minor aneuploidy marker found during standard ultrasound examination
Other condition affecting the fetus
Congenital infection (Chaps. 67, 68)
Substance abuse
Alloimmunization (Chap. 18, p. 352)
Amnionic fluid volume abnormality
Suspected placenta accreta spectrum or associated risk factors

Adapted with permission from American Institute of Ultrasound in Medicine (AIUM): Practice parameter for the performance of detailed second- and third-trimester diagnostic obstetric ultrasound examinations. J Ultrasound Med 38(12):3093, 2019.

increased odds of a neural-tube defect (1.9), ventriculomegaly (1.7), cardiovascular anomaly (1.3), cleft lip/palate (1.2), anorectal atresia (1.5), and limb reduction defect (1.7) (Stothard, 2009). Subsequently, Biggio and colleagues (2010) reported that obesity was associated with a higher anomaly prevalence only in the setting of diabetes. Maternal age ≥35 years is considered another indication for detailed sonographic examination. However, the fetal anomaly risk may be related to the associated increase in aneuploidy. Goetzinger and colleagues (2017) found that the anomaly rate among euploid fetuses born to older mothers was not increased.

Fetal Echocardiography

This specialized examination of fetal cardiac structure and function is designed to identify and characterize abnormalities. Echocardiography indications include suspected fetal cardiac structural or functional abnormality; heart rate abnormality or arrhythmia; extracardiac anomaly or hydrops; chromosomal abnormality; nuchal translucency ≥3.5 mm; in vitro fertilization; monochorionic twin gestation; first-degree relative to the fetus with a congenital cardiac defect; first- or second-degree relative to the fetus with a Mendelian syndrome and childhood cardiac manifestation; prior fetus with heart block in the setting of maternal anti-Ro or La antibodies; retinoid exposure; and metabolic risk factor such as pregestational diabetes or phenylketonuria (American Institute of Ultrasound in Medicine, 2020a). Selected cardiac anomalies are reviewed in Chap. 15 (p. 291).

Limited Ultrasound Examination

A *limited* second- or third-trimester examination is performed to address a specific clinical question. Evaluation of fetal number, presentation, and cardiac activity; amnionic fluid volume; and placental location with respect to the internal os are common indications (American Institute of Ultrasound in Medicine, 2018b). The examination may include fetal biometry but not a complete anatomical survey. In the absence of an emergency, a limited examination is performed only if a standard ultrasound survey has already been completed. Otherwise, provided that the gestational age is at least 18 weeks, a standard ultrasound examination is recommended.

Fetal Anomaly Detection

With current advances in imaging technology, approximately 60 percent of major fetal abnormalities may be detected during standard ultrasound examinations (Byrne, 2020; Rydberg, 2017). For detailed ultrasound surveys performed in pregnancies at increased risk for anomalies, detection rates may exceed 90 percent (Dashe, 2009; Levi, 1998). The sensitivity of the examination varies according to factors such as gestational age, maternal habitus, fetal position, equipment features, examination type, operator skill, and the specific abnormality. For example, maternal obesity lowers the anomaly detection rate by 20 percent (Dashe, 2009).

Detection rates vary considerably according to the abnormality. In the EUROCAT network of 28 population-based registries, 40 percent of major fetal abnormalities are detected prenatally (EUROCAT, 2019). Detection rates of selected abnormalities are as follows: anencephaly, 98 percent; spina bifida, 89 percent; hydrocephaly, 82 percent; cleft lip/palate, 70 percent; hypoplastic left heart, 88 percent; transposition of the great vessels, 69 percent; diaphragmatic hernia, 73 percent; gastroschisis, 92 percent; omphalocele, 90 percent; bilateral renal agenesis, 94 percent; posterior urethral valves, 80 percent; limb reduction defects, 60 percent; and clubfoot, 60 percent. In contrast, anomalies with poor sonographic detection rates in the second trimester include microcephaly, choanal atresia, cleft palate, Hirschsprung disease, anal atresia, and congenital skin disorders. Although clinicians tend to focus on abnormalities amenable to sonographic detection, those that are undetectable can be no less devastating to families. *Every sonographic examination should include a frank discussion of examination limitations.*

Three-Dimensional Ultrasound Examination

Over the past three decades, three-dimensional (3-D) ultrasound has gone from a novelty to a feature of all modern equipment. After a region of interest is identified, a volume is acquired using a 3-D transducer. This volume can be rendered to display axial, sagittal, coronal, or oblique images. Sequential slices may be generated, similar to computed tomographic (CT) images. Unlike two-dimensional (2-D) scanning, which appears to be happening in real time on the screen, 3-D imaging is static and obtained by processing a volume of stored images. With *four-dimensional ultrasound*, rapid reconstruction of the rendered images conveys the impression that the scanning is in real time.

For selected anomalies, such as those of the face and skeleton, for tumors, and for some cases of neural-tube defects, 3-D sonography can add useful information (American College of Obstetricians and Gynecologists, 2020; Goncalves, 2005). That said, comparisons of 3-D and conventional 2-D sonography for the diagnosis of most congenital anomalies have not demonstrated better overall detection rates (Goncalves, 2006; Reddy, 2008). The American College of Obstetricians and Gynecologists (2020b) has concluded that proof of a clinical advantage of 3-D ultrasound for prenatal diagnosis is generally lacking.

PLACENTA AND CERVIX

The standard examination includes evaluation of the anatomical relationship between the placenta and the internal cervical os, the umbilical cord insertion into the placenta, and cervical length assessment. (American Institute of Ultrasound in Medicine, 2018a). Evaluation for placenta accreta spectrum is a detailed examination type (see Table 14-6).

Placenta Previa and Low-lying Placenta

The location of the placenta with respect to the cervix may be accurately assessed by approximately 16 weeks' gestation. If transabdominal visualization is limited, transvaginal ultrasound is recommended. *Placenta previa* is diagnosed if the placenta overlies the internal cervical os to any degree or

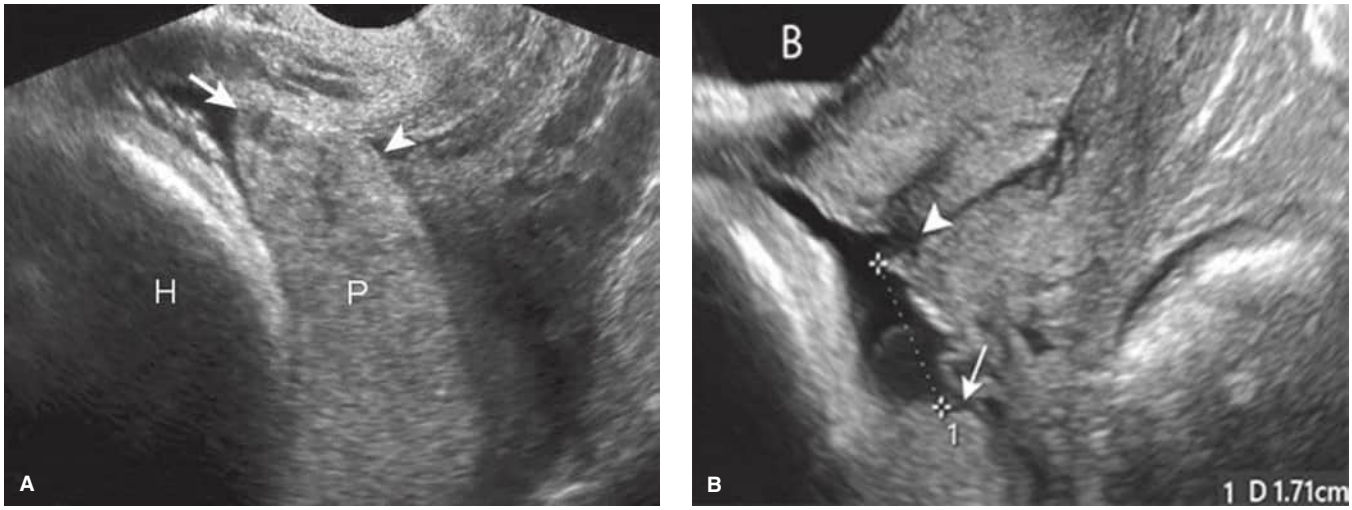


FIGURE 14-2 A. Placenta previa. In this transvaginal image, the inferior edge (*arrow*) of the posterior placenta (*P*) overlies the internal cervical os (*arrowhead*). H = head. **B.** Low-lying placenta. The inferior placental edge (*arrow*) is within 2 cm of the internal cervical os (*arrowhead*) in this transvaginal image. The bladder (B) is seen anterior to the cervix.

reaches its margin (Fig. 14-2A). If the inferior placental edge is within 2 cm of the internal os but does not reach the cervix, the diagnosis is *low-lying placenta* (see Fig. 14-2B). Whenever placenta previa or low-lying placenta are diagnosed, a follow-up ultrasound examination is recommended at approximately 32 weeks' gestation, with transvaginal evaluation if needed to verify the relationship between the placenta and cervix. If findings persist, a 36-week ultrasound examination also is recommended. Management of these placenta types are discussed in Chapter 43 (p. 757).

The umbilical cord insertion into the placenta should be interrogated. Marginal cord insertion, also known as *battledore placenta*, is diagnosed if the umbilical cord inserts into the edge of the placenta or within 2 cm of the placental margin. If the umbilical cord does not insert into the placenta—but rather into the membranes—the diagnosis is *velamentous cord insertion* (Fig. 6-6, p. 115). With the latter, the umbilical arteries and vein traverse the membranes along the uterine wall unprotected by Wharton jelly before entering the placental margin. If umbilical vessels course within the portion of membrane overlying the cervix or within 2 cm of the cervix, the diagnosis is *vasa previa* (Fig. 6-7, p. 116). Vasa previa may also occur if there are two or more placental lobes—as with a succenturiate lobe—and the interconnecting vessels traverse the intervening membranes over or in proximity to the internal cervical os. Transvaginal ultrasound with color Doppler highlights the vessels, and pulsed-wave Doppler of the spanning arterial vessel demonstrates a fetal heart rate, which confirms the diagnosis. A subsequent detailed ultrasound examination is recommended at 32 weeks' gestation (Society for Maternal-Fetal Medicine, 2015b). Chapter 6 (p. 114) contains content on management of these entities.

■ Placenta Accreta Spectrum

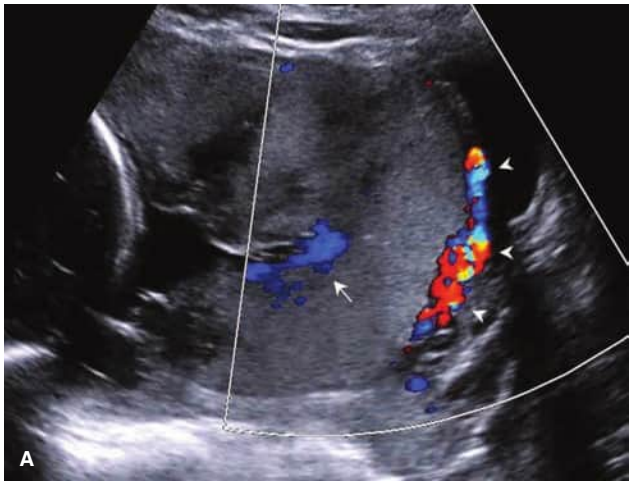
Placenta accreta, increta, and percreta comprise the placenta accreta spectrum (PAS). They are characterized by abnormal placental invasion onto, into, or through the myometrium, respectively (Chap. 43, p. 759). Evaluation includes transabdominal and transvaginal imaging, with and without color or power Doppler and with the patient's bladder partially filled. In one metaanalysis that included more than 3200 pregnancies, the sensitivity of ultrasound to identify placenta accreta, increta, and percreta was 91, 93, and 89 percent, respectively. Corresponding specificities were 97, 98, and 99 percent, respectively (Pagani, 2018). Five ultrasound criteria assist with detection and characterization of PAS (Fig. 14-3):

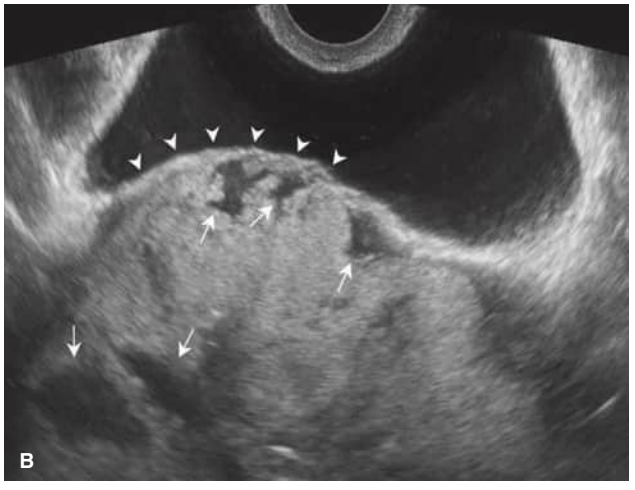
1. Placental *lacunae*, which are vascular spaces that may contain prominent color Doppler flow
2. Attenuation or thinning of the retroplacental myometrium, such that the *smallest myometrial thickness* measurement is <1 mm. This is also referred to as loss of the retroplacental clear space
3. Disruption of the bladder-uterine serosal interface, which appears as an irregular, echogenic boundary between the bladder and uterine serosa with gray-scale imaging
4. Bridging vessels, which are demonstrated with color Doppler to course from the placenta to the bladder-serosal interface
5. A placental "bulge" that pushes outward and distorts the contour of the uterus or other organs. In some cases of placenta percreta, a focal exophytic mass also is seen.

The accuracy of these criteria varies in published series and is affected by the number and predictive value of given findings and by associated risk factors such as placenta previa and number of prior cesarean deliveries (Jauniaux, 2016; Rac, 2015). Serial evaluation may be helpful, particularly in the third trimester. With concurrent placenta previa and history of cesarean delivery, any of these ultrasound findings prompts a detailed ultrasound evaluation. The role of magnetic resonance (MR) imaging as an adjunct in pregnancies with suspected PAS is reviewed later (p. 268).

■ Cesarean Scar Pregnancy

Placental implantation within a prior hysterotomy scar—termed cesarean scar pregnancy (CSP)—is often a precursor





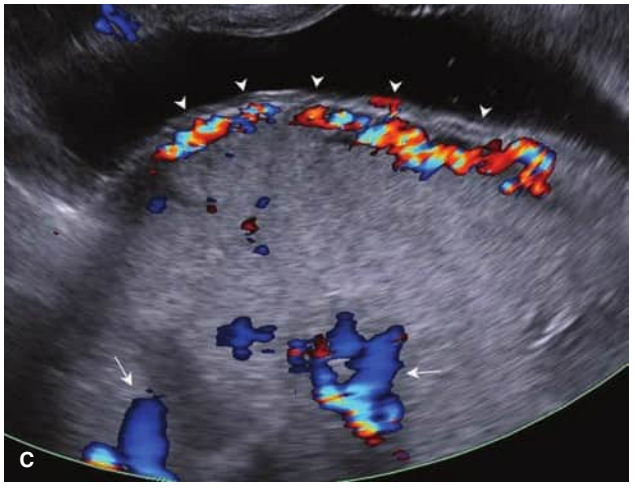


FIGURE 14-3 These third-trimester sonograms demonstrate findings that characterize placenta accreta spectrum. **A.** Transabdominal color mapping depicts bridging vessels between the bladder and the uterine serosa (*arrowheads*) and shows large intraplacental lacunae (*arrow*). **B.** Transvaginal transverse image showing a large bulge (suggesting placenta percreta) along the bladder-uterine serosal interface (*arrowheads*) and multiple large, irregular lacunae (*arrows*). **C.** Disruption of the bladder-serosal interface. The echogenic interface between bladder and serosa appears irregular (*arrowheads*). The smallest myometrial thickness measures <1 mm, and bridging vessels are highlighted by color Doppler. Large lacunae also are shown (*arrows*).

to second- or third-trimester PAS (Happe, 2020; Rac, 2016; Timor-Trisch, 2014). Sonographically, the gestational sac lies low and anteriorly in the uterus. CSPs may appear to rest on the prior scar or may fill the *niche*, which is a myometrial pocket defect in the thinned hysterotomy scar (Kaelin Agten, 2017). Placental sonolucencies, a precursor to PAS lacunae, may be seen. The retroplacental myometrium may be attenuated to a degree that the distance from the anterior trophoblastic border to the uterine serosa measures <3 mm (D'Antonio, 2018; Moschos, 2014; Happe, 2020). Color Doppler may demonstrate prominent vascularity in the region of the prior hysterotomy scar (Fig. 14-4). In some cases, the gestational sac may bulge toward the bladder. CSP evaluation and management are discussed in Chapter 12 (p. 229).

■ Cervical Length

Although the cervix may be imaged transabdominally (Fig. 14-5A), visualization is often limited by maternal habitus, cervical position, or shadowing by the fetal presenting part. In addition, the maternal bladder or pressure from the transducer may artificially elongate the cervix's appearance. As a result, values from transabdominal or transvaginal measurement of the cervix can differ significantly.

If the cervix appears short or is inadequately visualized during transabdominal evaluation, transvaginal assessment should be considered (American Institute of Ultrasound in Medicine, 2018a). Clinical decision-making should use only cervical length measurements obtained transvaginally (Fig. 14-5B). Measurement should be performed at or beyond 16 weeks' gestation. A short cervix is associated with an elevated risk for preterm birth, particularly in those with prior preterm birth. Risk rises proportionally with the degree of cervical shortening (Chap. 45, p. 793).

To measure the cervix transvaginally, the imaging criteria shown in Table 14-7 are followed. The endocervical canal should be visible in its entirety, and images ideally are obtained over several minutes to capture dynamic change. *Funneling* is a protrusion of amnionic membranes into a portion of the endocervical canal that has dilated (Fig. 14-6). Funneling is not an independent predictor of preterm birth but is associated with cervical shortening. Transvaginal assessment is recommended if a funnel is suspected transabdominally. The cervical length is measured distal to the funnel, because the funnel's base becomes the functional internal os. If the cervix is dilated, as with cervical insufficiency, the membranes may prolapse through the endocervical canal and into the vagina to produce an hourglass appearance. *Sludge* represents an aggregate of particulate matter (debris) within the amnionic sac and close to the internal os. In pregnancies at risk for preterm birth, sludge further raises the risk.

AMNIONIC FLUID

■ Physiology

Amnionic fluid serves several roles. Fetal breathing is essential for normal lung growth, and fetal swallowing permits

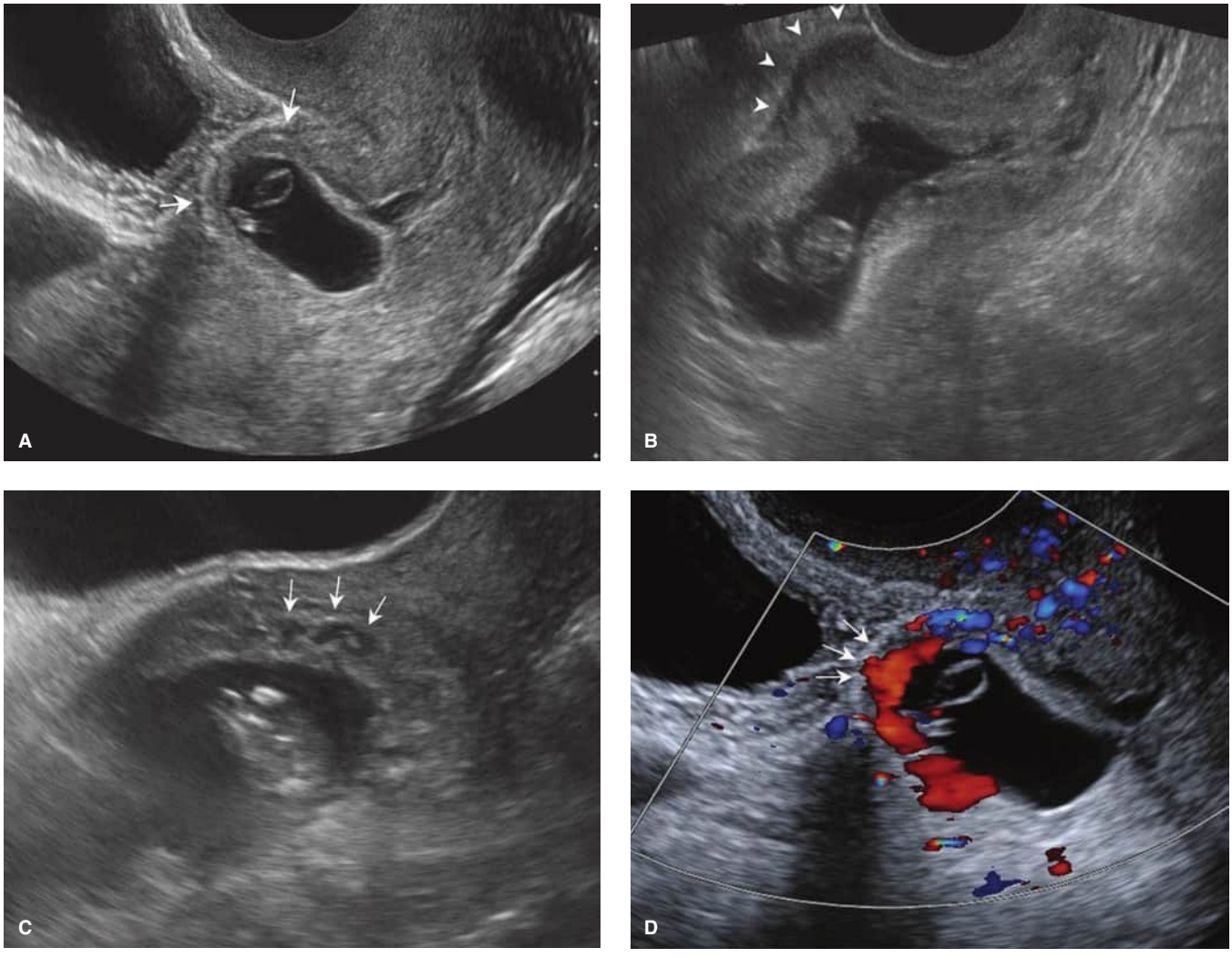


FIGURE 14-4 Cesarean scar pregnancy, transvaginal images. **A.** The trophoblast appears to fill the scar "niche" (*arrows*). **B.** Outward bulging of the gestational sac toward the bladder (*arrowheads*). **C.** Placental sonolucencies (*arrows*). **D.** Attenuation of the retroplacental myometrium. The distance from the anterior trophoblastic border to the uterine serosa is <1 mm (*arrows*). Color Doppler demonstrates vascularity in the region of the prior hysterotomy scar.

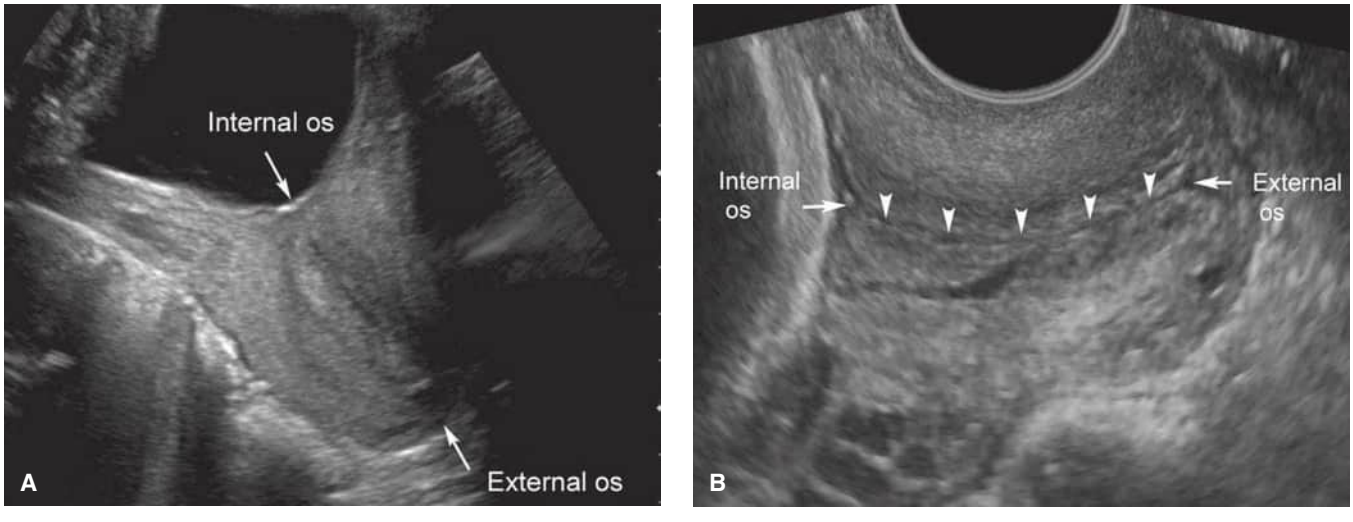


FIGURE 14-5 **A.** Transabdominal image of the cervix depicting the internal os and external os. **B.** Transvaginal imaging provides a more accurate evaluation of the cervix and should be used for medical decision-making. In this image, arrowheads mark the endocervical canal. (Reproduced with permission from Dr. Emily Adhikari.)

TABLE 14-7. Criteria for Transvaginal Evaluation of the Cervix

Imaging the Cervix

- Maternal bladder should be empty.
- Transducer is inserted under real-time observation, identifying midsagittal plane, internal os, and then external os, while keeping the internal os in view.
- Internal os, external os, and entire endocervical canal should be visible. The internal os may appear as a small triangular indentation at the junction of the amnionic cavity and endocervical canal.
- Image is enlarged so that the cervix fills approximately 75% of the screen.
- Anterior and posterior width of the cervix should be approximately equal.
- Transducer is pulled back slightly until the image begins to blur, ensuring that pressure is not placed on the cervix, then inserted only enough to restore a clear image.
- Images should be obtained with and without fundal or suprapubic pressure, to assess for dynamic change or shortening on real-time imaging.

Measuring the Cervix

- Calipers are placed at the point where anterior and posterior walls of cervix meet.
- Endocervical canal appears as a faint, linear echodensity.
- If canal has a curved contour, a straight line between the internal and external os will deviate from the path of the endocervical canal.
- If midpoint of the line between the internal and external canal deviates by ≥3 mm from the endocervical canal, measure the cervical length in two linear segments.
- Funneling, sludge (debris), or dynamic change is noted.
- At least three separate images are measured during a period of at least 3 minutes to allow for dynamic change. Visualization of cervical shortening on real-time imaging, with or without fundal or suprapubic pressure, raises preterm birth risks.
- Shortest cervical length image that meets all criteria should be used.

Adapted from American Institute of Ultrasound in Medicine, 2018a; Iams, 2013.

gastrointestinal (GI) tract development. The fluid also creates a physical space for fetal movement, which is necessary for neuromusculoskeletal maturation. Amnionic fluid further guards against umbilical cord compression and protects the fetus from trauma. It also has bacteriostatic properties.

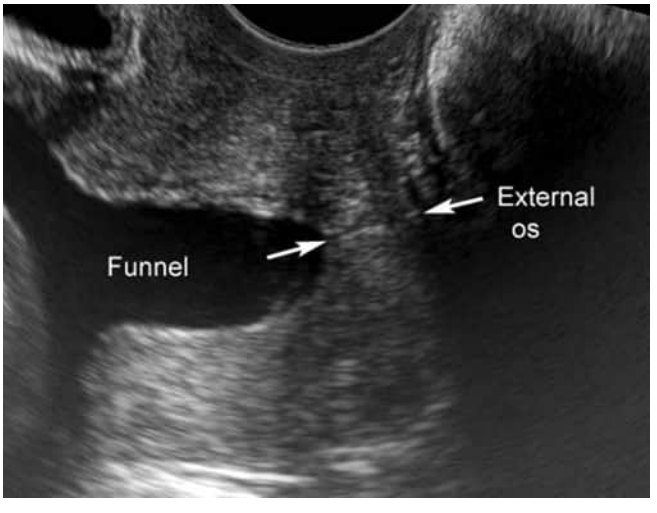


FIGURE 14-6 Transvaginal image depicting a foreshortened cervix with funneling. Funneling is a protrusion of amnionic membranes into a portion of the endocervical canal that has dilated. The distal protruding edge of the funnel becomes the functional internal os (*left arrow*). Thus, the measured cervical length, which lies between the arrows, should not include the funnel. (Reproduced with permission from Dr. Emily Adhikari.)

Early in pregnancy, amnionic fluid is similar in composition to extracellular fluid. Amnionic fluid arises as a transudate of plasma either from the fetus through its nonkeratinized skin or from the mother across the uterine decidua and placenta surface (Beall, 2007). Specifically, early transfer of water and other small molecules occurs via three mechanisms: across the amnion—*transmembranous flow*; across fetal vessels on the placental surface—*intramembranous flow*; and across fetal skin—*transcutaneous flow*. Fetal urine production does not become a major component of amnionic fluid until the second trimester, which explains why fetuses with lethal renal abnormalities may not manifest severe amnionic volume declines until after 18 weeks' gestation. Water transport across the fetal skin continues until keratinization occurs at 22 to 25 weeks. In the second half of pregnancy, fetal urination is the primary source of amnionic fluid. In late gestation, the fetal respiratory tract also produces approximately 350 mL of lung fluid per day. Fetal swallowing is the primary mechanism for amnionic fluid resorption and averages 500 to 1000 mL per day (Mann, 1996). By term, the entire amnionic fluid volume is recirculated on a daily basis (Table 14-8). However, impaired swallowing, secondary to either a central nervous system (CNS) abnormality or GI tract obstruction, can result in impressive amnionic fluid volume expansion.

The osmolality of amnionic fluid is similar to that of fetal urine and *hypotonic* to that of maternal and fetal plasma. Specifically, the osmolality of maternal and fetal plasma approximates 280 mOsm/mL, whereas that of amnionic fluid is about

TABLE 14-8. Amnionic Fluid Volume Regulation in Late Pregnancy

Pathway	Effect on Volume	Approximate Daily Volume (mL)
Fetal urination	Production	1000
Fetal lung fluid secretion	Production	350
Fetal swallowing	Resorption	750
Intramembranous flow across fetal vessels on the placental surface	Resorption	400
Transmembranous flow across amnionic membrane	Resorption	Minimal

Data from Magann, 2011; Modena, 2004; Moore, 2010.

260 mOsm/L. The hypotonicity of amnionic fluid accounts for up to 400 mL per day of intramembranous fluid transfer across and into fetal vessels on the placental surface (Mann, 1996). Maternal dehydration can lead to higher maternal osmolality, which favors fluid transfer from the fetus to mother and then from the amnionic fluid compartment into the fetus (Moore, 2010).

Amnionic fluid volume expands from approximately 30 mL at 10 weeks' gestation to 200 mL by 16 weeks and reaches 800 mL by the mid-third trimester (Brace, 1989; Magann, 1997). Using dye dilution, Magann and associates (1997) reported that the average amnionic fluid volume was approximately 400 mL between 22 and 30 weeks' gestation, then rose to 800 mL until 40 weeks, and subsequently declined by 8 percent per week. There was a wide normal range, particularly in the third trimester. Abnormally decreased fluid volume is termed *oligohydramnios*, whereas abnormally increased fluid volume is termed *hydramnios* or *polyhydramnios*.

■ Semi-quantitative Assessment

Evaluation of amnionic fluid volume is a component of every second- or third-trimester ultrasound examination. Volume is measured semi-quantitatively using the single deepest pocket of fluid or the amnionic fluid index (AFI). Both measurements are reproducible and, in the setting of a fluid abnormality, can be followed serially over time to assess trends and aid communication among providers. For this reason, subjective assessment alone is not recommended.

The single deepest pocket of fluid is measured in a sagittal plane with the ultrasound transducer held perpendicular to the floor and parallel to the long axis of the woman. A pocket should be at least 1 cm wide to be considered adequate, and the measurement should not include fetal parts or loops of umbilical cord. Color Doppler is generally used to verify that umbilical cord is not within the measurement. The measurement is considered normal if it is >2 cm and <8 cm. Values below and above this range indicating oligohydramnios and hydramnios, respectively. These thresholds correspond to the 3rd and 97th percentiles (Chamberlain, 1984). When evaluating twins and other multifetal gestations, a single deepest pocket is assessed in each gestational sac, using the same normal range (Hernandez, 2012; Society for Maternal-Fetal Medicine, 2013). The fetal biophysical profile similarly uses a single deepest vertical pocket threshold of >2 cm to indicate normal amnionic fluid volume (Chap. 20, p. 389).

To measure the AFI, the uterus is divided into four equal quadrants—the right and left upper and lower quadrants, respectively. The AFI is the sum of the single deepest pocket from each quadrant. In a study of 1400 measurements obtained from the INTERGROWTH-21st trial, the mean intra- and interobserver variability of AFI measurements were each below 1 cm (Sande, 2015). Two standard deviations from the mean, however, reached 5 and 7 cm, respectively. As useful rule of thumb, the AFI is generally three times higher than the single deepest pocket of fluid.

The AFI is considered normal if >5 cm and <24 or 25 cm. Using an AFI nomogram based on cross-sectional evaluation of nearly 800 uncomplicated pregnancies, the mean AFI ranged between 12 and 15 cm from 16 weeks until 40 weeks' gestation (Moore, 1990). Other investigators have published nomograms with similar mean values (Fig. 14-7) (Hinh, 2005; Machado, 2007).

■ Hydramnios

Abnormally increased amnionic fluid volume complicates 1 to 2 percent of singleton pregnancies (Dashe, 2002; Khan, 2017; Pri-Paz, 2012). Hydramnios may be categorized as *mild* if the AFI is 25 to 29.9 cm; *moderate*, if 30 to 34.9 cm; and *severe*, if ≥35 cm (Luo, 2017; Odibo, 2016). Using a single deepest pocket of amnionic fluid, as is done in multifetal gestations, mild hydramnios is defined as 8 to 9.9 cm, moderate as 10 to 11.9 cm, and severe hydramnios as ≥12 cm (Fig. 14-8). Mild hydramnios accounts for approximately two thirds of cases and is frequently idiopathic and benign. By comparison, severe hydramnios is far more likely to have an underlying etiology and to have consequences for the pregnancy.

Underlying causes of hydramnios include fetal structural abnormalities or genetic syndromes in approximately 15 percent and diabetes in 15 to 20 percent (Table 14-9). Selected anomalies and the likely mechanism by which they cause hydramnios are shown in Table 14-10. Congenital infection, red blood cell alloimmunization, and placental chorioangioma are less frequent etiologies. Hydramnios may also complicate syphilis and cytomegalovirus, toxoplasmosis, and parvovirus infections (Chaps. 67 and 68, pp. 1183 and 1206). Hydramnios is often seen with *hydrops fetalis* (Chap. 18, p. 360). The

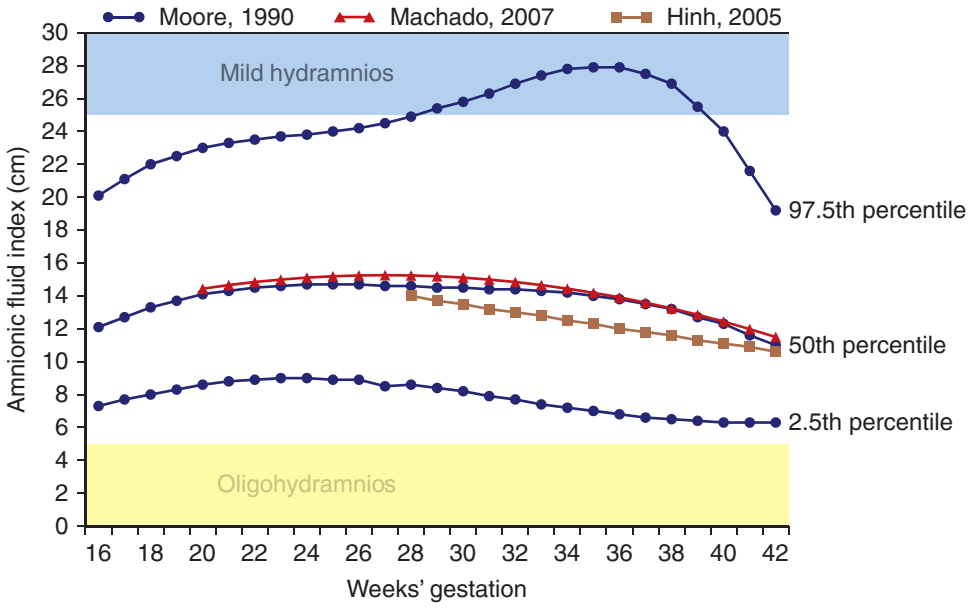


FIGURE 14-7 Amnionic fluid index (AFI) according to gestational age–specific and threshold values. The blue curves represent the 2.5th, 50th, and 97.5th AFI percentile values, based on the nomogram by Moore (1990). Red and tan curves represent 50th percentile values for AFI from Machado (2007) and from Hinh and Ladinsky (2005), respectively. The light blue and yellow shaded bars indicate threshold values used to define hydramnios and oligohydramnios, respectively.

underlying pathophysiology in such cases is frequently related to a high-cardiac-output state, and severe fetal anemia a classic example. A detailed ultrasound examination is indicated whenever hydramnios is identified. If a fetal abnormality is identified at that time, the aneuploidy risk is significantly elevated.

The degree of hydramnios positively correlates with the likelihood of an anomalous fetus. At Parkland Hospital, the prevalence of an anomalous neonate approximated 8 percent with mild hydramnios, 12 percent with moderate hydramnios, and more than 30 percent with severe hydramnios (Dashe, 2002). Even if no abnormality was detected during targeted sonographic evaluation, the likelihood of a major anomaly identified at birth was 1 to 2 percent if hydramnios was mild or moderate and 10 percent if hydramnios was severe. The overall reported risk that an underlying anomaly will be discovered after delivery ranges from 9 percent in the neonatal period to 28 percent among infants followed to 1 year of age (Abele, 2012; Dorleijn, 2009).

The amnionic fluid glucose concentration is higher in diabetic women than in those without diabetes, and the AFI may correlate positively with the amnionic fluid glucose concentration (Dashe, 2000; Spellacy, 1973; Weiss, 1985). Such findings support the hypothesis that maternal hyperglycemia causes fetal hyperglycemia, which leads to fetal osmotic diuresis into the amnionic fluid compartment. Repeat screening for gestational diabetes in pregnancies with hydramnios does not appear to be beneficial if the second-trimester glucose tolerance test result was normal (Frank Wolf, 2017).

Hydramnios is more frequently noted in multifetal gestations than in singleton ones. In a review of nearly 2000 twin gestations, Hernandez and coworkers (2012) identified hydramnios in 18 percent of both monochorionic and dichorionic pregnancies. In monochorionic gestations, hydramnios in one sac and oligohydramnios in the other are diagnostic criteria for twin-twin transfusion syndrome (TTTS) (Chap. 48, p. 848). Isolated hydramnios solely in one sac also may precede this syndrome's development (Chon, 2014). In the absence of a fetal abnormality or TTTS, complication risks are not generally higher (Hernandez, 2012).

Idiopathic hydramnios is a diagnosis of exclusion. It accounts for up to 70 percent of all hydramnios cases, is mild in approximately 80 percent of idiopathic cases, and subsequently resolves in more than one third (Odibo, 2016; Wiegand, 2016).

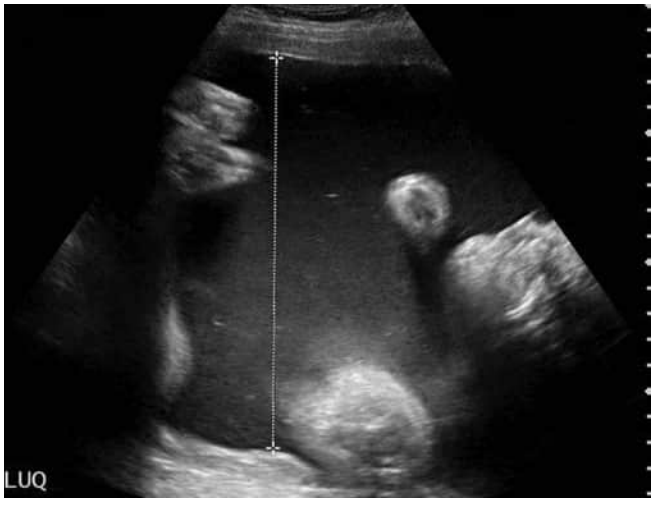


FIGURE 14-8 Severe hydramnios. This pocket of amnionic fluid measured >15 cm, and the amnionic fluid index measured nearly 50 cm.

Management

Severe hydramnios occasionally results in early preterm labor or maternal respiratory compromise. In such cases, large-volume amniocentesis—termed *amnioreduction*—may be needed. The technique is similar to that for genetic amniocentesis but is generally done with an 18- or 20-gauge needle. Fluid is collected in either a vacuum container bottle or a larger syringe (Chap. 17, p. 344). Approximately 1000 to 2000 mL of fluid is slowly withdrawn over 20 to 30 minutes, depending on the severity of hydramnios and gestational age. The goal is to restore amnionic fluid volume to the upper normal range. Subsequent amnioreduction procedures may be required as often as weekly or semiweekly.

In a review of 138 singleton pregnancies requiring amnioreduction for hydramnios, a fetal GI malformation was identified in 20 percent, a chromosomal abnormality or genetic condition

TABLE 14-9. Hydramnios: Prevalence and Associated Etiologies—Values in Percent

	Golan (1993) n = 149	Many (1995) n = 275	Biggio (1999) n = 370	Dashe (2002) n = 672	Pri-Paz (2012) n = 655
Prevalence	1	1	1	1	2
Amnionic fluid index					
Mild 25–29.9 cm	—	72	—	66	64
Moderate 30–34.9 cm		20		22	21
Severe >35 cm		8		12	15
Etiology					
Idiopathic	65	69	72	82	52
Fetal anomaly[a]	19	15[a]	8	11[a]	38[a]
Diabetes	15	18	20	7	18

[a]A significant correlation was identified between severity of hydramnios and likelihood of an anomalous infant.

in almost 30 percent, and a neurological abnormality in 8 percent (Dickinson, 2014). In only 20 percent of cases was the hydramnios idiopathic. The initial amnioreduction procedure was performed at 31 weeks' gestation, and the median gestational age at delivery was 36 weeks.

Outcomes

Hydramnios can be associated with preterm birth, placental abruption, uterine dysfunction during labor, and postpartum hemorrhage. When an underlying cause is identified, the severity of hydramnios positively correlates with risk for preterm delivery, small-for-gestational age newborn, and perinatal mortality (Pri-Paz, 2012). However, *idiopathic* hydramnios is generally not associated with preterm birth (Magann, 2010; Many, 1995; Panting-Kemp, 1999). Placental abruption may result from rapid decompression of an overdistended uterus following rupture of membranes or therapeutic amnioreduction, occasionally days or weeks later. Uterine dysfunction from

TABLE 14-10. Selected Anomalies and Mechanism for Hydramnios

Mechanism	Anomaly Examples
Impaired swallowing (CNS)	Anencephaly Hydranencephaly Holoprosencephaly
Impaired swallowing (craniofacial)	Cleft lip/palate Micrognathia
Tracheal compression or obstruction	Neck venolymphatic abnormality CHAOS[a]
Thoracic etiology (mediastinal shift)	Diaphragmatic hernia[a] Cystic adenomatoid malformation[a] Pulmonary sequestration[a]
High-output cardiac state	Ebstein anomaly[a] Tetralogy of Fallot with absent pulmonary valve[a] Thyrotoxicosis[a]
Functional cardiac etiology	Cardiomyopathy, myocarditis[a]
Cardiac arrhythmia	Tachyarrhythmia[a]: atrial flutter, atrial fibrillation, supraventricular tachycardia Bradyarrhythmia[a]: heart block
GI obstruction	Esophageal atresia Duodenal atresia
Renal-urinary	Ureteropelvic junction obstruction ("paradoxical hydramnios") Bartter syndrome
Neurological or muscular etiology	Arthrogryposis, akinesia sequence Myotonic dystrophy
Neoplastic etiology	Sacrococcygeal teratoma[a] Mesoblastic nephroma[a] Placental chorioangioma[a]

[a]Poses risk for hydrops.
CNS = central nervous system; CHAOS = congenital high-airway obstruction sequence; GI = gastrointestinal.

overdistention may lead to postpartum atony and associated postpartum hemorrhage.

With idiopathic hydramnios, birthweight exceeds 4000 g in nearly 25 percent of cases, and the likelihood is greater if the hydramnios is moderate or severe (Luo, 2017; Odibo, 2016; Wiegand, 2016). A rationale for this association is that larger fetuses have higher urine output, by virtue of their increased volume of distribution, and fetal urine is the largest contributor to amnionic fluid volume. Cesarean delivery rates are also higher in pregnancies with idiopathic hydramnios, and reported rates range from 35 to 55 percent (Dorleijn, 2009; Khan, 2017; Odibo, 2016).

An unresolved question is whether hydramnios alone raises the risk for perinatal mortality (Khan, 2017; Pilliod, 2015; Wiegand, 2016). Using birth certificate data from California, Pilliod and colleagues (2015) reported that at 37 weeks' gestation, the stillbirth risk was sevenfold higher in pregnancies with hydramnios. Risks appear to be compounded when fetal-growth restriction is comorbid with hydramnios (Erez, 2005).

Oligohydramnios

Abnormally decreased amnionic fluid volume complicates 1 to 2 percent of pregnancies (Casey, 2000; Petrozella, 2011). Oligohydramnios is diagnosed if the AFI measures <5 cm or the single deepest pocket is <2 cm (American College of Obstetricians and Gynecologists, 2020). An AFI threshold of 5 cm is below the 2.5th percentile throughout the second and third trimesters (see Fig. 14-7). Importantly, use of AFI rather than single deepest pocket will identify more pregnancies as having oligohydramnios but without evidence of improved pregnancy outcomes (Kehl, 2016; Nabhan, 2010). When evaluating multifetal pregnancies for TTTS, a single deepest pocket <2 cm is used to define oligohydramnios (American College of Obstetricians and Gynecologists, 2021c). When no measurable pocket of amnionic fluid is identified, the term *anhydramnios* is used.

By 18 weeks' gestation, the fetal kidneys are the main contributor to amnionic fluid volume. Selected renal abnormalities that lead to absent fetal urine production include bilateral *renal agenesis*, bilateral *multicystic dysplastic kidney*, unilateral renal agenesis with contralateral multicystic dysplastic kidney, and the infantile form of *autosomal recessive polycystic kidney disease*. Lower urinary abnormalities may also cause oligohydramnios because of fetal *bladder outlet obstruction* (Figs. 15-58 through 15-61, p. 300). Complex fetal genitourinary abnormalities such as *persistent cloaca* and *sirenomelia* similarly may result in a lack of amnionic fluid. With oligohydramnios before the mid-second trimester, particularly before 20 to 22 weeks, pulmonary hypoplasia is a significant concern. The prognosis is extremely poor unless fetal therapy is an option (Chap. 19, p. 377).

Oligohydramnios is also associated with exposure to drugs that block the renin-angiotensin system. These include angiotensin-converting enzyme (ACE) inhibitors, angiotensin-receptor blockers, and nonsteroidal antiinflammatory drugs (NSAIDs). When taken in the second or third trimester, ACE inhibitors and angiotensin-receptor blockers may result in fetal hypotension, renal hypoperfusion, and renal ischemia, leading to subsequent anuric renal failure (Bullo, 2012; Guron, 2000). Fetal skull bone hypoplasia and limb contractures also have been described (Schaefer, 2003). Additionally, NSAIDs can be associated with fetal ductus arteriosus constriction and impaired fetal urine production (Chap. 8, p. 151).

Oligohydramnios in the late second trimester or in the third trimester is often associated with uteroplacental insufficiency. A placental abnormality or a maternal complication such as preeclampsia or vascular disease are examples. Initially, ruptured membranes should be excluded. Then, particularly in the second trimester, a detailed ultrasound examination should be performed to search for fetal and placental abnormalities. If a placental hematoma or chronic abruption is sufficiently severe to result in oligohydramnios—the chronic abruption-oligohydramnios sequence (CAOS)—then it commonly also causes growth restriction (Chap. 43, p. 750).

Management

Oligohydramnios detected before 36 weeks' gestation in the presence of normal fetal anatomy and growth is generally managed expectantly and coupled with fetal surveillance (Chap. 20, p. 392). For late-preterm and early-term pregnancies, risks of fetal compromise outweigh potential complications of preterm delivery. The American College of Obstetricians and Gynecologists (2021b) recommends delivery between $36^{0/7}$ and $37^{6/7}$ weeks. In a review of 16 trials of pregnancies with apparent isolated oligohydramnios, oral or intravenous hydration was associated with a significantly improved AFI. However, it was unclear whether this translated into better pregnancy outcomes (Gizzo, 2015).

Outcomes

In a review of pregnancies with oligohydramnios at Parkland Hospital, Petrozella and associates (2011) found that an AFI <5 cm identified between 24 and 34 weeks' gestation was associated with increased risks for perinatal morbidity and mortality (Table 14-11). Similarly, a metaanalysis comprising more than 10,000 pregnancies found that oligohydramnios conferred a twofold risk for cesarean delivery due to nonreassuring fetal status and a fivefold risk for an Apgar score <7 at 5 minutes compared with pregnancies with a normal AFI (Chauhan, 1999).

As discussed, if oligohydramnios is defined as an AFI <5 cm rather than a single deepest pocket <2 cm, more pregnancies will be classified as such. Kehl and coworkers (2016) performed a prospective trial with more than 1000 term pregnancies in which women with an AFI <5 cm or a single deepest pocket <2 cm were randomly assigned to labor induction or expectant care. Significantly more pregnancies were diagnosed with oligohydramnios using the AFI criterion—10 percent compared with just 2 percent—when single deepest pocket was used. This led to a higher rate of labor induction in the AFI group but not to a difference in neonatal outcomes.

Borderline Oligohydramnios

This diagnosis is somewhat controversial. Also called *borderline AFI.* It usually refers to an AFI between 5 and 8 cm (Magann, 2011; Petrozella, 2011). During the mid-third trimester, an

TABLE 14-11. Pregnancy Outcomes in Women Diagnosed with Oligohydramnios between 24 and 34 Weeks' Gestation at Parkland Hospital

Factor	AFI ≤5 cm (n = 166)	AFI 8 to 24 cm (n = 28,185)	*p* Value
Major malformation	42 (25)	634 (2)	<.001
Stillbirth	8 (5)	133 (<1)	<.001
Gestational age at delivery[a]	35.1 ± 3.3	39.2 ± 2.0	<.001
Preterm birth, spontaneous[a]	49 (42)	1698 (6)	<.001
Preterm birth, indicated[a]	23 (20)	405 (2)	<.001
Cesarean delivery for nonreassuring fetal status[a]	10 (9)	1083 (4)	<.001
Birthweight <10th percentile[a]	61 (53)	3388 (12)	<.001
<3rd percentile[a]	43 (37)	1130 (4)	<.001
Neonatal death[a]	1 (1)	24 (<1)	<.001[b]

Data expressed as No. (%) and mean ± standard deviation.
[a]Anomalous infants excluded.
[b]This difference was no longer significant after adjustment for gestational age at delivery.
Data from Petrozella LN, Dashe JS, McIntire DD, et al: Clinical significance of borderline amniotic fluid index and oligohydramnios in preterm pregnancy. Obstet Gynecol 117(2 pt 1):338, 2011.

AFI value of 8 cm is below the 5th percentile on the Moore nomogram (see Fig. 14-7). Petrozella (2011) found that pregnancies between 24 and 34 weeks' gestation with an AFI between 5 and 8 cm were not more likely than those with an AFI >8 cm to have maternal hypertensive complications or an increased risk for stillbirth and neonatal death. Wood and colleagues (2014) reported a higher rate of fetal-growth restriction in pregnancies with borderline AFI but not an increase in rates of preterm delivery or need for neonatal intensive care. In a study of late-preterm pregnancies that were otherwise uncomplicated, borderline AFI conferred no increased risk for preterm delivery, nonreassuring fetal heart rate tracing, low Apgar score, or neonatal respiratory compromise (Sahin, 2018). Evidence is insufficient to support fetal surveillance or delivery in this setting (Magann, 2011).

DOPPLER

When sound waves strike a moving target, the frequency of the waves reflected back is shifted in proportion to the velocity and direction of that moving target—a phenomenon known as the *Doppler shift*. Because magnitude and direction of the frequency shift depend on the motion of a moving target, Doppler can help evaluate flow within blood vessels.

An important component of the Doppler equation is the angle of insonation, abbreviated as theta (θ) (Fig. 14-9). This is the angle between the sound waves from the transducer and flow within the vessel. Measurement error becomes large when θ is not close to zero, in other words, when blood flow is not coming *directly* toward or away from the transducer. For this reason, ratios are often used to compare different waveform components and allow cosine θ to cancel out of the equation. Figure 14-10 is a schematic of the Doppler waveform and describes the three ratios commonly used. The simplest is the *systolic-diastolic ratio (S/D ratio),* which compares the maximal (or peak) systolic flow with end-diastolic flow to evaluate downstream impedance to flow. Currently, two types of Doppler modalities are available for clinical use.

Continuous-wave Doppler equipment contains two types of crystals, one to transmit high-frequency sound waves and another to continuously capture signals. In M-mode imaging, continuous-wave Doppler is used to evaluate motion through time, however, it cannot image individual vessels.

Pulsed-wave Doppler uses only one crystal, which transmits the signal and then waits until the returning signal is received before transmitting another one. It allows precise visualization and color-flow mapping of the vessel of interest. By convention,

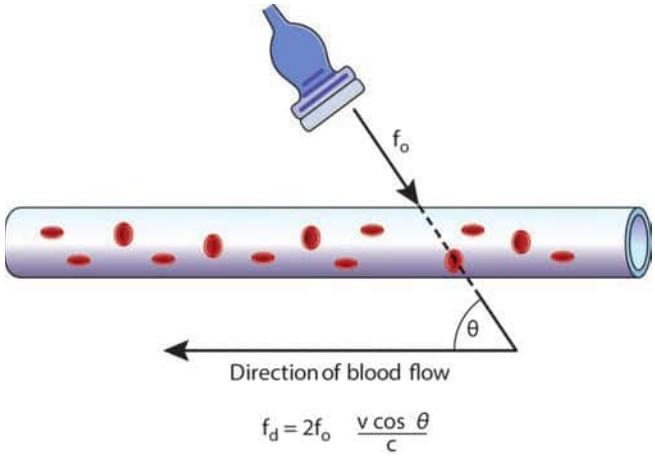


FIGURE 14-9 Doppler equation. Ultrasound emanating from the transducer with initial frequency f_o strikes blood moving at velocity v. Reflected frequency f_d is dependent on angle θ between beam of sound and vessel.

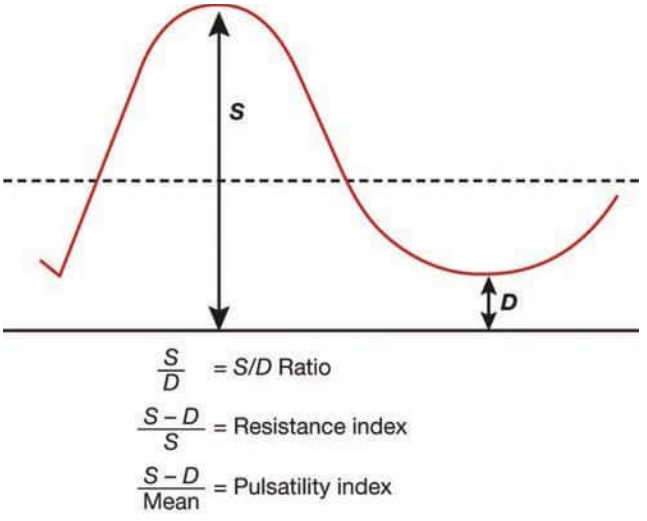


FIGURE 14-10 Doppler systolic–diastolic waveform indices of blood flow velocity. S represents the peak systolic flow or velocity, and D indicates the end-diastolic flow or velocity. The mean, which is the time-average mean velocity, is calculated from computer-digitized waveforms.

blood flowing toward the transducer is displayed in red and that flowing away from the transducer appears in blue.

Umbilical Artery

The umbilical artery differs from other vessels in that it normally has forward flow throughout the entire cardiac cycle. With advancing gestation, the amount of flow during diastole increases because of decreasing placental impedance. The S/D ratio approximates ≤4.0 after 20 weeks' gestation, <3.0 after 30 weeks', and close to 2.0 at term. More end-diastolic flow is observed at the placental cord insertion than at the fetal ventral wall, a reflection of downstream impedance to flow. Thus, abnormalities such as absent or reversed end-diastolic flow will appear first at the cord insertion site into the fetus. The International Society of Ultrasound in Obstetrics and Gynecology recommends that umbilical artery Doppler measurements be made in a free loop of cord (Bhide, 2013). However, assessment close to the ventral wall insertion may optimize measurement reproducibility in cases in which flow is diminished (Berkley, 2012).

The waveform is considered abnormal if the S/D ratio is >95th percentile for gestational age. Threshold values are listed in the Appendix (p. 1242). In extreme cases of growth restriction, end-diastolic flow can become absent or even reversed (Fig. 47, p. 830). Such reversal of end-diastolic flow has been associated with greater than 70-percent obliteration of the small muscular arteries in placental tertiary stem villi (Kingdom, 1997; Morrow, 1989).

Umbilical artery Doppler has been rigorously investigated to test of fetal well-being. As described in Chapter 47 (p. 830), this tool aids management of fetal-growth restriction and is associated with improved outcome in these cases (American College of Obstetricians and Gynecologists, 2019a). It is not recommended for other indications. Similarly, its use as a screening tool for growth-restriction is not advised (Berkley, 2012). Abnormal umbilical artery Doppler findings should prompt a detailed fetal evaluation, if not already done, because abnormal measurements are often associated with major fetal anomalies and aneuploidy (Wenstrom, 1991).

Ductus Arteriosus

Doppler evaluation of the ductus arteriosus is used primarily to monitor fetuses exposed to indomethacin and other NSAIDs. Indomethacin may cause ductal constriction or closure, particularly when used in the third trimester (Huhta, 1987). The resulting increased pulmonary flow can cause reactive hypertrophy of the pulmonary arterioles and eventual development of fetal pulmonary hypertension. In a review of 12 randomized trials involving more than 200 exposed pregnancies, Koren and coworkers (2006) reported that NSAIDs raised the odds of ductal constriction 15-fold. The risk is typically limited to drug use greater than 72 hours' duration. Monitoring for ductal constriction should be considered in such cases, so that the NSAID can be discontinued if ductal constriction is identified. Fortunately, effects are often reversible after NSAID discontinuation.

Uterine Artery

Uterine blood flow is estimated to rise from 50 mL/min early in gestation to 500 to 750 mL/min by term. The uterine artery Doppler waveform is characterized by high diastolic flow velocities and turbulent flow. Greater resistance to flow and development of a *diastolic notch* are associated with later development of gestational hypertension, preeclampsia, and fetal-growth restriction. Zeeman and associates (2003) also found that women with chronic hypertension who had elevated uterine artery impedance at 16 to 20 weeks' gestation were at greater risk to develop superimposed preeclampsia. However, the technique, best testing interval, and defining criteria for this indication have not been standardized. As the predictive value of uterine artery Doppler testing is considered to be low, its use for screening for hypertensive complications of pregnancy or for fetal-growth restriction is not recommended in either high-risk or low-risk pregnancies (American College of Obstetricians and Gynecologists, 2019a, 2020b).

Middle Cerebral Artery

Doppler velocimetry of the middle cerebral artery (MCA) has become the primary method of detecting fetal anemia and is central to surveillance of alloimmunized pregnancies. Anatomically, the path of the MCA is such that flow often approaches the transducer "head-on," which allows accurate determination of flow velocity (Fig. 14-11). The MCA is imaged in an axial view of the head at the base of the skull and ideally within 2 mm of the internal carotid artery origin. Velocity measurement is optimal when the insonating angle θ is close to zero, and no more than 30 degrees of angle correction should be used. In general, other fetal vessels are not suitable for velocity assessment, because a larger insonating angle is needed and confers significant measurement error.

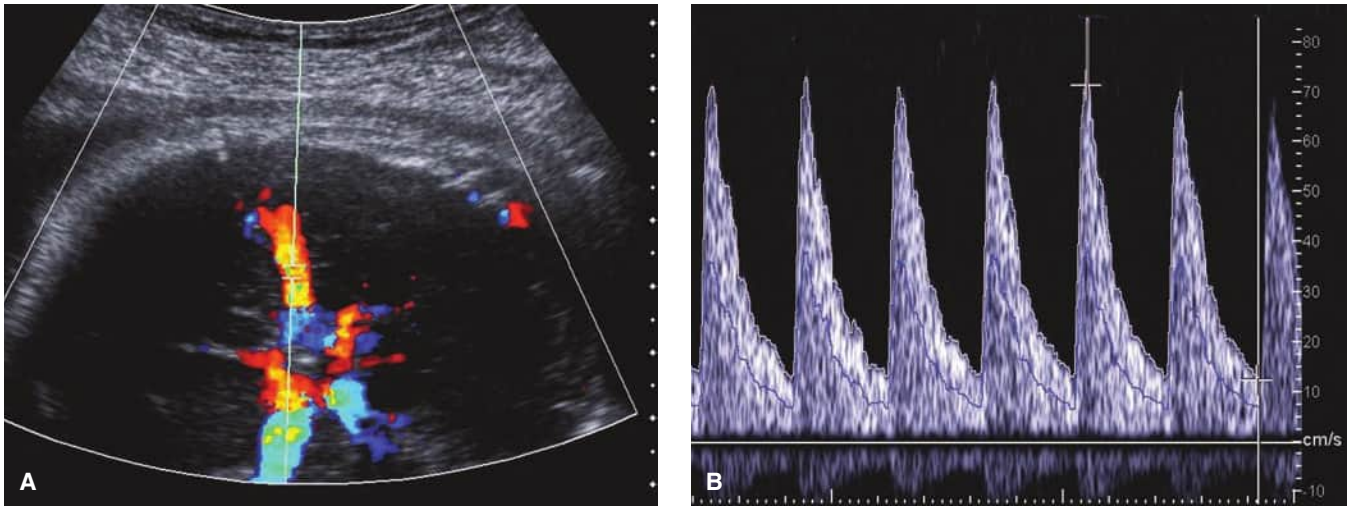


FIGURE 14-11 Middle cerebral artery (MCA) Doppler. **A.** Color Doppler of the circle of Willis demonstrates the correct location to sample the MCA. **B.** The waveform shows a peak systolic velocity exceeding 70 cm/sec in a 32-week fetus with severe fetal anemia secondary to Rh alloimmunization.

With fetal anemia, the *peak systolic velocity* is enhanced due to greater cardiac output and decreased blood viscosity (Segata, 2004). This permits the reliable, noninvasive detection of fetal anemia in cases of blood-group alloimmunization. Mari and colleagues (2000) demonstrated that an MCA peak systolic velocity threshold of 1.50 multiple of the median (MoM) could reliably identify fetuses with moderate or severe anemia. As discussed in Chapter 18 (p. 355), MCA peak systolic velocity has replaced invasive testing with amniocentesis as the preferred test for fetal anemia detection (Society for Maternal-Fetal Medicine, 2015a).

MCA Doppler has also been studied as an adjunct in evaluation of fetal-growth restriction (Chap. 47, p. 830). Fetal hypoxemia is associated with increased blood flow to the brain, heart, and adrenal glands, which leads to greater end-diastolic flow in the MCA. This phenomenon, called "brain-sparing," is actually a misnomer, as it does not protect the fetus but rather is associated with perinatal morbidity and mortality (Bahado-Singh, 1999; Cruz-Martinez, 2011). To evaluate redistribution of blood flow, investigators have studied a ratio of the MCA pulsatility index (PI) to the umbilical artery PI–termed the *cerebroplacental ratio*. Like the S/D ratio, the PI estimates downstream impedance to flow (Fig. 14-10). In the PORTO (Prospective Observational Trial to Optimize Paediatric Health in IUGR) study of ultrasound-dated pregnancies with estimated fetal weights <10th percentile, fetuses with a cerebroplacental PI ratio <1 had an 11-fold greater risk for adverse perinatal outcomes (Flood, 2014). Such findings can further our understanding of fetal pathophysiology. However, the utility of MCA Doppler to aid the timing of delivery is uncertain, and it has not been adopted as standard practice in the management of growth restriction (American College of Obstetricians and Gynecologists, 2021a; Martins, 2020).

■ Ductus Venosus

The fetal ductus venosus shunts oxygenated blood from the intrahepatic portion of the umbilical vein directly to the inferior vena cava, thus bypassing the liver (Fig. 7-9, p. 127). The ductus venosus is imaged as it branches from the umbilical vein at approximately the level of the diaphragm. The waveform is biphasic and normally has forward flow throughout the entire cardiac cycle (Fig. 14-12). The first peak reflects ventricular systole, and the second is ventricular diastolic filling. These are followed by a nadir during atrial contraction—termed the *a-wave*.

It is believed that Doppler findings in preterm fetuses with growth restriction show a progression in which umbilical artery Doppler abnormalities are followed by ones in the MCA and then in the ductus venosus. With severe fetal-growth restriction, cardiac dysfunction may lead to flow in the a-wave that is decreased, absent, and eventually reversed and to pulsatile flow in the umbilical vein (see Fig. 14-12). However, ductus venosus Doppler assessment has not improved perinatal outcomes, and neither the American College of Obstetricians and Gynecologists (2021a) nor the Society for Maternal-Fetal Medicine (Martins, 2020) recommend its use in the routine management of fetal growth-restriction.

MAGNETIC RESONANCE IMAGING

MR imaging is based on the excitation of hydrogen ions in the body by pulsing radiofrequencies with high field-strength magnets (1.5 to 3 Tesla). High-resolution fetal imaging is now possible, in part due to faster acquisition times of less than one second per slice. The relaxing hydrogen ions can be manipulated through various pulse sequences to produce different representations on images. The classic example is simple fluid, such as amnionic fluid or urine in the bladder, which appears bright on T2-weighted and dark on T1-weighted image acquisitions.

Image resolution with MR is often superior to that with sonography because MR is less hindered by bony interfaces, maternal obesity, oligohydramnios, or an engaged fetal head. Thus, it can complement sonography in evaluating suspected fetal abnormalities. Examples include complex abnormalities of the fetal thorax and of the central nervous, GI, genitourinary,

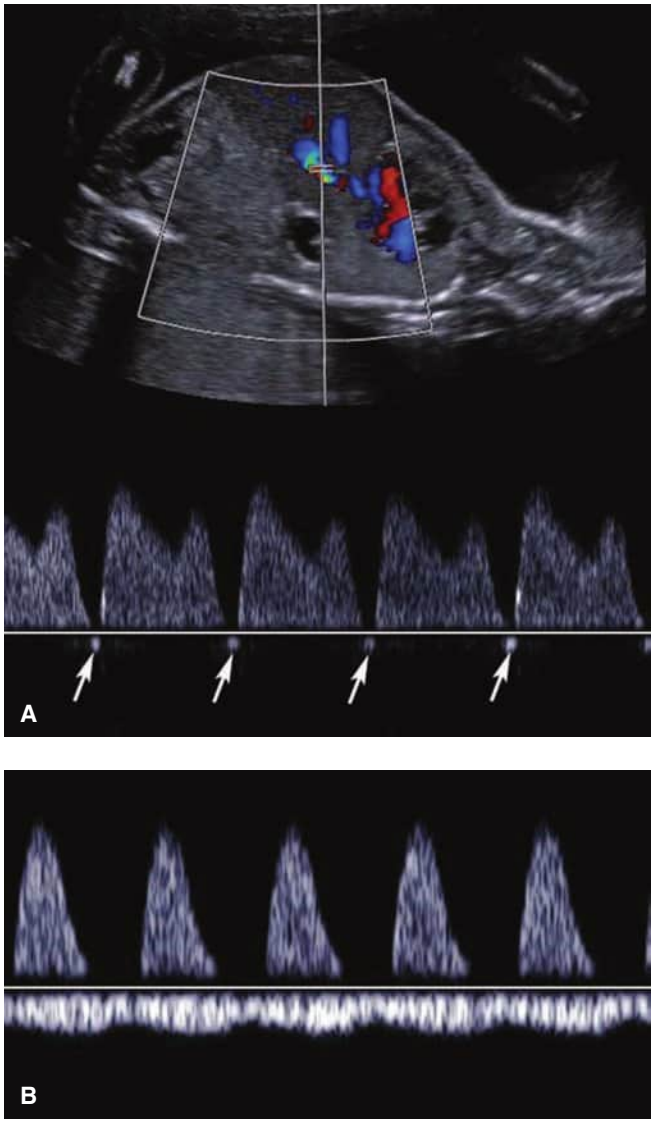


FIGURE 14-12 Venous Doppler abnormalities. **A.** Reversal of a-wave flow in the ductus venosus. Arrows depict a-waves below the baseline. This finding may be identified with cardiac dysfunction in the setting of severe fetal-growth restriction. **B.** Pulsatile flow in the umbilical vein. The undulating umbilical venous waveform below the baseline indicates tricuspid regurgitation. Above the baseline is the umbilical artery waveform, in which there is no visible end-diastolic flow. Because the venous waveform is below the baseline in this image, it is not possible to determine whether the umbilical artery end-diastolic flow is reversed.

and musculoskeletal systems. MR imaging is also used to evaluate maternal pelvic masses and placental invasion. This modality, however, is not portable, is time-consuming, and is generally limited to referral centers with expertise in fetal imaging.

To guide clinical use, the American College of Radiology and Society for Pediatric Radiology (2020b) have developed a practice guideline for fetal MR imaging. This document acknowledges the primacy of sonography as the preferred screening modality. Moreover, it recommends that fetal MR imaging be used for problem solving to contribute to prenatal diagnosis, counseling, treatment, and delivery planning. At Parkland Hospital, MR imaging is performed in 15 percent of pregnancies with major fetal abnormalities (Herrera, 2020). Specific indications are listed in Table 14-12 and are discussed subsequently (American College of Radiology, 2020b).

Safety

MR imaging is not associated with known adverse fetal effects if performed without administration of contrast media (Ray, 2016). It uses no ionizing radiation, and human and tissue studies support its safety (Clements, 2000; Reeves, 2010; Vadeyar, 2000; Wiskirchen, 1999). The strength of the magnetic field is measured in *tesla (T).* Both 1.5T and 3T fetal MR imaging can be done safely and successfully, assuming expertise of the imagers with the physical principles of MR (Prayer, 2017). All clinical examinations must adhere to the specific absorption rate, which is regulated by the FDA, and the ALARA principle should be followed. Specifically, the amount of heat generated in the MR is reflected in the specific absorption rate and must be monitored.

The Society for Pediatric Radiology recommends 3T MR imaging because of its improved signal-to-noise ratio, which results in better resolution (Barth, 2017). We prefer 1.5T for diagnostic imaging given its better field homogeneity. We reserve 3T for functional imaging, which requires higher field strength.

Gadolinium-based MR contrast agents are gadolinium (Gd^{3+}) chelates. These contrast agents enter the fetal circulation and are excreted via fetal urination into amnionic fluid. Here, they may remain for an indeterminate period before being ingested and reabsorbed. The longer time the gadolinium-chelate molecule remains in a protected space such as the amnionic sac, the greater the potential for dissociation of the toxic Gd^{3+} ion. In a population-based review from Ontario, children exposed to gadolinium-enhanced MR imaging in utero were at slightly increased risk for a broad set of rheumatological, inflammatory, or infiltrative skin conditions (Ray, 2016). In adults with renal disease, this contrast agent is associated with development of nephrogenic systemic fibrosis, a potentially severe complication. MR imaging with gadolinium is not recommended in pregnancy without a life-threatening indication.

Technique

Before MR imaging, all women complete a written safety questionnaire that includes information about metallic implants, pacemakers, or other metal- or iron-containing devices. High-level magnetization may cause dangerous movement in these devices, causing adjacent tissue damage and malfunction. (American College of Radiology, 2020a). Iron supplementation may cause image artifact in the colon but does not usually affect the resolution of fetal images. In more than 4500 MR procedures performed at Parkland Hospital in pregnancy during the past 18 years, <1 percent of our patients suffered maternal anxiety secondary to claustrophobia. To reduce anxiety in this small group, a single oral dose of diazepam, 5 to 10 mg, or lorazepam, 1 to 2 mg, may be given.

TABLE 14-12. Fetal Conditions for Which Magnetic Resonance Imaging May Be Indicated[a]

Brain and spine
Agenesis of the corpus callosum
Cavum septum pellucidum abnormalities
Cephalocele
Cerebral cortical malformation or migrational abnormalities
Family history conferring a risk for brain anomaly
Hemorrhage
Holoprosencephaly
Hydranencephaly
Infarctions
Monochorionic twin pregnancy complications
Neural-tube defects
Posterior fossa abnormalities
Sacral agenesis (caudal regression)
Sacrococcygeal teratoma
Sirenomelia
Solid or cystic masses
Vascular malformations
Ventriculomegaly
Vertebral anomalies

Skull, face, and neck
Facial clefts
Goiter
Hemangiomas
Teratomas
Venolymphatic malformations
Other abnormalities with potential airway obstruction

Thorax
Bronchogenic cyst or congenital lobar overinflation
Congenital cystic adenomatoid malformation
Diaphragmatic hernia
Effusions
Extralobar pulmonary sequestration
Esophageal atresia
Mediastinal masses
Evaluation of pulmonary hypoplasia secondary to diaphragmatic hernia, oligohydramnios, chest mass, or skeletal dysplasia

Abdomen, pelvis, and retroperitoneum
Abdominopelvic cystic mass
Bowel anomalies (anorectal malformations, complex obstructions)
Complex genitourinary anomalies (bladder outlet obstruction syndromes, bladder exstrophy, cloacal exstrophy)
Renal anomalies with oligohydramnios
Tumors (sacrococcygeal teratoma, neuroblastoma, hemangioma, suprarenal or renal masses)

Complications of monochorionic twins
Assess morbidity after death of a monochorionic co-twin
Determine vascular anatomy prior to laser treatment
Evaluate conjoined twins

Fetal surgery assessment
Anomalies for which fetal surgery is planned
Fetal brain anatomy before and after surgical intervention

[a]In some cases, magnetic resonance imaging is indicated only if the anomaly is suspected but cannot be adequately characterized sonographically, which is assessed on a case-by-case basis.
Summarized from American College of Radiology, Society for Pediatric Radiology: ACR-SPR practice parameter for the safe and optimal performance of fetal magnetic resonance imaging (MRI). Resolution No. 45, 2020.

To begin an MR examination, women are placed in a supine or left lateral decubitus position. A torso coil is used in most circumstances to send and receive the radiofrequency pulses, but a body coil can be used alone to accommodate large maternal habitus. A series of three-plane localizers, or scout views, are obtained relative to the maternal coronal, sagittal, and axial planes. The gravid uterus is imaged in the maternal axial plane (7-mm slices, 0 gap) with a T2-weighted fast acquisition. Typically, these may be a single-shot fast spin echo sequence (SSFSE), half-Fourier acquisition single-shot turbo spin echo (HASTE), or rapid acquisition with relaxation enhancement (RARE), depending on the machine. Next, a fast T1-weighted acquisition such as spoiled gradient echo (SPGR) is performed (7-mm thickness, 0 gap). These large-field-of-view acquisitions through the maternal abdomen and pelvis are particularly good for identifying fetal and maternal anatomy.

Orthogonal images of targeted fetal or maternal structures are then obtained. In these cases, 3- to 5-mm slice thickness, 0 gap T2-weighted acquisitions are performed in the coronal, sagittal, and axial planes. Depending on the anatomy and underlying suspected abnormality, T1-weighted images can be performed to evaluate for subacute hemorrhage, fat, or location of normal structures that appear bright on these sequences, such as liver and meconium in the colon (Brugger, 2006; Zaretsky, 2003b).

Short T1 inversion recovery (STIR) and frequency-selective fat-saturated T2-weighted images may help differentiation in cases in which the water content of the abnormality is similar to that of the normal structure. An example is a thoracic mass compared with normal lung. Diffusion-weighted imaging may be employed to evaluate for restricted diffusion, which can be seen in ischemia, cellular tumors, or clotted blood (Brugger, 2006; Zaretsky, 2003b).

Fetal Anatomy Evaluation

A fetal anatomical survey is generally completed during the MR examination, regardless of the fetal indication. Nearly 95 percent of anatomical components recommended by the International Society of Ultrasound in Obstetrics and Gynecology were visible at 30 weeks' gestation (Millischer, 2013). The aorta and pulmonary artery were the most difficult to evaluate. Zaretsky and coworkers (2003a) similarly found that with the exclusion of cardiac structures, fetal anatomical evaluation was possible in 99 percent of cases.

Central Nervous System

For intracranial anomalies, fast T2-weighted images produce excellent tissue contrast. Cerebrospinal fluid–containing structures appear bright, which allows exquisite detail of the posterior fossa, midline structures, and cerebral cortex. T1-weighted images are used to identify hemorrhage. CNS biometry obtained with MR imaging is comparable with that obtained using sonography, and nomograms are available for the corpus callosum and cerebellar vermis (Harreld, 2011; Katorza, 2016; Twickler, 2002; Xi, 2016).

MR imaging may provide valuable added information when cerebral abnormalities are identified or suspected sonographically (Benacerraf, 2007; Li, 2012). Additional information is more likely to be gained when the examination is performed beyond 24 weeks' gestation. In studies, MR imaging has identified additional CNS findings or led to a changed diagnosis in nearly 50 percent of cases and affected prognosis or management in 20 percent (Griffiths, 2017, Twickler, 2003).

MR imaging accurately portrays cerebral gyration and sulcation patterns (Fig. 14-13) (Levine, 1999). It may assist with identifying agenesis or dysgenesis of the corpus callosum and characterizing migrational abnormalities (Benacerraf, 2007; Li, 2012; Twickler, 2003). In cases of septo-optic dysplasia, MR imaging may confirm absence of the septum pellucidum and display hypoplastic optic tracts (Fig. 14-14). When fetal intracranial hemorrhage (ICH) is suspected, MR imaging can help to characterize the extent of bleeding and to estimate when bleeding occurred. Risk factors for fetal ICH include atypical-appearing ventriculomegaly, concern for neonatal alloimmune thrombocytopenia, and severe TTTS or demise of one monochorionic twin (Hu, 2006). With congenital fetal infections, MR imaging can delineate the variable degrees of neural parenchymal abnormality and subsequent maldevelopment (Soares de Oliveira-Szejnfeld, 2016).

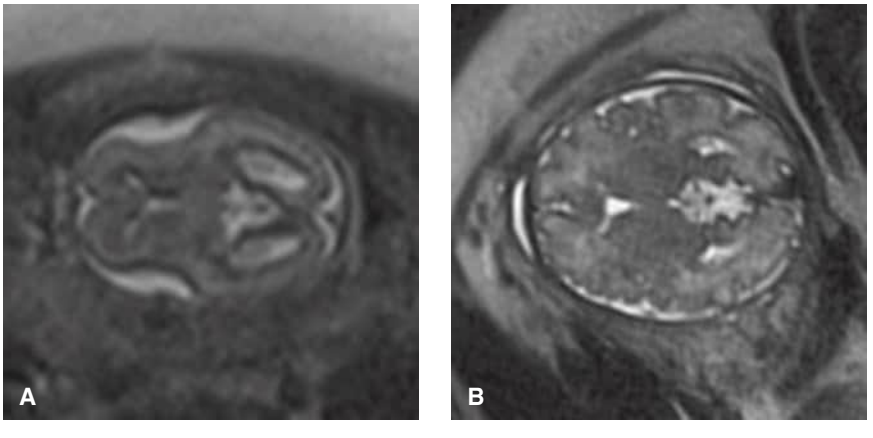


FIGURE 14-13 Axial images of the fetal brain demonstrate the normal gyration and sulcation progression during fetal development. **A.** 23 weeks' gestation. **B.** 33 weeks' gestation. These images were obtained using a Half Fourier Acquisition Single Shot Turbo Spin Echo (HASTE) sequence because it is relatively motion insensitive.

Thorax

MR imaging can delineate the location and size of space-occupying thoracic lesions and quantify the volume of lung tissue. If needed, it can characterize blood flow to a thoracic mass to differentiate cystic adenomatoid malformation from pulmonary sequestration (Chap. 15, p. 287). With congenital diaphragmatic hernia, MR imaging can help verify and quantify the abdominal organs within the thorax (Debus, 2013; Lee, 2011; Mehollin-Ray, 2012). This includes the volume

of herniated liver and of compressed lung tissue (Fig. 14-15). MR imaging can also measure lung volumes in pregnancies with prolonged oligohydramnios secondary to renal abnormalities or ruptured membranes (Messerschmidt, 2011; Zaretsky, 2005).

Abdomen

Meconium accumulation within the GI tract gives a predictable pattern and has high signal intensity on T1-weighted sequences. Thus, MR imaging is a complementary tool in diagnosing GI abnormalities and complex cloacal malformations (Furey, 2016). With cystic abdominal abnormalities, differences in signal characteristics may also help distinguish between meconium in the fetal colon and urine in the bladder (Farhataziz, 2005). Peritoneal calcifications related to meconium peritonitis are more readily apparent sonographically, whereas pseudocysts and resultant abnormalities of meconium migration are better delineated with MR imaging.

Adjunct to Fetal Therapy

Prior to fetal surgery, MR imaging is often used. In cases of myelomeningocele, it precisely displays brain and spine anatomy. For sacrococcygeal teratomas, if fetal surgery is considered, MR imaging may identify tumor extension into the fetal pelvis (Avni, 2002; Neubert, 2004; Perrone, 2018). When a fetal neck mass is identified with ultrasound, MR imaging may help delineate a lesion's extent and its mass effect on the oral cavity and trachea. This can help identify cases that are at risk for adverse outcome and that may benefit from an ex utero intrapartum treatment (EXIT) procedure (Lazar, 2012; Ogamo, 2005; Ng, 2019). MR imaging can also calculate a jaw index when an EXIT procedure may be needed for severe micrognathia (Kooiman, 2018; Morris, 2009). At some centers, before laser ablation of placental anastomoses for TTTS, MR imaging is performed to identify fetal ICH or periventricular leukomalacia (Hu, 2006; Kline-Fath, 2007). Fetal therapy is discussed in Chapter 19 (p. 367).

Placenta

Despite improvements in ultrasound detection of PAS, particularly when the placenta is anterior, characterization of the extent of invasion remains a challenge. MR findings concerning for invasion are depicted in Figure 14-16. They include dark intraplacental bands on T2-weighted images, a focal bulge, placental heterogeneity, involvement of the bladder-uterine

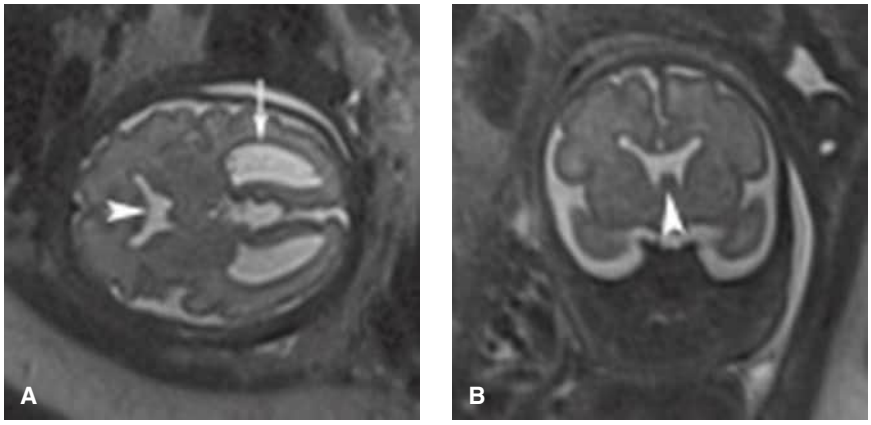


FIGURE 14-14 Septo-optic dysplasia. **A.** Axial. **B.** Coronal. Images at 30 weeks' gestation confirm absence of the cavum septum pellucidum (*arrowheads*) in both. There is also associated mild ventriculomegaly (*arrow*).

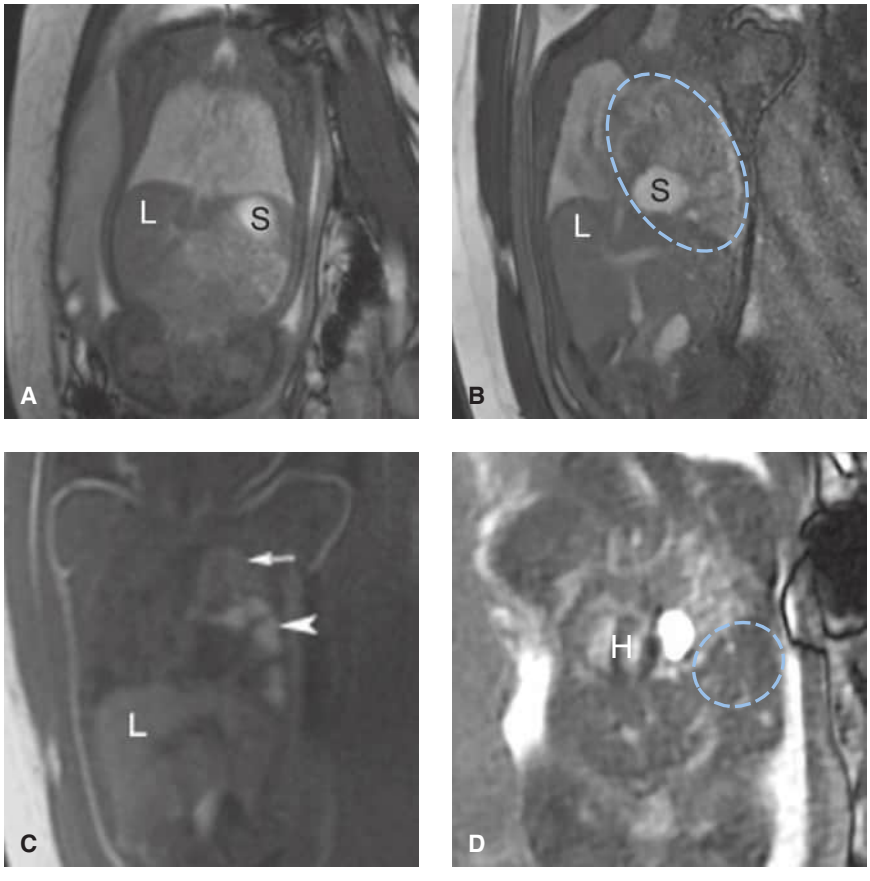


FIGURE 14-15 **A.** Coronal image of normal lungs on a balanced sequence at 29 weeks' gestation. The liver (*L*) and stomach (*S*) lie below the diaphragm. **B.** Left-sided congenital diaphragmatic hernia (CDH) (*dotted ellipse*) seen on balanced sequence at 33 weeks. **C.** The T1-weighted sequence confirms the subdiaphragmatic position of the liver and better delineates the small bowel (*arrow*) and meconium-containing colon (*arrowhead*) that have herniated into the chest. **D.** Another image of a left-sided CDH at 22 weeks demonstrates no normal lung, the heart (*H*) displaced into the right chest, and an elevated liver (*dotted ellipse*).

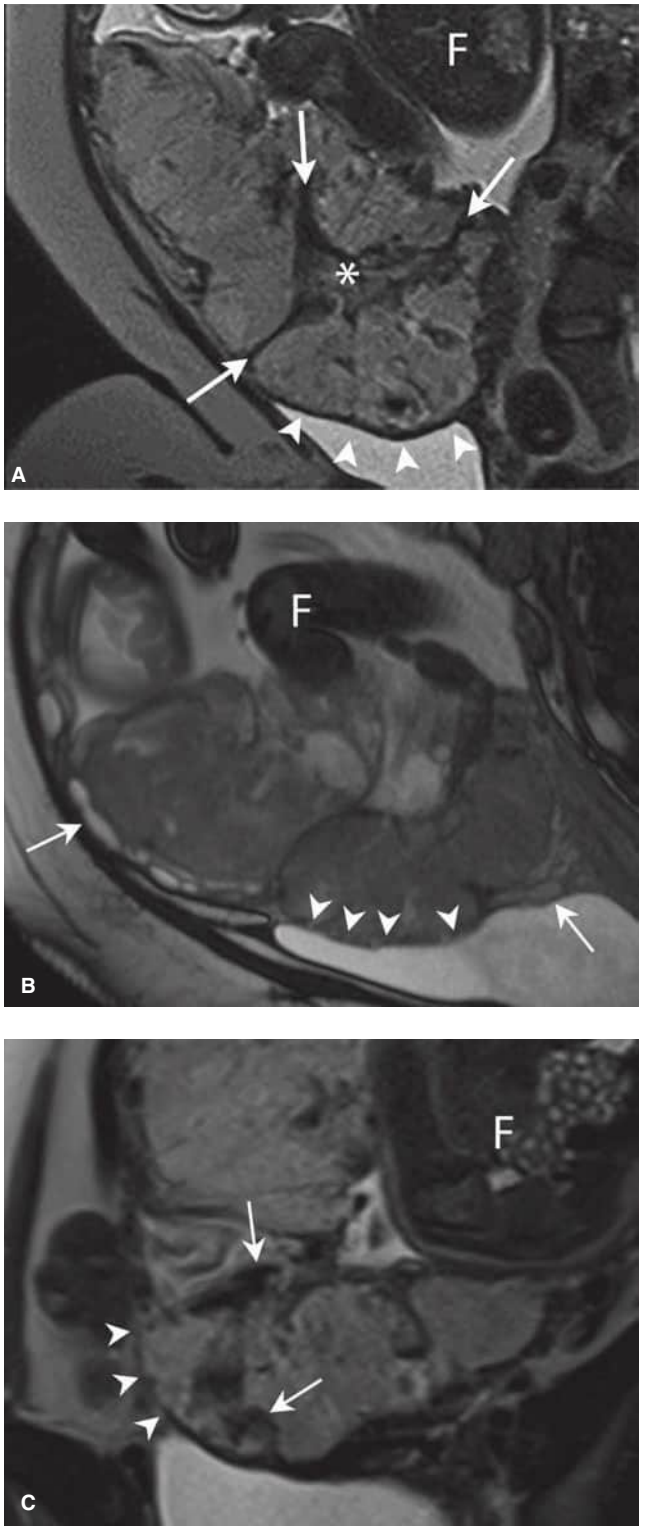


FIGURE 14-16 A. Sagittal T2-weighted image of the placenta demonstrates placenta accreta spectrum (PAS), in this case placenta percreta. There are intraplacental, dark, linear bands (*arrows*), a large bulge along the bladder-serosal interface (*arrowheads*), and a central area of marked inhomogeneity (*asterisk*). **B.** A coronal image from the same study demonstrates the bulge with right lateral extension (*arrowheads*) and multiple, dark, linear bands (*arrows*). **C.** A sagittal, balanced, steady state free precession (SSFE) image shows a bulge, retroplacental vessels, and irregularity of the bladder-serosal interface (*arrowheads*). These contrast with the large maternal varices (*arrows*). F = fetus.

serosal interface, and fibrin deposition (Clark, 2020; Leyendecker, 2012). When used to complement ultrasound, MR imaging's sensitivity to detect invasion is high. Clark and associates (2020) reported that MR imaging findings positively correlated with need for cesarean hysterectomy and with histological and surgical impressions of invasion. Clinical risk factors and ultrasound findings (p. 253) should be incorporated when interpreting MR placental images (Chap. 43, p. 759).

Two emerging technologies also are being employed to investigate placental insufficiency and PAS. Arterial spin labelling is a technique for functional assessment of perfusion and excites maternal red blood cells to serve as endogenous contrast agents (Zun, 2018). Second, radiomics textural analysis characterizes placental morphology in vivo. MR textural features may help select pregnancies requiring cesarean hysterectomy (Do, 2020).

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CHAPTER 15

Normal and Abnormal Fetal Anatomy

The ability to detect and characterize abnormalities before birth is one of the marvels of modern obstetrics. Sonography can image the fetus with remarkable precision. Components of the standard anatomic survey are listed in Table 15-1. These have been termed *essential elements* by the American College of Obstetricians and Gynecologists (2020) and *minimal elements* by the American Institute of Ultrasound in Medicine (2018). Ideally, residency training in Obstetrics and Gynecology includes education in acquisition and interpretation of these views. Resources provided by national societies assist with this endeavor (Abuhamad, 2018).

A *detailed fetal anatomic survey* is a specialized examination that may include more than 60 components, each determined on a case-by-case basis. It is the primary method of evaluating at-risk pregnancies and characterizing fetal abnormalities, thereby aiding consultation and delivery planning. Indications are shown in Table 14-6 and discussed further in Chapter 14 (p. 251). At Parkland hospital, the detailed survey includes, at minimum, an attempt to visualize all components required by the American Institute of Ultrasound in Medicine for normal detailed case submission (see Table 15-1).

This chapter presents the standard and detailed anatomic surveys and some of the many fetal abnormalities that may be detected when visualization is optimal. When imaging or measuring any fetal structure, care should be taken to place the focal zone at the appropriate level and to magnify the image appropriately (Abuhamad, 2018). Whenever a fetal abnormality is identified, a detailed anatomic survey is recommended. With rare exception, amniocentesis with chromosomal microarray analysis also is offered. If a cardiac abnormality is identified, fetal echocardiography is indicated. Additional indications for these specialized examinations and for fetal magnetic resonance (MR) imaging are reviewed in Chapter 14.

BIOMETRY

In the first trimester, crown-rump length (CRL) measurement is used to establish or confirm gestational age (Appendix, p. 1234). The earlier that sonography is performed, the more accurate this estimation. Gestational age assessment is reviewed in Chapter 14 (p. 248). The fetus is imaged in the midsagittal plane in a neutral, nonflexed position so that its length can be measured in a straight line (Fig. 15-1). The average of three measurements is used. First-trimester nuchal translucency measurement is reviewed in Chapter 14 (p. 249).

In the second and third trimesters, the biparietal diameter, head circumference, abdominal circumference, and femur length are measured to confirm gestational age, if not already established in the

TABLE 15-1. Components of Standard and Detailed Anatomic Surveys

Standard Ultrasound	Detailed Ultrasound, Additional Components
Head, face, and neck	**Head, face, and neck**
Midline falx	Cranial integrity and shape[a]
Cavum septum pellucidum	Brain parenchyma[a]
Lateral ventricles	Lateral ventricle wall/lining and contour
Choroid plexus	Third ventricle
Cerebellum	Fourth ventricle
Cisterna magna	Corpus callosum
Upper lip	Cerebellar vermis[a] and lobes
Nuchal skinfold measurement, 15–20 weeks	Transverse cerebellar diameter
	Nasal bone measurement, 15–22 weeks[a]
	Profile[a]
	Coronal view of lenses, nose[a], lips
	Orbits with measurement
	Maxilla[a], mandible[a], palate, tongue
	Ear position, size
	Neck[a]
Thorax and heart	**Thorax and heart**
Situs	Interventricular septum
Heart rate (M-mode)	Superior/inferior venae cavae[a]
Four-chamber view of the heart	Aortic arch[a]
Left ventricular outflow tract	Ductal arch
Right ventricular outflow tract	3-vessel view[a]
3-vessel view, if feasible	3-vessel and trachea view[a]
3-vessel trachea view, if feasible	Lungs[a]
	Diaphragm integrity[a]
	Ribs
Abdomen	**Abdomen**
Stomach: presence, size, and situs	Bowel, small and large
Kidneys	Liver
Urinary bladder	Gallbladder
Umbilical cord insertion into fetal abdomen	Spleen
Umbilical cord vessel number	Renal arteries
	Adrenal glands
	Ventral wall integrity
Spine	**Spine**
Cervical, thoracic, lumbar, and sacral spine	Shape[a], curvature[a], conus medullaris
	Integrity of spine and overlying tissue[a]
Extremities (presence only)	**Extremities**
Arms and legs	Architecture, position, number[a]
Hands and feet	Long-bone measurements
	Fingers and toes (number, position)[a]
External genitalia	**External genitalia**
When indicated, e.g., multifetal gestation	

[a]In addition to all standard anatomy components, these detailed ultrasound components are required by the American Institute of Ultrasound in Medicine for normal cases submitted as part of the detailed ultrasound accreditation process. Modified from the American Institute of Ultrasound in Medicine, 2018, 2019, 2020a.

first trimester, and to estimate fetal weight. Ultrasound equipment and report packages calculate these estimates using standardized nomograms (Hadlock, 1991). If an abnormality involving one of the parameters is suspected, consideration is given to excluding it from the gestational age calculation. Fetal weight nomograms are available that do not include the head measurements or the femur measurement (Hadlock, 1984; Shepard, 1982).

The biparietal diameter and head circumference are measured in the *transthalamic view*. This is a transverse image that includes the midline falx cerebri, cavum septum pellucidum,

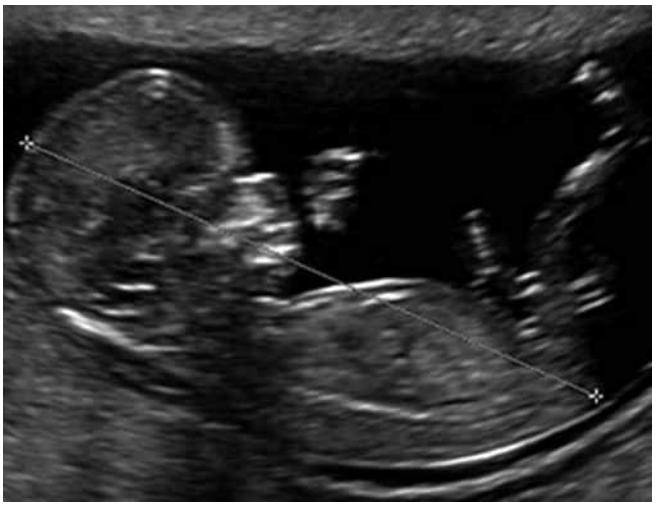

FIGURE 15-1 The crown-rump length measures 61 mm in this 12-week, 4-day fetus.

thalami, and insula (Fig. 15-2A). The cerebral hemispheres should appear symmetric, and the cerebellum should not be visible. The biparietal diameter is measured perpendicular to the falx cerebri, from the outer edge of the skull in the near field to the inner edge of the skull in the far field. The head circumference is measured by placing an ellipse around the outer edge of the skull. The head circumference may also be calculated by averaging the biparietal diameter and the occipito-frontal diameter and multiplying by π.

The abdominal circumference is measured in a transverse image that includes the stomach and the J-shaped confluence of the umbilical vein with the portal sinus. An ellipse is placed just outside the fetal skin edge (Fig. 15-2B). The image should appear as round as possible and ideally contain no more than 1 rib on either side. The spine should be visible in cross-section at the 3 o'clock or 9 o'clock position, whereas the kidneys should not be visible, as they are lower in the abdomen. Abdominal circumference is the biometric parameter most affected by fetal growth. An abdominal circumference below the 10th percentile may be used to diagnose fetal-growth restriction (Chap. 47, p. 825).

The femur length is measured with the ultrasound beam perpendicular to the long axis of the shaft. Calipers are placed at each end of the calcified diaphysis (Fig. 15-2C). Throughout the second and third trimesters, the femur length to abdominal circumference ratio is normally 20 to 24 percent. If this ratio is below 18 percent, a skeletal dysplasia should be considered, particularly if other long-bone measurements are lagging (p. 302). As discussed in Chapter 17 (p. 340), a mildly foreshortened femur length measurement is also a minor marker for Down syndrome (Herrera, 2020b).

Various nomograms exist for other fetal structures, including the transverse cerebellar diameter, ocular distances, nasal bone, ear length, jaw index, thoracic circumference, and lengths of the liver, kidneys, long bones, and feet. They may be used to address specific questions regarding organ system abnormalities, congenital infection, or genetic syndromes (Appendix, pp. 1238–1241).

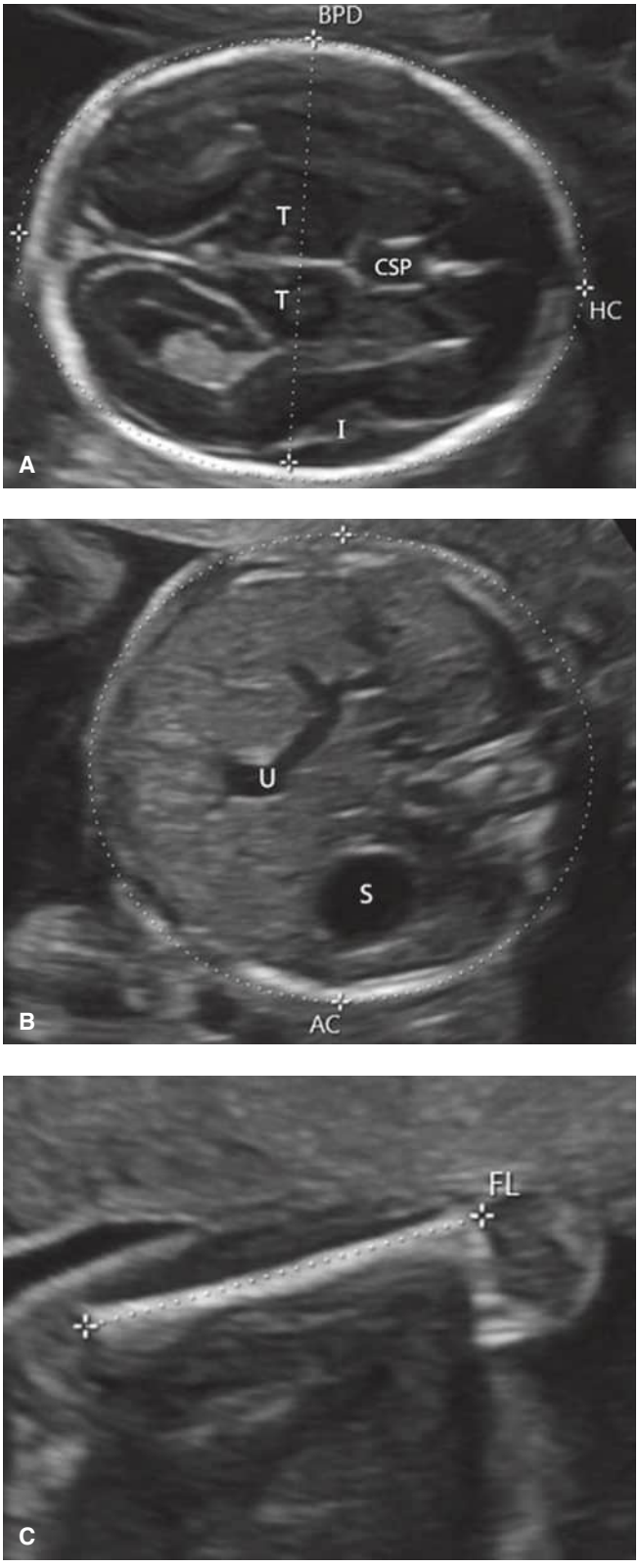

FIGURE 15-2 Normal biometry. **A.** Transthalamic view depicts measurement of the biparietal diameter (*BPD*) and head circumference (*HC*). Landmarks include the cavum septum pellucidum (*CSP*), thalami (*T*), and insula (*I*). **B.** Abdominal circumference view (*AC*) shows measurement and landmarks, which include the stomach (*S*) and the confluence of the umbilical vein (*U*) and the left portal vein. **C.** Femur length measurement (*FL*).

BRAIN AND SPINE

Standard sonographic evaluation of the fetal brain includes three transverse (axial) views. As noted, the *transthalamic view* should contain the midline falx cerebri, cavum septum pellucidum (CSP), thalami, and insula (see Fig. 15-2A). The CSP is the space between the two laminae that separate the frontal horns of the lateral ventricles. It should be visible between approximately 17 and 37 weeks' gestation, but after this, fusion of the septi pellucidi may obliterate the cavum. Inability to visualize a normal CSP may indicate a midline brain abnormality (Fig. 15-3). For example, the frontal horns are widely spaced apart in agenesis of the corpus callosum (ACC), whereas in cases of septo-optic dysplasia (de Morsier syndrome) and lobar holoprosencephaly, the frontal horns communicate. Discussed in Chapter 16 (p. 312), an abnormally wide CSP may also be found with trisomy 18.

The *transventricular view* lies superior to the transthalamic view and, as the name implies, includes the lateral ventricles. The ventricles are measured at their atrium, which is the confluence of the temporal and occipital horns (Fig. 15-4). The measurement is normally 5 to 9 mm throughout the second and third trimesters. Cerebrospinal fluid is produced within the ventricles by the *choroid plexus.* Choroid plexus cysts are present in 0.5 to 2 percent of uncomplicated pregnancies and approximately 30 to 50 percent of pregnancies with trisomy 18 (Fig. 16-5, p. 312) (Reddy, 2014). A detailed ultrasound examination is generally offered when found. In the absence of an associated ultrasound abnormality, or unless an aneuploidy screening test indicates increased risk for trisomy 18, a choroid plexus cyst is considered a normal variant.

For the *transcerebellar view*, the transducer is angled back through the posterior fossa (Fig. 15-5). Structures visible in this image include the

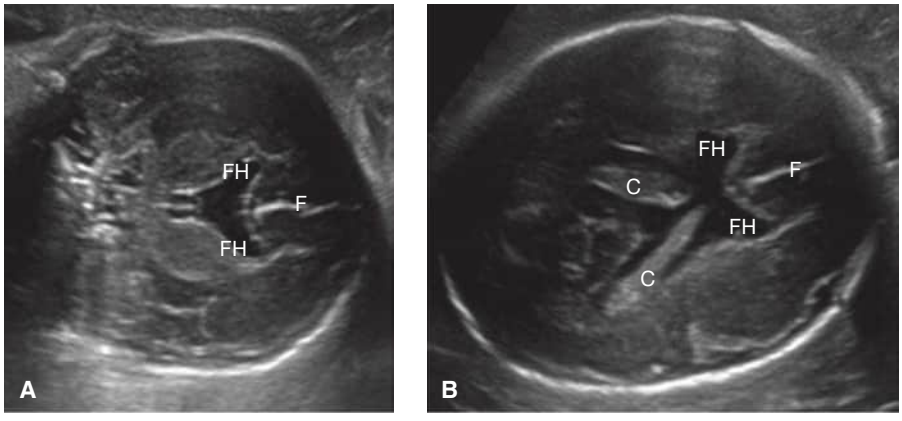

FIGURE 15-3 Absence of the cavum septum pellucidum, with coronal **(A)** and transverse **(B)** images showing communication between the frontal horns (*FH*) of the lateral ventricles. This may be isolated but can occur in the setting of septo-optic dysplasia or lobar holoprosencephaly. C = choroid plexus; F = falx cerebri.

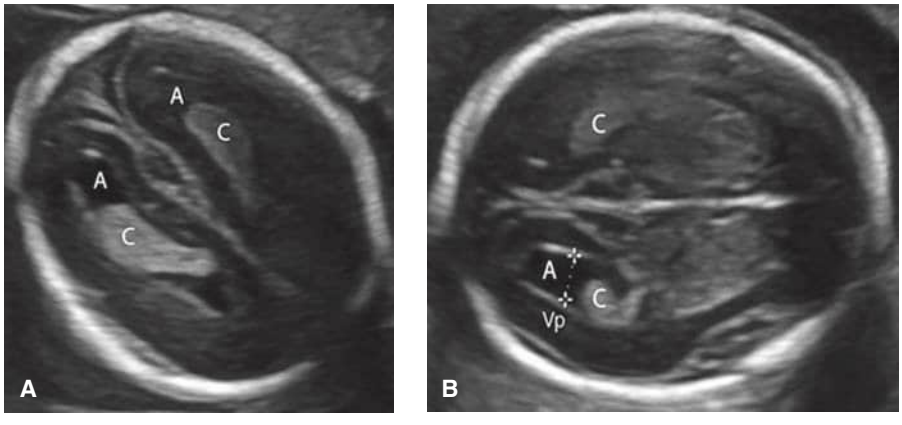

FIGURE 15-4 Transventricular view. **A.** Transverse image of the lateral ventricles, which contain the choroid plexus (*C*). **B.** The ventricles are measured at the atria (*A*), the confluence of the temporal and occipital horns. The measurement is normally 5–9 mm. Vp = lateral ventricle. (Reproduced with permission from Rosa Robles, RDMS.)

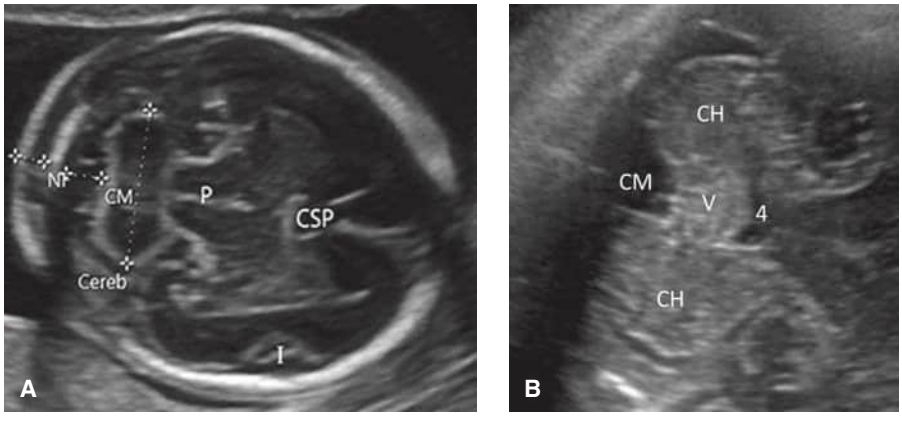

FIGURE 15-5 Transcerebellar view. **A.** Transverse image of the posterior fossa showing measurement of the cerebellum (*Cereb*), cisterna magna (*CM*), and nuchal skinfold thickness (*NF*). **B.** Third-trimester image depicting the cerebellar hemispheres (*CH*) and cerebellar vermis (*V*). The fourth ventricle (4) is anterior to the vermis. CSP = cavum septum pellucidum; I = insula; P = cerebral peduncles.

midline falx cerebri, cavum septum pellucidum, thalami, cerebellum, and cisterna magna. The cerebellum and cisterna magna are measured, and between 15 and 20 weeks' gestation, the nuchal skinfold thickness also is measured. From 15 until 22 weeks, the cerebellar diameter in millimeters is roughly equivalent to the gestational age in weeks (Chavez, 2003). *Cerebellar hypoplasia* has been associated with various central nervous system (CNS) and non-CNS abnormalities (Howley, 2018). The cisterna magna should measure between 2 and 10 mm throughout the second trimester and may reach 12 mm in the latter part of the third trimester. It becomes effaced when the Chiari II malformation is present (p. 277). If the cisterna magna is enlarged, the differential diagnosis includes absence of all or part of the vermis (p. 279), a cyst such as an arachnoid cyst within the posterior fossa, or mega-cisterna magna, which is a diagnosis of exclusion and has an excellent prognosis. An increased nuchal skinfold measurement is associated with increased risk for Down syndrome, other genetic syndromes, and structural abnormalities (Chap. 17, p. 341).

Imaging of the spine includes evaluation of the cervical, thoracic, lumbar, and sacral regions (Fig. 15-6). Representative images are often obtained in the sagittal or coronal plane. However, imaging of each spinal segment in the transverse plane is more sensitive for anomaly detection. Transverse images demonstrate three ossification centers. The anterior ossification center is the vertebral body, and the posterior paired ossification centers represent the junction of vertebral laminae and pedicles. Ossification of the spine proceeds in a cranial-caudal fashion. The ossification of the upper sacrum (S_1-S_2) is not generally visible before 16 weeks' gestation, and ossification of the entire sacrum may not be visible until 21 weeks (De Biasio, 2003). Thus, detection of some spinal abnormalities can be challenging in the early second trimester.

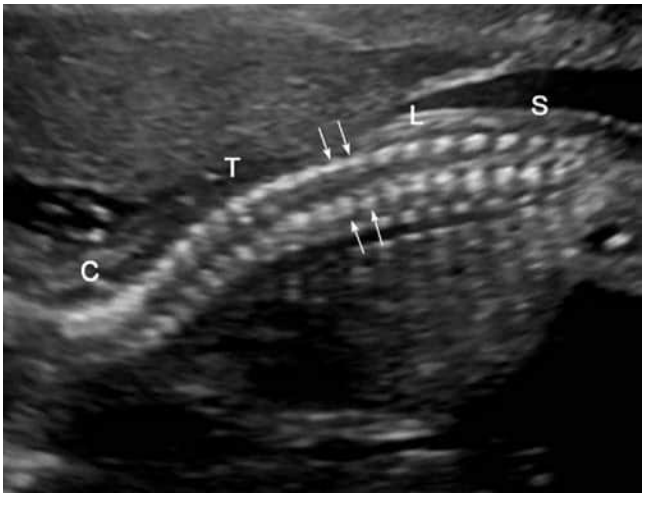

FIGURE 15-6 Normal fetal spine. This sagittal image depicts the cervical (*C*), thoracic (*T*), lumbar (*L*), and sacral spine (*S*). Arrows denote the parallel rows of paired posterior ossification centers, which represent the junction of vertebral lamina and pedicles.

Neural-tube Defects

These defects include anencephaly, myelomeningocele (spina bifida), cephalocele, and rare spinal dysraphisms. Normally, the neural tube closes by the embryonic age of 26 to 28 days (Chap. 7, p. 124). The birth prevalence of neural-tube defects approximates 0.9 in 1000 in the United States and most of Europe and 1.3 in 1000 in the United Kingdom (Cragan, 2009; Dolk, 2010). Many neural-tube defects can be prevented with folic acid supplementation. When isolated, neural-tube defect inheritance is multifactorial, and the recurrence risk without periconceptional folic acid supplementation is 3 to 5 percent (Chap. 16, p. 324).

Screening for neural-tube defects may be performed with either ultrasound alone or ultrasound in addition to maternal serum alpha-fetoprotein (MSAFP) level measurement (American College of Obstetricians and Gynecologists, 2019a). Between 15 and 20 weeks' gestation, an upper MSAFP threshold of 2.5 multiples of the median (MoM) is anticipated to detect 95 percent with fetal anencephaly and 80 percent with myelomeningocele. However, detection with standard sonography is at least comparable to that with MSAFP (Dashe, 2006; Norem 2005). A detailed ultrasound examination is the preferred diagnostic test and may identify other abnormalities or conditions that also elevate MSAFP levels (Table 17-5, p. 338).

Anencephaly is an absence of the cranium and telencephalon above the level of the skull base and orbits (Fig. 15-7). *Acrania* is absence of the cranium with protrusion of disorganized brain tissue, and herniation of the latter tissue is *exencephaly*. Importantly, brain tissue visible in the late first trimester is often not seen when ultrasound is performed in the second or third trimester. Thus, anencephaly is the final stage of exencephaly. It is often diagnosed in the late first trimester, and with adequate visualization, virtually all cases may be diagnosed in the second trimester.

Sonographically, the cranial contour may appear abnormal in the first trimester and may resemble a "shower cap" in the late first or early second trimester. The face often appears triangular, and sagittal images demonstrate lack of an ossified cranium. Hydramnios from impaired fetal swallowing is common in the third trimester. Anencephaly is uniformly lethal. If the pregnancy is continued, perinatal palliative care consultation should be considered (American College of Obstetricians and Gynecologists, 2019b).

Cephalocele is the herniation of meninges through a cranial defect, typically located in the midline occipital region (Fig. 15-8). When brain tissue herniates through the skull defect, the anomaly is termed an *encephalocele.* Herniation of the cerebellum and other posterior fossa structures constitutes a *Chiari III malformation*. Microcephaly is common by the third trimester. Associated intracranial abnormalities are frequently visible, and survivors have a high incidence of neurological deficits and intellectual disability. Cephalocele is an important feature of the autosomal recessive *Meckel-Gruber syndrome*, which includes cystic renal dysplasia and polydactyly. A cephalocele not located in the occipital midline raises suspicion for *amnionic-band sequence* (Chap. 6, p. 113).

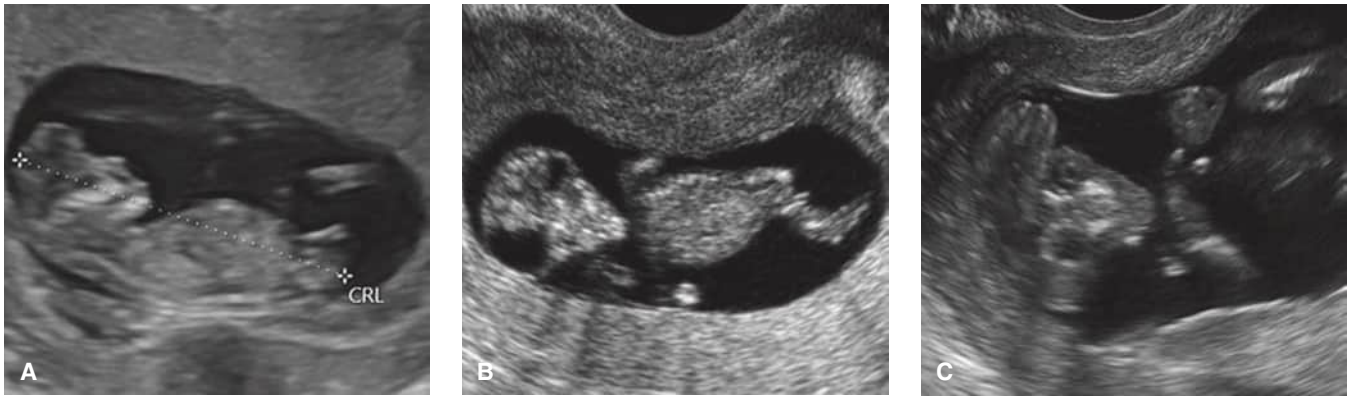

FIGURE 15-7 Anencephaly/acrania. **A.** This transabdominal image at 11 weeks' gestation depicts relatively subtle absence of the cranium. **B.** A transvaginal image at 11 weeks demonstrates more clearly the protrusion of a disorganized mass of brain tissue. **C.** By 14 weeks, this tissue resembles a "shower cap." CRL = crown–rump length.

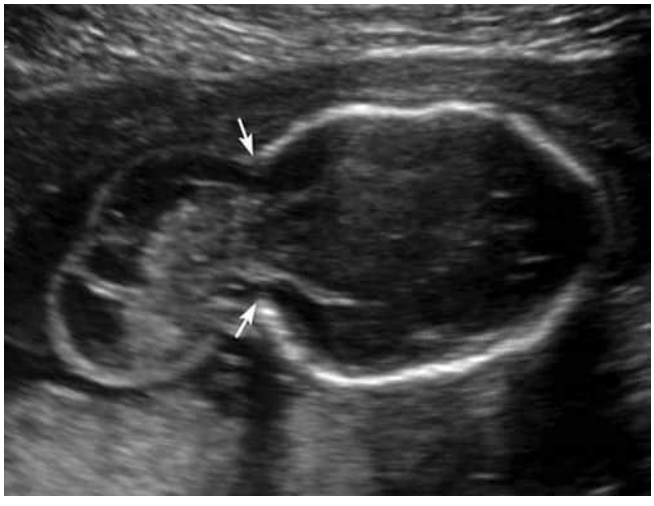

FIGURE 15-8 Encephalocele. This transverse image depicts a large defect in the occipital region of the cranium (*arrows*) through which meninges and brain tissue have herniated.

Spina bifida is characterized by defects in the vertebrae, typically the dorsal arches, and subsequent exposure of the meninges and nerve roots. The prevalence approximates 1 in 2000 births (Cragan, 2009; Dolk, 2010). Herniation of a meningeal sac and neural elements is a *myelomeningocele* (Fig. 15-9A). Less commonly, only an empty meningeal sac herniates, which is a *meningocele.* Transverse images are helpful to demonstrate separation or splaying of the lateral processes and characterize the level of the defect. Most cases are *open spina bifida*, which means that the defect includes skin and soft tissues. Closed defects are skin-covered and more challenging to detect prenatally.

Detection of spina bifida is aided by two characteristic cranial findings (Nicolaides, 1986). Flatting or scalloping of the frontal bones is termed the "*lemon sign,*" and anterior curvature of the cerebellum with effacement of the cisterna magna is the "*banana sign*" (Fig. 15-9B,C). These findings are manifestations of the Arnold-Chiari or Chiari II malformation. This develops when downward displacement of the spinal cord pulls a portion of the cerebellum through the foramen magnum and into the upper cervical canal. The biparietal diameter measurement often lags behind the other biometric parameters. *Ventriculomegaly* is common after mid-gestation, and 80 to 90 percent of infants with myelomeningocele require ventriculoperitoneal

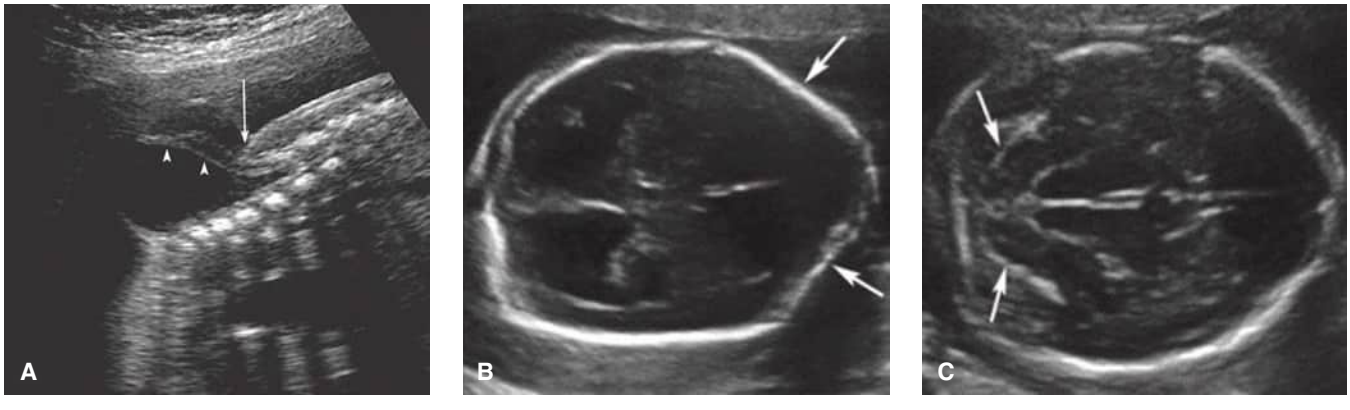

FIGURE 15-9 Myelomeningocele. **A.** Sagittal image of a lumbosacral myelomeningocele. Arrowheads indicate nerve roots within the anechoic herniated sac. The overlying skin abruptly stops at the defect (*arrow*). **B.** Transthalamic image demonstrating flattening of the frontal bones (*arrows*)—the *lemon sign*. **C.** Transcerebellar image depicting the *banana sign*, an anterior curvature of the cerebellum (*arrows*) and effacement of the cisterna magna.

shunt placement (Adzick 2011, Chao, 2010). Affected children require multidisciplinary care to address problems related to the defect such as deficits in swallowing, bladder and bowel function, and ambulation. Fetal myelomeningocele surgery is discussed in Chapter 19 (p. 372).

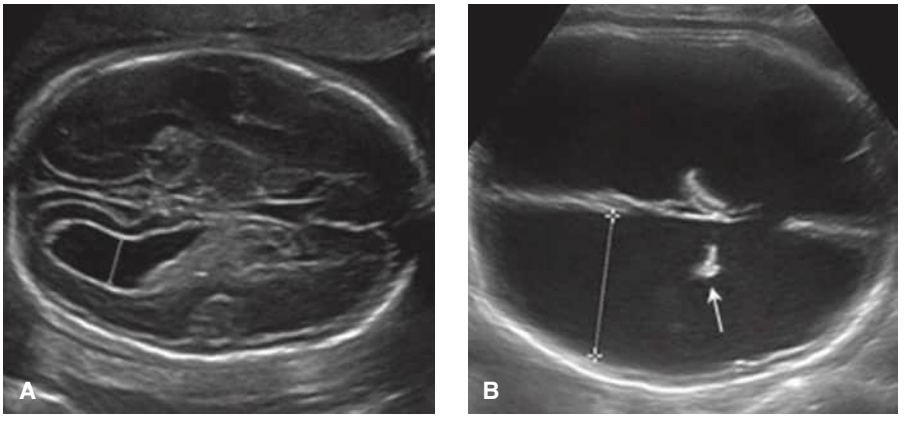

FIGURE 15-10 Ventriculomegaly. **A.** Mild ventriculomegaly. The atria measured 11 mm. No associated abnormality or underlying etiology was identified. **B.** Severe ventriculomegaly. In this fetus with aqueductal stenosis, the atria measured 45 mm. Arrow denotes the dangling choroid plexus.

Ventriculomegaly

Distention of the lateral ventricles is considered a nonspecific marker of abnormal brain development (Pilu, 2018). *Mild ventriculomegaly* is diagnosed when the atrial width measures 10 to 12 mm; *moderate ventriculomegaly*, when the measurement is 13 to 15 mm; and *severe ventriculomegaly* when >15 mm (Society for Maternal-Fetal Medicine, 2018). Representative images are depicted in Figure 15-10. The choroid plexus may appear *dangling* in severe cases.

Ventriculomegaly may occur secondary to a variety of central nervous system abnormalities and is associated with numerous genetic and infectious etiologies. Initial evaluation includes a detailed examination of fetal anatomy, amniocentesis for chromosomal microarray analysis, and testing for congenital infections such as cytomegalovirus and toxoplasmosis (Chap. 16, p. 326). Genetic syndromes resulting in ventriculomegaly include L1 X-linked aqueductal stenosis, Joubert syndrome, Walker Warburg syndrome, hydrolethalus syndrome, and lissencephaly syndromes (Kousi, 2016). Ventriculomegaly does not typically result in significant skull enlargement. Two exceptions—when macrocrania often occurs—are aqueductal stenosis and the asymmetric ventriculomegaly interhemispheric cyst callosal dysgenesis (AVID) syndrome (Oh, 2019). Fetal MR imaging should be considered to assess for associated abnormalities that may not be detectable sonographically (Herrera, 2020a; Katz, 2018) (Chap. 14, p. 263).

Prognosis is determined by etiology, severity, and progression. In a systematic review of nearly 1500 mild to moderate cases, 1 to 2 percent were associated with congenital infection; 5 percent, with aneuploidy; and 12 percent, with neurological abnormality (Devaseelan, 2010). With chromosomal microarray analysis, genetic abnormalities may be identified in 10 to 15 percent (Society for Maternal-Fetal Medicine, 2018). The larger the atria, the greater the likelihood of an underlying CNS abnormality and subsequent abnormal outcome (Gaglioti, 2009; Joó, 2008). If ventriculomegaly is isolated and remains mild, development is normal in at least 90 percent, and if moderate, development is normal in at least 75 percent (Society for Maternal-Fetal Medicine, 2018). Progression significantly raises the likelihood of abnormal neurological development.

Agenesis of the Corpus Callosum

The corpus callosum is a major fiber bundle that connects reciprocal regions of the cerebral hemispheres. It is best viewed in the midsagittal plane, and color Doppler may demonstrate the pericallosal artery (Fig. 15-11). Agenesis of the corpus callosum has characteristic sonographic findings. The frontal horns are widely separated, and the occipital horns are rounded—which is called colpocephaly. Together these findings give the lateral ventricles a teardrop shape (Fig. 15-12). A normal cavum septum pellucidum is not visible because of frontal horn displacement. In the midline, *bundles of Probst* represent fiber tracts that no longer cross in the midline. Ventriculomegaly is not uncommon, and without the corpus callosum bordering the third ventricle superiorly, the third ventricle may be elevated and mildly enlarged.

In population-based series, agenesis of the corpus callosum occurs in 1 in 4000 to 5000 pregnancies (Ballardini, 2018; Stoll, 2019; Szabo, 2011). It is associated with other anomalies, aneuploidy, and more than 200 genetic syndromes. Thus, chromosomal microarray analysis should be offered, and genetic counseling can be challenging. In a review of apparently isolated cases, fetal MR imaging identified additional brain abnormalities in more than 20 percent of cases (Sotiriadis, 2012). If MR imaging does not identify associated abnormalities, normal developmental outcome in 67 to 75 percent of cases and severe disability in about 10 percent has been reported (des Portes, 2018; Sotiriadis, 2012).

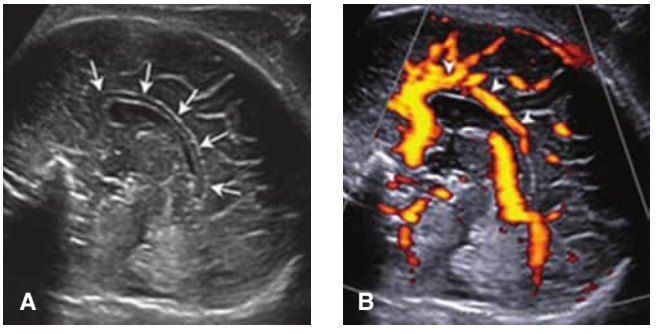

FIGURE 15-11 Normal corpus callosum. **A.** Arrows point to the corpus callosum in this midsagittal image. **B.** Power Doppler image of the pericallosal artery (*arrowheads*).

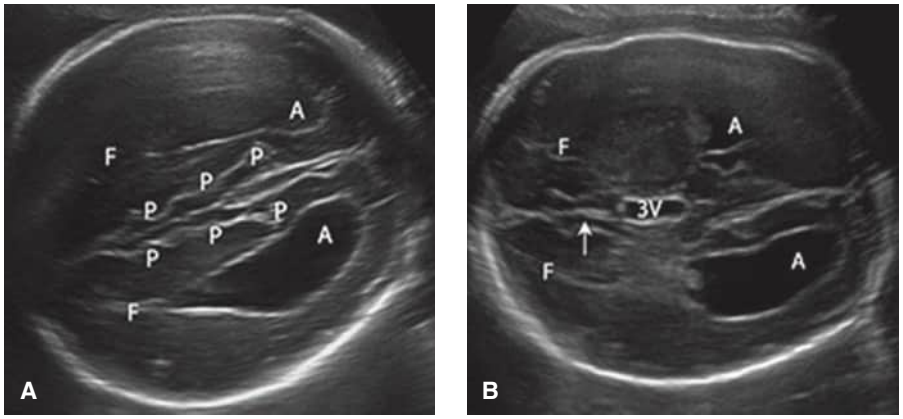

FIGURE 15-12 Agenesis of the corpus callosum. **A.** This transverse image demonstrates a teardrop-shaped ventricle. The frontal horns (*F*) are widely separated, no cavum septum pellucidum is visible, and bundles of Probst (*P*) line the midline. **B.** There is mild ventriculomegaly, no cavum septum pellucidum is visible (*arrow*), and the third ventricle (*3V*) is elevated and enlarged. A = atria.

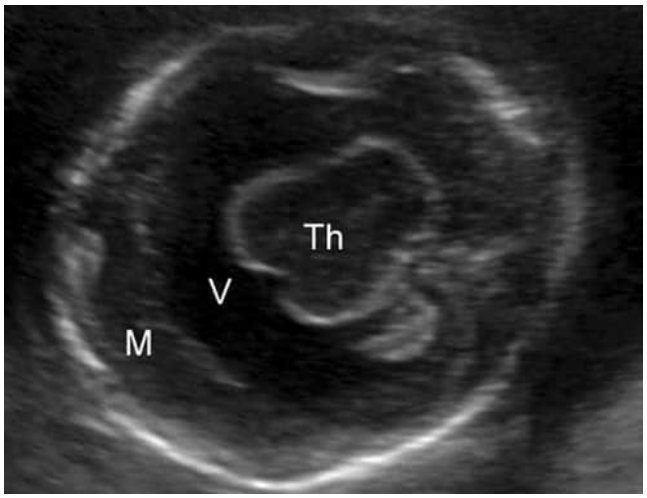

FIGURE 15-13 Alobar holoprosencephaly. The thalami (*Th*) are fused and encircled by a monoventricle (*V*) with a covering mantle (*M*) of cortex. The midline falx is absent. (Reproduced with permission from Rafael Levy, RDMS.)

Holoprosencephaly

During early normal brain development, the prosencephalon or forebrain divides as it becomes the telencephalon and diencephalon. With holoprosencephaly, the prosencephalon fails to divide completely into two separate cerebral hemispheres and underlying paired diencephalic structures. The most severe form, *alobar holoprosencephaly,* is characterized by a single monoventricle that surrounds fused thalami (Fig. 15-13). In *semilobar holoprosencephaly*, hemispheres partially separate. *Lobar holoprosencephaly* refers to a variable degree of fusion of frontal structures and is more challenging to detect with prenatal ultrasound. The lobar form is among possible diagnoses when a normal cavum septum pellucidum cannot be visualized. Last, the *middle interhemispheric variant of holoprosencephaly* is characterized by communication between the midportion of the bodies of the lateral ventricles with separation of the frontal horns, such that the choroid plexus may prolapse from one lateral ventricle into the other. Differentiation into two cerebral hemispheres is induced by prechordal mesenchyme, which is also responsible for differentiation of the midline face. Craniofacial anomalies associated with holoprosencephaly are reviewed later (p. 283).

The birth prevalence of holoprosencephaly is only 1 in 10,000. However, the abnormality has been identified in nearly 1 in 250 early abortuses, which attests to extremely high in-utero lethality (Orioli, 2010; Yamada, 2004). The alobar form accounts for 40 to 75 percent of cases, and 30 to 40 percent have a numerical chromosomal abnormality, particularly trisomy 13 (Orioli, 2010; Solomon, 2010). Conversely, of trisomy 13 cases, two thirds are found to have holoprosencephaly.

Dandy-Walker Malformation

This posterior fossa abnormality is characterized by agenesis of the cerebellar vermis, posterior fossa enlargement, and elevation of the tentorium cerebelli. The cerebellar hemispheres are visibly separated, and fluid in the cisterna magna communicates with the fourth ventricle through the cerebellar vermis defect (Fig. 15-14). The birth prevalence approximates 1 in 12,000 (Long, 2006). Associated anomalies and aneuploidy are common. These include ventriculomegaly in 30 to 40 percent, other anomalies in approximately 50 percent, and aneuploidy in 40 percent (Ecker, 2000; Long, 2006). Dandy-Walker malformation is also associated with numerous genetic and sporadic syndromes, congenital viral infections, and teratogen exposure, all of which greatly affect the prognosis. Thus, the initial evaluation mirrors that for ventriculomegaly (p. 278).

Inferior vermian agenesis is a term used when only the inferior portion of the vermis is absent. Even with partial and relatively subtle vermian agenesis, the prevalence of associated anomalies and aneuploidy is still high, and the prognosis is often poor (Ecker, 2000; Long, 2006).

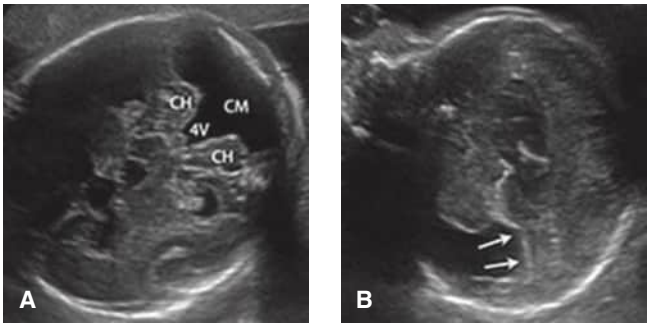

FIGURE 15-14 Dandy-Walker malformation. **A.** The cerebellar hemispheres (*CH*) are widely separated by a fluid collection that connects the 4th ventricle (*4V*) to the enlarged cisterna magna (*CM*). **B.** Sagittal image depicts elevation of the tentorium (*arrows*).

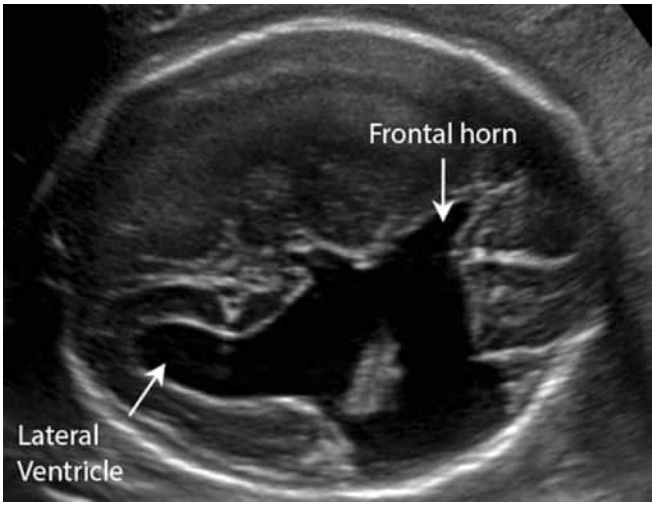

FIGURE 15-15 Schizencephaly. This transverse image shows a large cleft extending from the right lateral ventricle through the cortex. Because the borders of the cleft are separate, the defect is termed *open-lipped*. (Reproduced with permission from Michael Davidson, RDMS.)

Schizencephaly and Porencephaly

Schizencephaly is a rare brain abnormality characterized by clefts in one or both cerebral hemispheres, typically involving the perisylvian fissure. The cleft is lined by heterotopic gray matter and communicates with the ventricle, extending through the cortex to the pial surface (Fig. 15-15). Schizencephaly is believed to be an abnormality of neuronal migration, which explains its typically delayed recognition until after midpregnancy (Howe, 2012). It is associated with absence of the cavum septum pellucidum, resulting in frontal horn communication. Ventriculomegaly is a common finding.

In contrast, porencephaly is a cystic space within the brain that is lined by white matter and may or may not communicate with the ventricular system. It is generally considered to be a destructive lesion. Porencephaly may develop following intracranial hemorrhage in the setting of neonatal alloimmune thrombocytopenia or in an individual with a COL4A-1 mutation—a genetic condition which causes *familial porencephaly*. In a monochorionic twin gestation, acute hypotension following death of a co-twin also may create porencephaly. Fetal MR imaging should be considered when either of these CNS anomalies is identified.

Microcephaly

This condition indicates that the size of the head is profoundly smaller than expected. The Society for Maternal-Fetal Medicine (2016) recommends that fetal microcephaly be defined as a head circumference at least 3 standard deviations (SD) below the mean for gestational age (Appendix, p. 1237). However, many fetuses with measurements in this range have normal head size at birth, and therefore the diagnosis of pathologic microcephaly is not considered *certain* until the head circumference reaches 5 SD below the mean (Society for Maternal-Fetal Medicine, 2016). The forehead is often upsloping. Microcephaly is associated with a wide range of underlying abnormalities, genetic syndromes, and congenital infections such as toxoplasmosis, rubella, and cytomegalovirus, herpes, or Zika infection (Chap. 67, p. 1183). Findings that suggest infection include parenchymal and periventricular echogenic foci, ventriculomegaly, and cerebellar hypoplasia. Amniocentesis should be offered, and fetal MR imaging should be considered. The Society for Maternal-Fetal Medicine (2016) recommends performing a detailed ultrasound examination of the fetal brain if the head circumference measures more than 2 SD below the mean. Another ultrasound evaluation follows in 3 or 4 weeks, with the understanding that it may be difficult to distinguish constitutionally small head size from pathologic findings.

Sacrococcygeal Teratoma

This germ cell tumor is one of the most common tumors in neonates, with a birth prevalence of approximately 1 in 28,000 (Derikx, 2006; Swamy, 2008). It is thought to arise from the totipotent cells along the Hensen node, anterior to the coccyx. Sacrococcygeal teratoma (SCT) classification includes four types (Altman, 1974). Type 1 is predominantly external with a minimal presacral component; type 2 is predominantly external but with a significant intrapelvic component; type 3 is predominantly internal and has abdominal extension; and type 4 is entirely internal with no external component. The tumor histological type may be mature, immature, or malignant.

Sonographically, SCT is a solid and/or cystic mass that arises from the anterior sacrum and usually extends inferiorly and externally as it grows (Fig. 15-16). Solid components often vary in echogenicity, appear disorganized, and may enlarge rapidly with advancing gestation. Fetal MR imaging should be considered because internal pelvic components may be challenging to visualize. Large, solid tumors frequently result in hydrops due to high-output cardiac failure, either as a consequence of tumor vascularity or secondary to bleeding within the tumor and resultant anemia. Hydramnios is common. Fetuses with tumors >5 cm often require cesarean delivery, and classical hysterotomy may be needed (Gucciardo, 2011). Fetal therapy for SCT is discussed in Chapter 19 (p. 373).

Caudal Regression Sequence

This rare anomaly is characterized by absence of the sacral spine and often portions of the lumbar spine. It is approximately 25 times more prevalent in pregnancies complicated by diabetes (Garne, 2012). Caudal regression is associated with genitourinary malformations and syndromes such as the VACTERL association (vertebral defects, anal atresia, cardiac defects, tracheo-esophageal fistula, renal anomalies, and limb abnormalities) (Vilanova-Sanchez, 2018). Sonographic findings include a spine that appears abnormally short, lacks normal lumbosacral curvature, and terminates abruptly above the level of the iliac wings (Fig. 15-17). Because the sacrum does not lie between the iliac wings, they are abnormally close together and may appear shield-like. The lower extremities lack normal soft tissue development and may be abnormally positioned.

Sirenomelia

This rare anomaly may be confused with caudal regression sequence but is quite different. Formerly termed mermaid

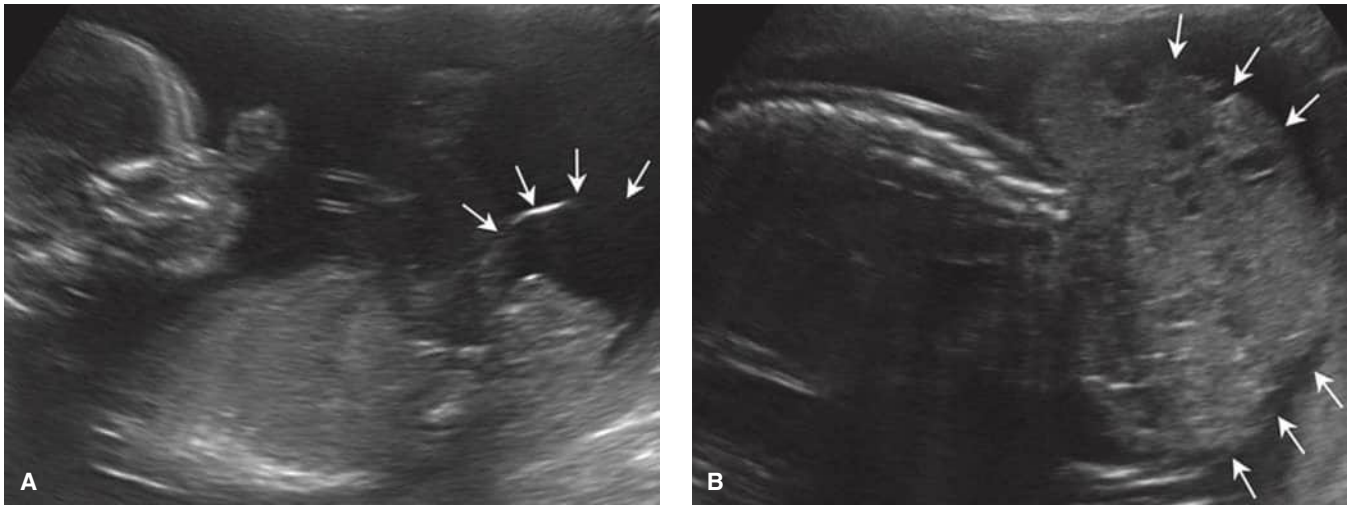

FIGURE 15-16 Sacrococcygeal teratoma. This tumor enlarged from 3 cm in diameter at 19 weeks' gestation **(A)** to 9 cm in diameter during a 5-week period **(B)**. Arrows depict the external borders of the mass.

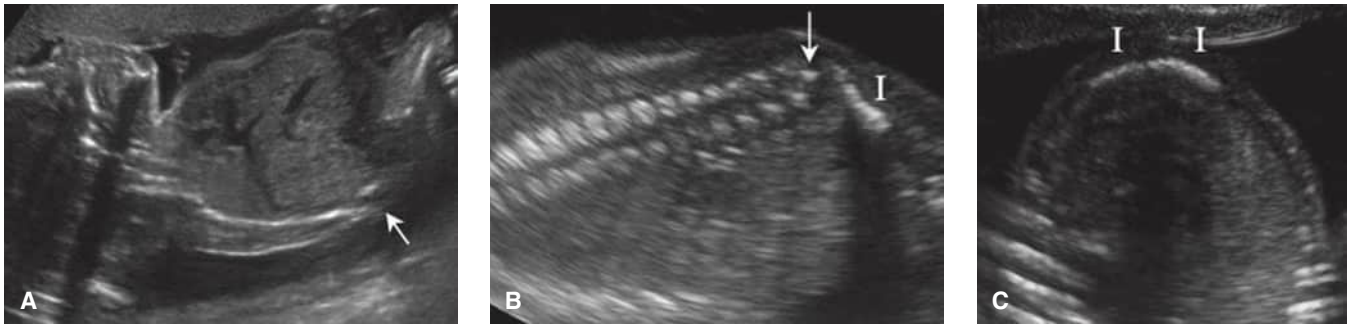

FIGURE 15-17 Caudal regression sequence. **A.** The spine is markedly foreshortened. The arrow shows where it terminates. **B.** The spine ends abruptly above the level of the iliac wings (*I*). **C.** Without a vertebral body between the iliac wings (*I*), they assume a shield shape.

syndrome, it is characterized by a single lower extremity in the midline and bilateral renal agenesis. The extremity may contain one or two sets of bones and feet (Fig. 15-18). The bladder, anus, and genitalia are absent. What may appear to be a single umbilical artery in these cases is instead a remnant of the vitelline artery. After 18 weeks' gestation, when the kidneys become the primary source of amniotic fluid production, resultant anhydramnios may complicate the diagnosis. Cases of surviving infants have a variant of sirenomelia in which there is some functioning renal tissue and urinary output (Pinette, 2005).

■ Hemivertebrae

These spinal *segmentation-fusion defects* are characterized by abnormal development of half of the vertebral

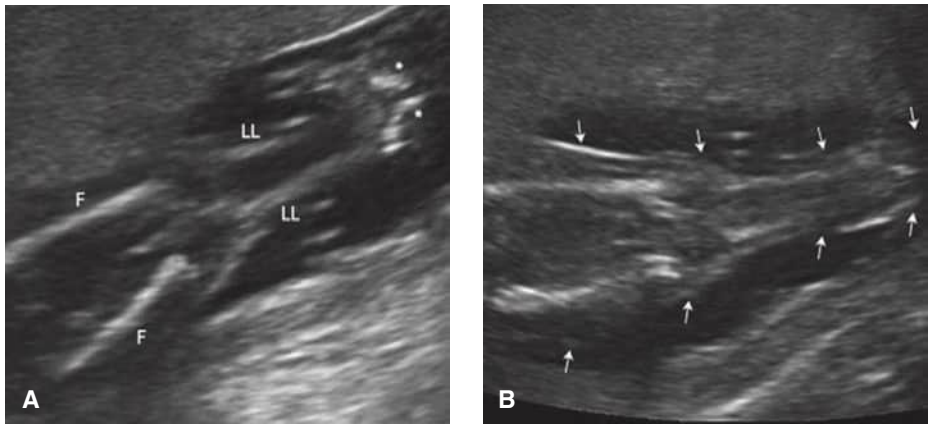

FIGURE 15-18 Sirenomelia. **A.** This single lower extremity contained two femur bones (*F*), two lower leg bones (*LL*), and a fused foot with toes pointing outward (*). **B.** Arrows show the soft tissue outline of the lower extremity. Amnionic fluid is visible only because the gestational age is 17 weeks' gestation. By 18 weeks, absence of kidneys and bladder resulted in anhydramnios. (Reproduced with permission from Melissa Salvie, RDMS.)

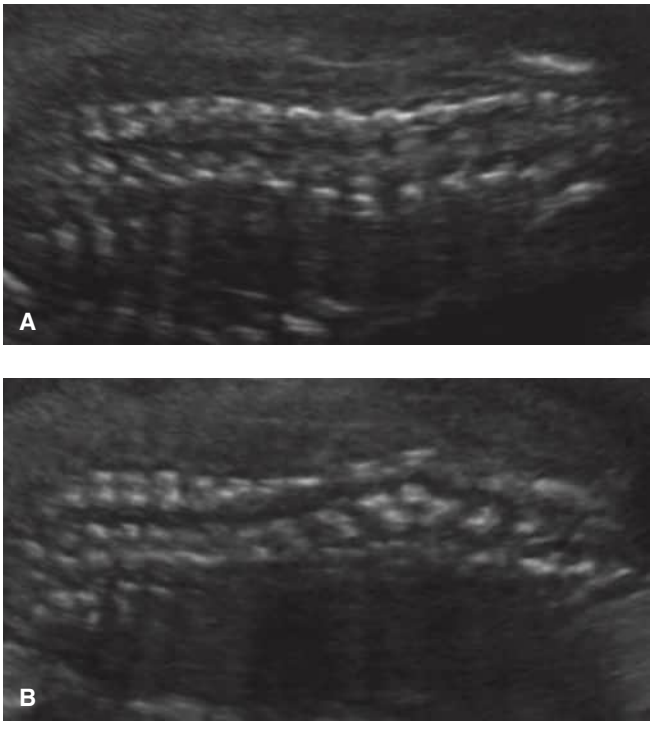

FIGURE 15-19 Hemivertebrae result in abnormal spinal curvature in these coronal images. (Reproduced with permission from Rose Muli, RDMS.)

body. Affected vertebrae are triangular and may be separate or fused to adjacent vertebral bodies. This leads to abnormal curvature of the spine such as scoliosis (Fig. 15-19). Prenatally diagnosed cases typically involve the thoraco–lumbar spine. Associated abnormalities are common, particularly skeletal, renal, and cardiac defects (Basude, 2015; Yulia, 2020). Hemivertebrae are also a component of several syndromes, including the VACTERL association.

HEAD, FACE, AND NECK

Craniofacial anatomy on the detailed anatomic survey may include cranial integrity and shape of the skull (Fig. 15-2A); images of the orbits, nose, and lips; views of the maxilla, mandible, hard palate, and tongue; images of the ears; and evaluation of the neck (Fig. 15-20). Of these structures, only the upper lip is a component of the standard examination. At Parkland Hospital, we include an image of the sagittal profile as part of our standard examination to help detect micrognathia prenatally.

When imaging the neck, particularly in the third trimester, identifying a nuchal cord is not uncommon (Fig. 15-21). This finding is not associated with adverse outcome, and we do not alter fetal surveillance if a nuchal cord is detected.

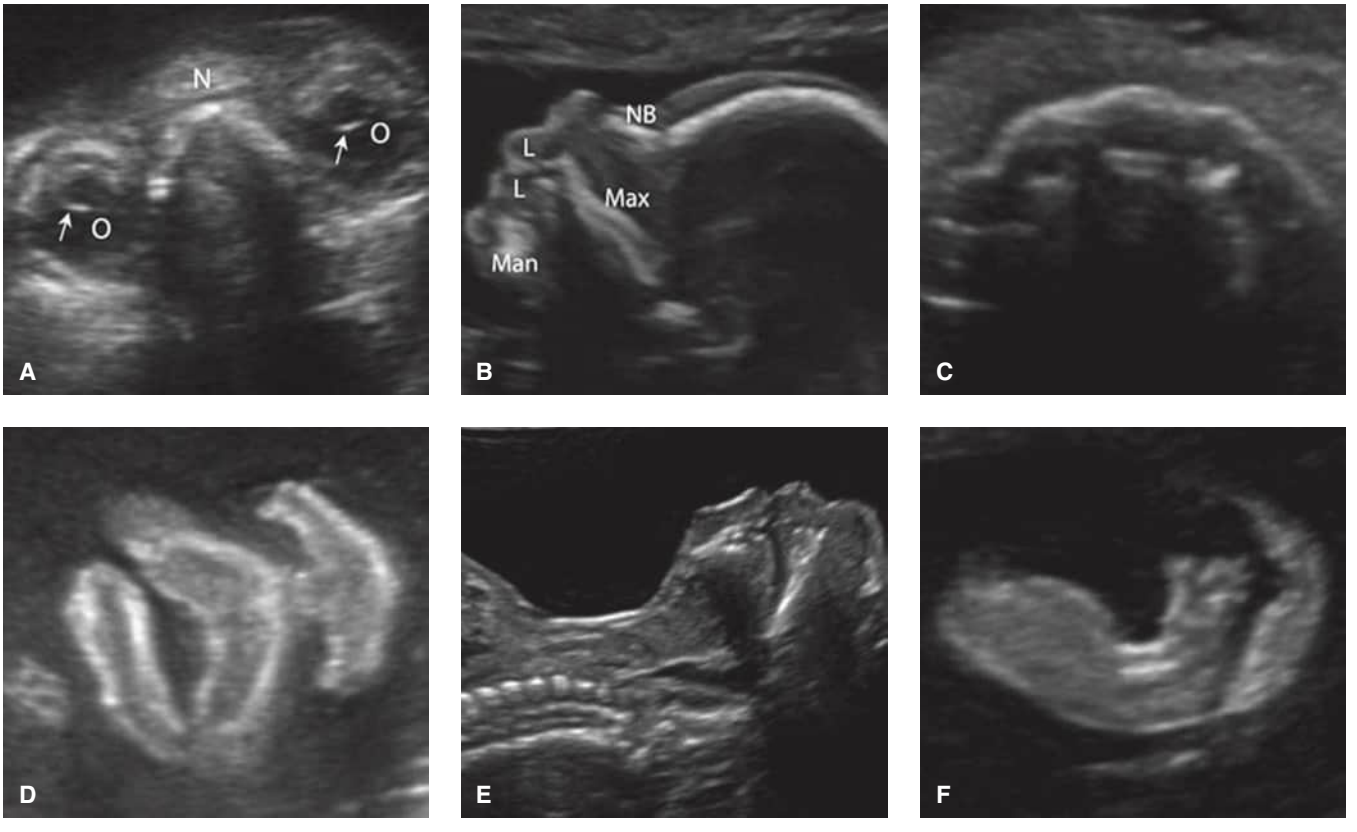

FIGURE 15-20 Normal craniofacial and neck anatomy. **A.** Transverse images of orbits (*O*) and nose (*N*). The small circle within each orbit is the lens. The distance between the orbits roughly approximates the width of each orbit. **B.** Sagittal view of the face, depicting the nasal bone (*NB*), lips (*L*), maxilla (*Max*), and mandible (*Man*). **C.** Transverse image of the alveolar ridge. **D.** Coronal view of the nose, upper lip, and lower lip. **E.** Sagittal image of the neck. **F.** Image of the ear. (Reproduced with permission from Devi Nanandhan, RDMS.)

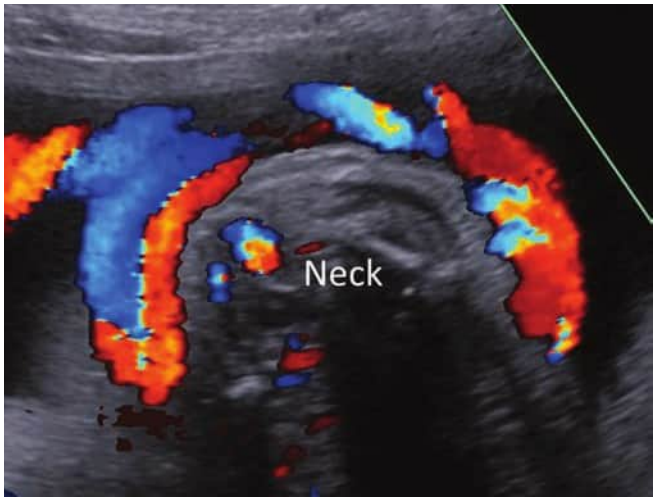

FIGURE 15-21 Nuchal cord incidentally noted with color Doppler in a transverse image of the fetal neck at 34 weeks' gestation.

■ Dolichocephaly and Brachycephaly

The *cephalic index* reflects the skull shape. It is measured by dividing the biparietal diameter by the occipitofrontal diameter. The cephalic index is normally 70 to 86 percent. It is smaller if the head shape is flattened—*dolichocephaly,* and larger if the shape is rounded—*brachycephaly.* In such cases, the head circumference measurement more reliably estimates gestational age than does the biparietal diameter (Fig. 15-22). These head shape variants may be normal or can be secondary to fetal position or oligohydramnios. Dolichocephaly can occur with neural-tube defects, and brachycephaly may be seen in fetuses with Down syndrome. A strawberry-shaped skull describes a pattern of angulation typical of trisomy 18 (Fig. 16-5, p. 312). With any abnormal skull shape, *craniosynostosis* is a consideration.

■ Abnormalities of Orbits and Nose

Subjectively, the distance in between the orbits is similar to the diameter of each orbit (see Fig. 15-20). The lens is often visible. Nomograms are available for the ocular diameter and for the interorbital and binocular distances (Appendix, p. 1240).

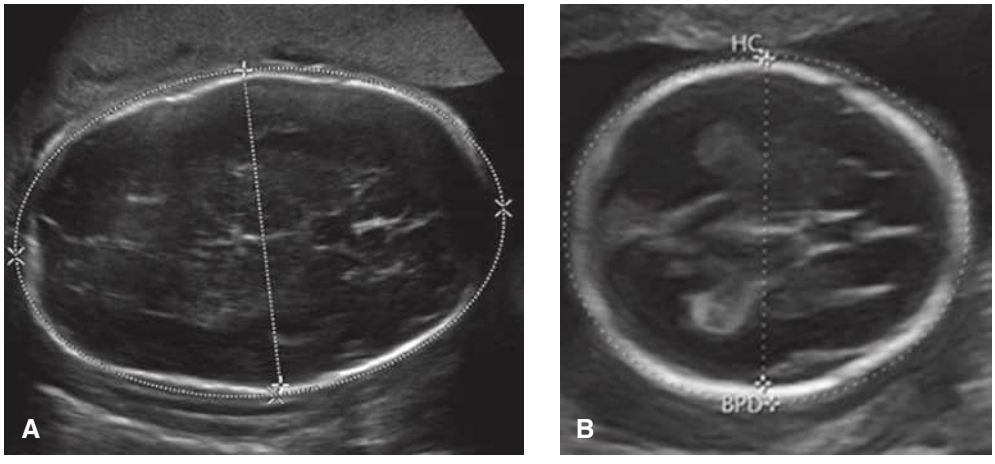

FIGURE 15-22 Transthalamic images demonstrating dolichocephaly **(A)** and brachycephaly **(B)**. The biparietal diameter (*BPD*) and head circumference (*HC*) are measured in each image.

Hypertelorism (Fig. 15-23) is a common finding in trisomy 18. Hypotelorism, with or without microphthalmia, may be found in the setting of holoprosencephaly. In its extreme form only a single orbit is visible—cyclopia. Other comorbid anomalies with holoprosencephaly include a single nostril—cebocephaly, or absence of the entire nose (arhinia) with proboscis (Fig. 15-24).

Nasal bone hypoplasia or sonographic absence is an aneuploidy marker that confers increased risk for fetal Down syndrome (Fig. 15-25). It is not a structural abnormality. Nasal bone measurement is part of the detailed ultrasound examination and is measured only between 15 and 22 weeks' gestation. The measurement is considered foreshortened if less than 2.5 mm or if more than 2 SD below the mean for gestational age (Chap. 17, p. 341). Hypoplasia of the nose is a different condition that can occur following warfarin exposure (Fig. 8-4, p. 156).

■ Facial Clefts

These are grouped into three main types. The first type, *cleft lip and palate*, always involves the lip, may also involve the hard palate, can be unilateral or bilateral, and has a birth prevalence that approximates 1 in 1000 (Cragan, 2009; Dolk, 2010). If isolated, the inheritance is multifactorial—with a recurrence risk of 3 to 5 percent for one prior affected child. If a cleft is visible in the upper lip, a transverse image at the level of the alveolar ridge may demonstrate that the defect also involves the primary palate (Fig. 15-26).

In one review of low-risk pregnancies, cleft lip was identified sonographically in only about half of cases (Maarse, 2010). Approximately 40 percent of those detected prenatally are associated with other anomalies or syndromes, and aneuploidy is common (Maarse, 2011; Offerdal, 2008). The rate of associated anomalies is highest for bilateral defects that involve the palate. In the Utah Birth Defect Network, aneuploidy was identified in 1 percent with cleft lip alone, 5 percent with unilateral cleft lip and palate, and 13 percent with bilateral cleft lip and palate (Walker, 2001).

The second type of cleft is *isolated cleft palate.* It begins at the uvula, may involve the soft palate, and occasionally involves the hard palate—but does not involve the lip. The birth prevalence approximates 1 in 2000 (Dolk, 2010). Identification of an isolated cleft palate has been described using detailed sonography, and particularly with three-dimensional imaging, but detection is not feasible in all cases (Ramos, 2010; Wilhelm, 2010). Isolated cleft palate is not expected to be visualized during a standard ultrasound examination (Maarse, 2011; Offerdal, 2008).

A third type of cleft is *median cleft lip,* which may

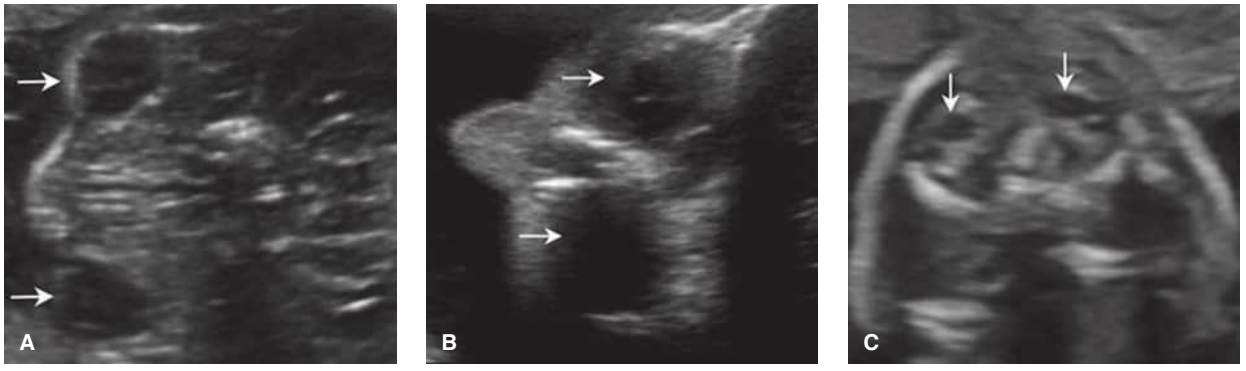

FIGURE 15-23 Abnormalities of the orbits. **A.** Hypertelorism in a fetus with trisomy 18. **B.** Hypotelorism in a fetus with trisomy 13 and alobar holoprosencephaly. **C.** Microphthalmia. This fetus also had trisomy 13. Arrows point to the eyes.

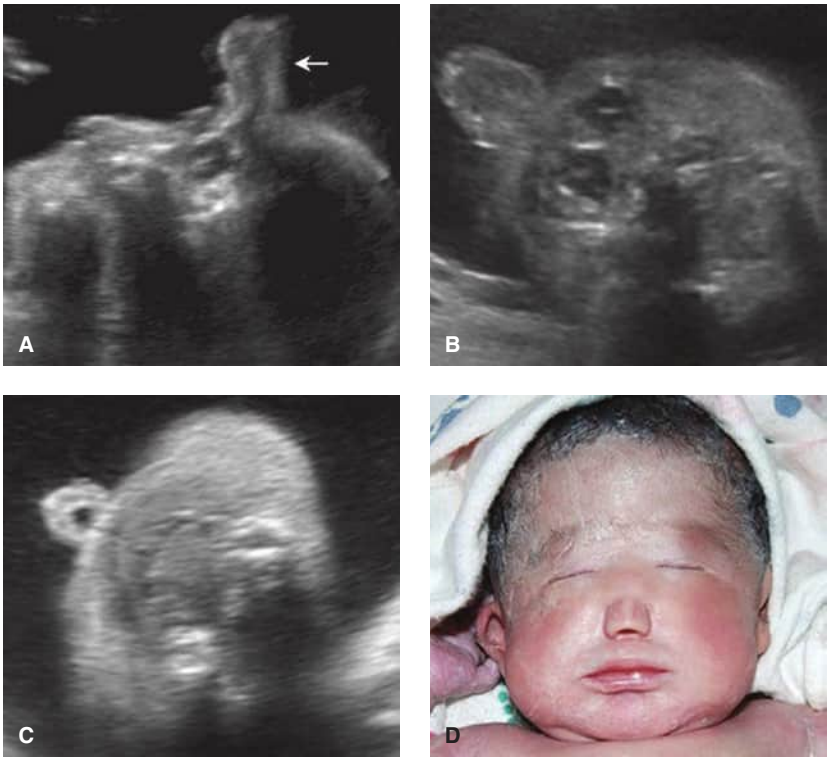

FIGURE 15-24 Nasal abnormalities associated with holoprosencephaly. **A.** Sagittal profile depicting a proboscis (*arrow*) protruding from the forehead. **B.** Coronal image demonstrating the proboscis along with hypotelorism and absence of the nose. **C.** Coronal image demonstrating a single nostril (cebocephaly). **D.** Photograph of a newborn with cebocephaly.

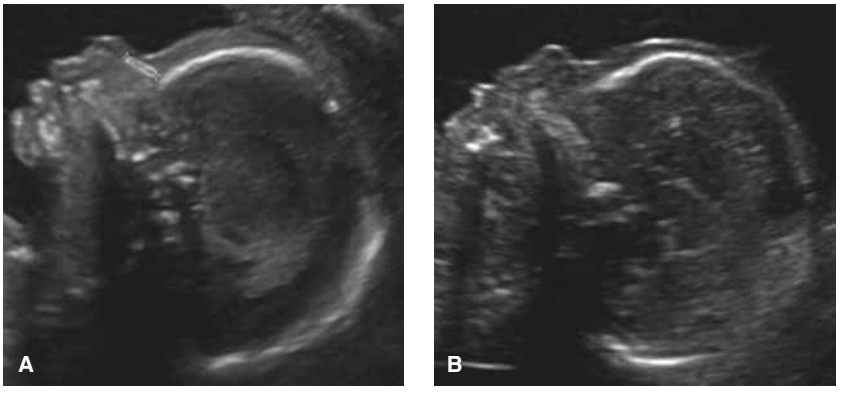

FIGURE 15-25 Nasal bone (and its absence). **A.** Sagittal image of the profile showing measurement of a normal nasal bone at 19 weeks. **B.** Fetus with trisomy 21, also at 19 weeks, with no visible nasal bone. (Reproduced with permission from Jason McWhirt, RDMS.)

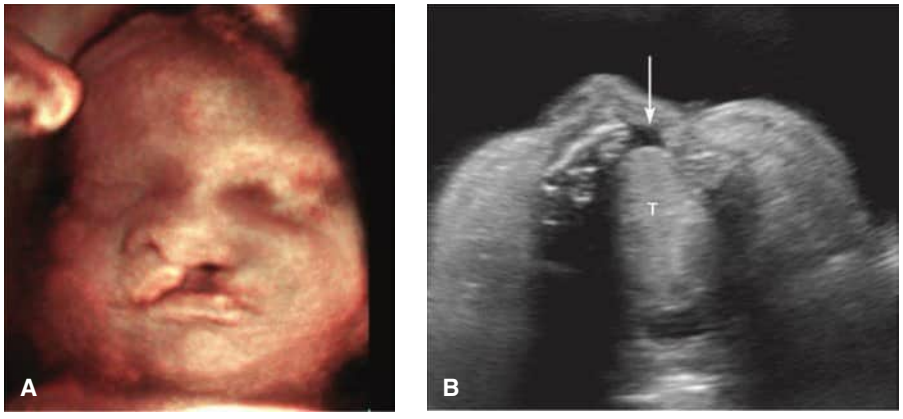

FIGURE 15-26 Cleft lip/palate. **A.** This fetus has a prominent unilateral (left-sided) cleft lip. **B.** Transverse view of the palate in the same fetus demonstrates a defect in the alveolar ridge (*arrow*). The tongue (*T*) is also visible.

be found in fetuses with holoprosencephaly, typically when hypotelorism is also present. Additionally, a median cleft may be associated with hypertelorism and frontonasal dysplasia, formerly called the *median cleft face syndrome*.

Micrognathia

The fetal profile can help identify cases of *micrognathia*—hypoplasia of the mandible, and *retrognathia*, which is recession of the mandible in relation to the maxilla (Fig. 15-27). To quantify micrognathia risk, a transverse image of the mandible can be used to calculate the jaw index, which is the anterior-posterior diameter of the mandible expressed as a percentage of the biparietal diameter (Paladini, 1999). Fetuses with micrognathia and retrognathia frequently have a posterior cleft palate and glossoptosis (recessed tongue)—a constellation of findings known as the Pierre Robin sequence. Micrognathia is also a feature of Treacher Collins syndrome, oral-facial-digital syndromes, trisomies 18 and 13, triploidy, and the 22 q11.2 deletion. Micrognathia may result in hydramnios and can cause airway obstruction at birth. Use of the *ex-utero intrapartum treatment (EXIT)* procedure for severe micrognathia is discussed in Chapter 19 (p. 379).

Micrognathia should not be confused with agnathia–otocephaly, a rare anomaly in which no mandible develops and the ears may fuse in the midline (Fig. 15-28). The latter confers an extremely poor prognosis and has been diagnosed as early as the late first trimester (Rodriguez, 2019).

Epignathus

This rare teratoma arises from the oral cavity or pharynx. It may grow outward or both outward and into the brain, the latter conferring an extremely poor prognosis (Fig. 15-29). If brain involvement is absent, an EXIT procedure, reviewed in Chapter 19 (p. 379), can help secure the airway at delivery (Chung, 2012).

Cystic Hygroma

This venolymphatic malformation is characterized by fluid-filled sacs that extend from the posterior neck (Fig. 15-30). Cystic hygromas may be diagnosed in the first trimester and vary widely in size. Impaired lymphatic drainage from the head into the jugular vein leads to an accumulation of fluid in jugular lymphatic sacs. The birth prevalence of cystic hygromas approximates 1 in 5000. However, reflecting the high in-utero lethality of the condition, the first-trimester incidence exceeds 1 in 300 (Malone, 2005).

Up to 70 percent of cystic hygromas are associated with aneuploidy. When cystic hygromas are diagnosed in the first trimester, trisomy 21 is the most common aneuploidy, followed by 45,X and trisomy 18 (Kharrat, 2006; Malone, 2005). First-trimester fetuses with cystic hygromas are five times more likely to be aneuploid than fetuses with a thickened nuchal translucency. When cystic hygromas are diagnosed in the second trimester, approximately 75 percent of aneuploid cases are 45,X—Turner syndrome (Johnson, 1993; Shulman, 1992).

Even in the absence of aneuploidy, cystic hygromas confer a significantly greater risk for other abnormalities, particularly flow-related cardiac defects. These include hypoplastic left heart and coarctation of the aorta (p. 292). Cystic hygromas may

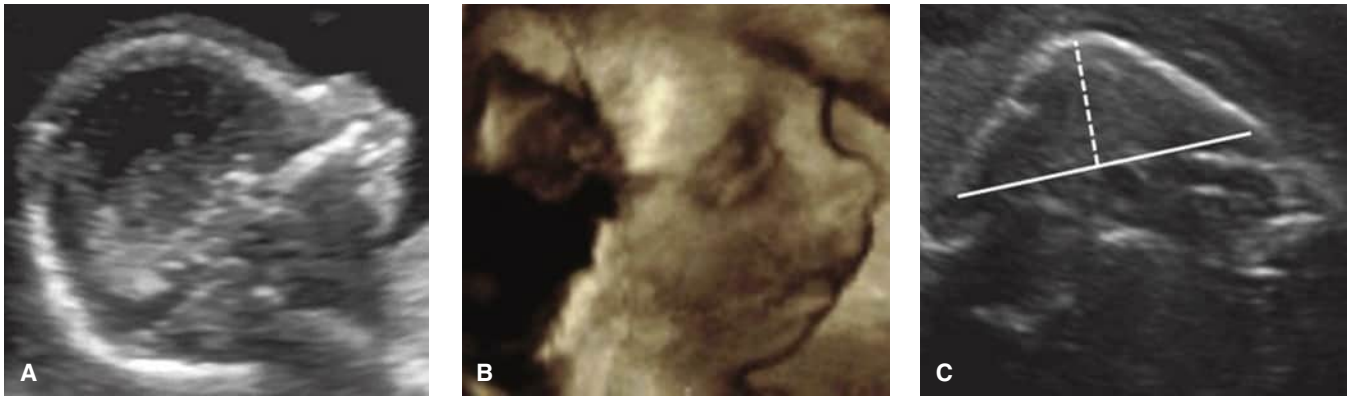

FIGURE 15-27 Micrognathia. **A.** Sagittal image of a fetus with severe micrognathia. **B.** 3-dimensional ultrasound rendering depicts the recessed chin and downslanting palpebral fissures. **C.** A transverse image of the mandible was used to calculate a jaw index for this fetus.

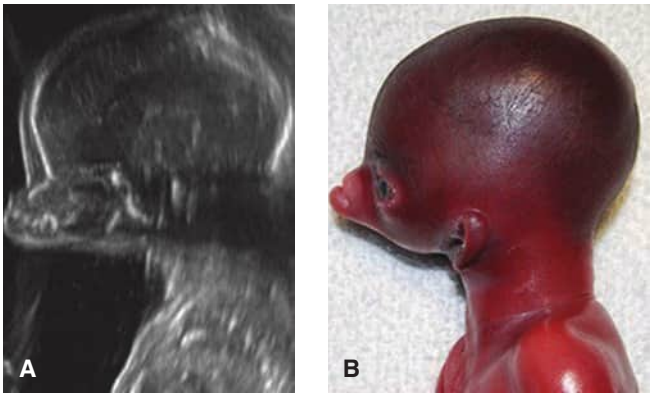

FIGURE 15-28 Agnathia-otocephaly, ultrasound **(A)** and postdelivery **(B)** images. With this rare, lethal anomaly the mandible fails to develop, and the ears are inferiorly displaced and may be fused in the midline.

also be part of a genetic syndrome such as *Noonan syndrome*, an autosomal dominant disorder that shares several features with 45,X. Noonan syndrome is characterized by short stature, lymphedema, high-arched palate, and often pulmonary valve stenosis.

Large cystic hygromas are usually associated with hydrops fetalis, rarely resolve, and carry a poor prognosis. Small hygromas may undergo spontaneous resolution, and provided that fetal karyotype and echocardiography results are normal, the prognosis *may* be good. The likelihood of a nonanomalous liveborn neonate with normal karyotype following identification of first-trimester hygroma approximates 1 in 6 (Kharrat, 2006; Malone, 2005).

THORAX

Thoracic anatomy imaged in the detailed anatomic survey may include the lungs, ribs, and diaphragm. The lungs should appear homogeneous and symmetric, each occupying approximately one third of the area in the four-chamber view of the heart (Fig. 15-31). The thoracic circumference is measured at the skin line in a transverse plane at the level of the four-chamber view. If pulmonary hypoplasia is suspected secondary to a small thorax, such as with a severe skeletal dysplasia, comparison with a reference table may be helpful (Appendix, p. 1238). Representative images of the diaphragm are usually obtained in the parasagittal or coronal plane. The diaphragm appears as a hypoechoic line between the lungs and liver. Thoracic abnormalities may appear sonographically as cystic or solid space-occupying lesions or as an effusion outlining the

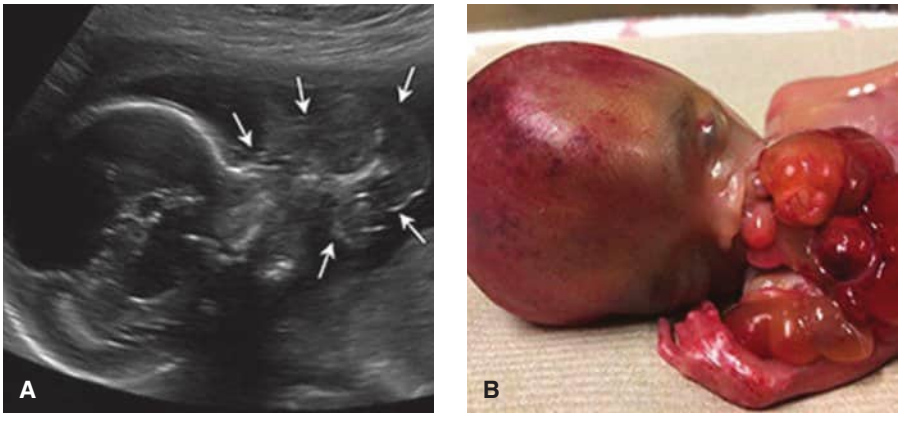

FIGURE 15-29 Epignathus, ultrasound **(A)** and postdelivery **(B)** images. This teratoma arises from the oral cavity or pharynx and may grow outward from the mouth or both outward and into the brain, as in this fetus (*arrowhead*). Arrows depict the external extent of the mass. (Reproduced with permission from Halima Abdirahman, RDMS.)

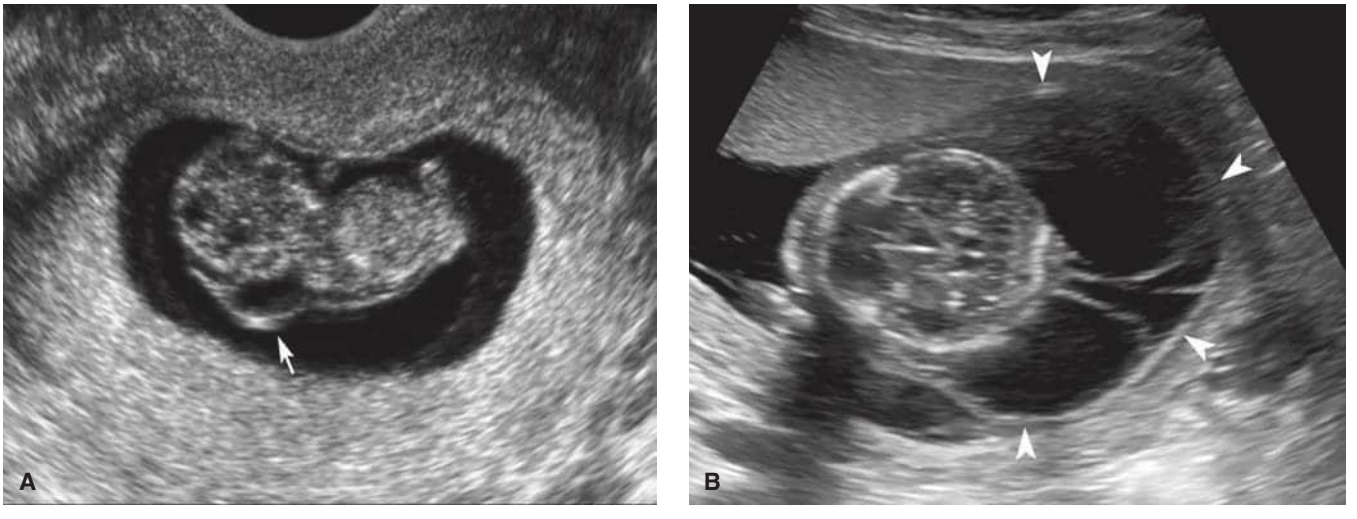

FIGURE 15-30 Cystic hygromas. **A.** This 9-week fetus with a cystic hygroma (*arrow*) was later found to have Noonan syndrome. **B.** Massive multiseptated hygromas (*arrowheads*) in the setting of hydrops fetalis at 15 weeks' gestation.

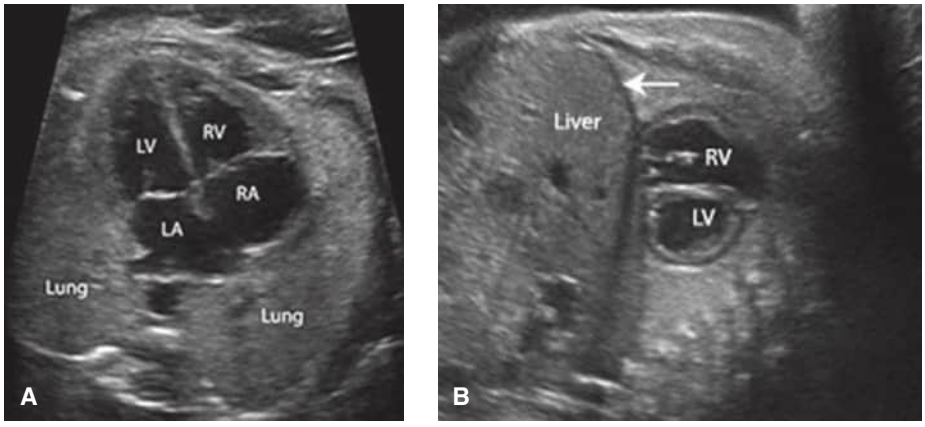

FIGURE 15-31 Normal thoracic anatomy. **A.** The lungs each occupy one third of the area in the four-chamber view of the heart. **B.** The diaphragm (*arrow*) appears as a hypoechoic line in between the lung and liver in this parasagittal view. LA = left atrium; LV = left ventricle; RA = right atrium; RV = right ventricle.

heart or lung(s). Fetal therapy for thoracic abnormalities is discussed in Chapter 19 (p. 376).

■ Diaphragmatic Hernia

This is a defect in the diaphragm through which abdominal organs herniate into the thorax. It is left-sided in approximately 75 percent of cases, right-sided in 20 percent, and bilateral in 5 percent (Gallot, 2007). The prevalence of congenital diaphragmatic hernia (CDH) is 1 in 3000 to 5000 births (Cragan, 2009; Dolk, 2010). Associated anomalies and aneuploidy are found in 40 percent of cases (Gallot, 2007; Stege, 2003). In population-based series, an associated abnormality reduces the overall survival rate of neonates with CDH from approximately 50 percent to about 20 percent (Colvin, 2005; Gallot, 2007). Without other abnormalities, the major causes of neonatal mortality are pulmonary hypoplasia and pulmonary hypertension.

Left-sided CDH typically causes dextroposition of the heart to the right side of the thorax, such that the cardiac axis points toward the midline (Fig. 15-32). Accompanying findings include the stomach bubble or bowel peristalsis in the chest and a wedge-shaped mass—the liver—located anteriorly in the left hemithorax. Liver herniation complicates at least 50 percent of cases and is associated with a 30-percent reduction in the survival rate (Mullassery, 2010). With large lesions, impaired swallowing and mediastinal shift may result in hydramnios and hydrops, respectively.

An effort to reduce neonatal mortality rates and need for extracorporeal membrane oxygenation (ECMO) has focused on prognostic indicators such as the sonographic lung-to-head ratio, described in Chapter 19 (p. 375). MR imaging parameters include measurements of lung volume and degree of liver herniation (Dutemeyer, 2020; Oluyomi-Obi, 2017; Worley, 2009).

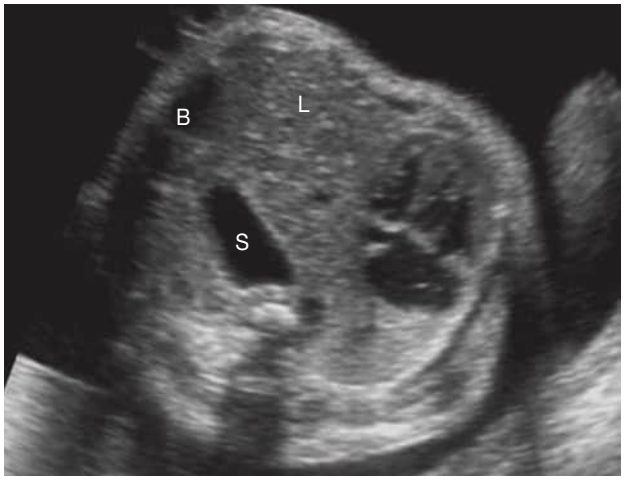

FIGURE 15-32 Congenital diaphragmatic hernia. In this transverse view of the thorax, the heart is shifted to the right side of the chest by a left-sided diaphragmatic hernia containing stomach (*S*), liver (*L*), and bowel (*B*).

■ Congenital Cystic Adenomatoid Malformation

This abnormality represents a hamartomatous overgrowth of terminal bronchioles that communicates with the tracheobronchial tree. It is also called *congenital pulmonary airway malformation (CPAM),* based on an understanding that not all histopathological types are *cystic* or *adenomatoid* (Azizkhan, 2008; Stocker, 1977 2002). The estimated prevalence is 1 in 6000 to 8000 births, and this rate is rising because of improved sonographic detection of milder cases (Burge, 2010; Duncombe, 2002; Lau, 2017).

With ultrasound, a congenital cystic adenomatoid malformation (CCAM) is as a well-circumscribed mass that may appear solid and echogenic or may have one or multiple variably sized cysts (Fig. 15-33). It usually involves one lobe, receives its blood supply from the pulmonary artery, and has pulmonary venous drainage. Lesions with cysts ≥5 mm are generally termed *macrocystic*, and lesions that appear solid or have cysts <5 mm are *microcystic* (Adzick, 1985).

In a review of 645 CCAM cases, the neonatal survival rate exceeded 95 percent, and 30 percent of cases demonstrated apparent prenatal resolution. The other 5 percent of cases—typically very large lesions with associated mediastinal shift—were complicated by hydrops and had poor prognosis (Cavoretto, 2008). Microcystic CCAMs usually become less conspicuous with advancing gestation, because in addition to occupying less of the thorax, their echogenicity more closely resembles surrounding lung tissue. However, a subset of CCAMs may demonstrate rapid growth between 18 and 26 weeks' gestation. Corticosteroid therapy has been used for large microcystic lesions to forestall growth and potentially ameliorate hydrops (Curran, 2010; Peranteau, 2016). If a large dominant cyst is present, thoracoamnionic shunt placement may lead to hydrops resolution. Fetal therapy for CCAM is discussed in Chapter 19 (p. 370).

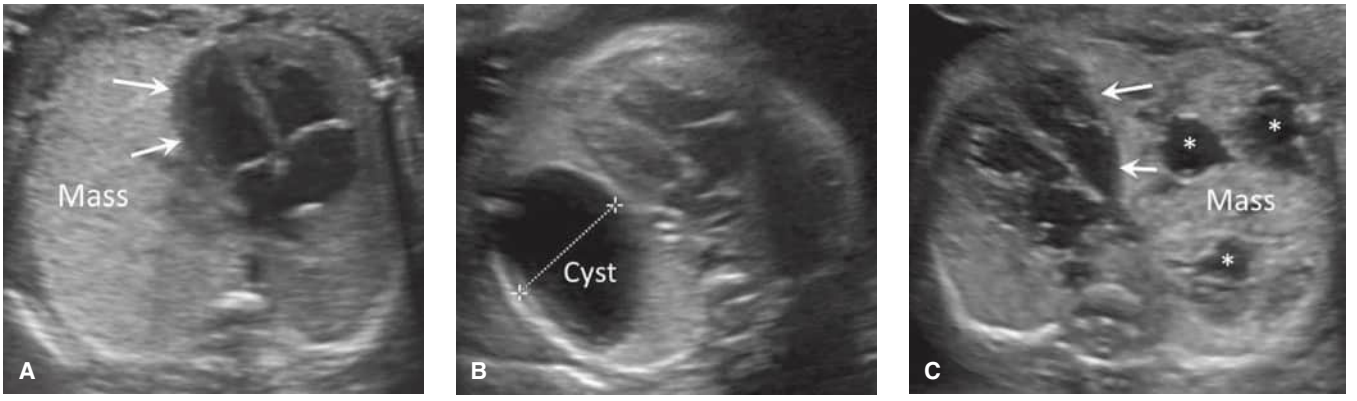

FIGURE 15-33 Congenital cystic adenomatoid malformation (CCAM). **A.** This left-sided microcystic CCAM is an echogenic mass that fills the left hemithorax and causes mediastinal shift, which displaces the heart (*arrows*) to the right side of the chest. **B.** This left-sided macrocystic CCAM contains a cyst as large as the heart and also displaces the heart to the right. **C.** This right-sided CCAM contains multiple cysts of varying size (*) and displaces the heart farther to the left side of the chest (*arrows*).

Pulmonary Sequestration

Also called a *bronchopulmonary sequestration*, this abnormality is an accessory lung bud "sequestered" from the tracheobronchial tree. It is nonfunctioning lung tissue. Most cases diagnosed prenatally are *extralobar,* which means they are enveloped in their own pleura. Overall, however, most sequestrations present in adulthood and are *intralobar*—within the pleura of another lobe. Extralobar pulmonary sequestration is considered significantly less common than CCAM, and no precise prevalence has been reported. Lesions have a left-sided predominance and most often involve the left lower lobe. Associated anomalies have been reported in approximately 10 percent of cases (Yildirim, 2008).

Sonographically, pulmonary sequestration presents as a homogeneous, echogenic thoracic mass (Fig. 15-34A). Thus, it may resemble a microcystic CCAM. However, the blood supply is from the systemic circulation—from the aorta—rather than the pulmonary artery (Fig. 15-34B). Approximately 10 to 20 percent are located below the diaphragm. A small percentage of fetuses with pulmonary sequestration develop a large ipsilateral pleural effusion, and without treatment, this may result in pulmonary hypoplasia or hydrops (Fig. 15-34C). Treatment with thoracoamnionic shunting is discussed in Chapter 19 (p. 376). Hydrops may also result from mediastinal shift or high-output cardiac failure due to the left-to-right shunt imposed by the mass. In the absence of a pleural effusion, the reported survival rate exceeds 95 percent, and 40 percent of cases demonstrate apparent prenatal resolution (Cavoretto, 2008).

Congenital High Airway Obstruction Sequence

This rare anomaly usually results from laryngeal or tracheal atresia. The normal egress of lung fluid is obstructed, and the tracheobronchial tree and lungs become massively distended. Sonographically, the lungs are brightly echogenic, the bronchi are dilated, the diaphragm is flattened or everted, and the heart is compressed (Fig. 15-35). Impaired venous return leads to development of ascites, typically followed by hydrops. In one review of 118 cases, associated anomalies were identified in more than 50 percent (Sanford, 2012). Congenital high airway obstruction sequence (CHAOS) is a feature of the autosomal recessive *Fraser syndrome* and has been associated with the 22q11.2 deletion syndrome. In some cases, the obstructed airway spontaneously perforates, which potentially confers a better prognosis. The EXIT procedure has significantly improved outcome in selected cases.

HEART

Cardiac malformations are the most common class of congenital anomalies. Their overall prevalence is 8 cases in 1000 births (Cragan, 2009). Almost 90 percent of cardiac defects are multifactorial or polygenic in origin, another 1 to 2 percent result from a single-gene disorder or gene-deletion syndrome, and 1 to 2 percent may occur from exposure to a teratogen such as maternal diabetes or isotretinoin. Based on data from population-based registries, approximately 1 in 8 liveborn and stillborn neonates with a congenital heart defect has a chromosomal abnormality (Dolk, 2010; Hartman, 2011). Trisomy 21 accounts for most of these cases, followed by trisomy 18, 22q11.2 deletion, trisomy 13, and monosomy X (Hartman, 2011). Approximately 50 to 70 percent of aneuploid fetuses with cardiac anomalies are also found to have noncardiac abnormalities.

Traditionally, congenital cardiac anomalies have been more challenging to detect than anomalies of other organ systems. Recent series suggest that standard ultrasound may identify 50 to 60 percent of those with major cardiac anomalies before 22 weeks' gestation (Byrne, 2020; Sun, 2018). Prenatal detection may improve neonatal survival, particularly for *ductal-dependent* lesions, that is, those requiring prostaglandin infusion after birth to keep the ductus arteriosus open (Franklin, 2002; Mahle, 2001; Tworetzky, 2001).

Standard Cardiac Examination

Standard cardiac assessment includes a four-chamber view, evaluation of rate and rhythm, evaluation of the left and right ventricular outflow tracts, and when feasible, documentation of the 3-vessel view and 3-vessel trachea view (Figs. 15-36 and

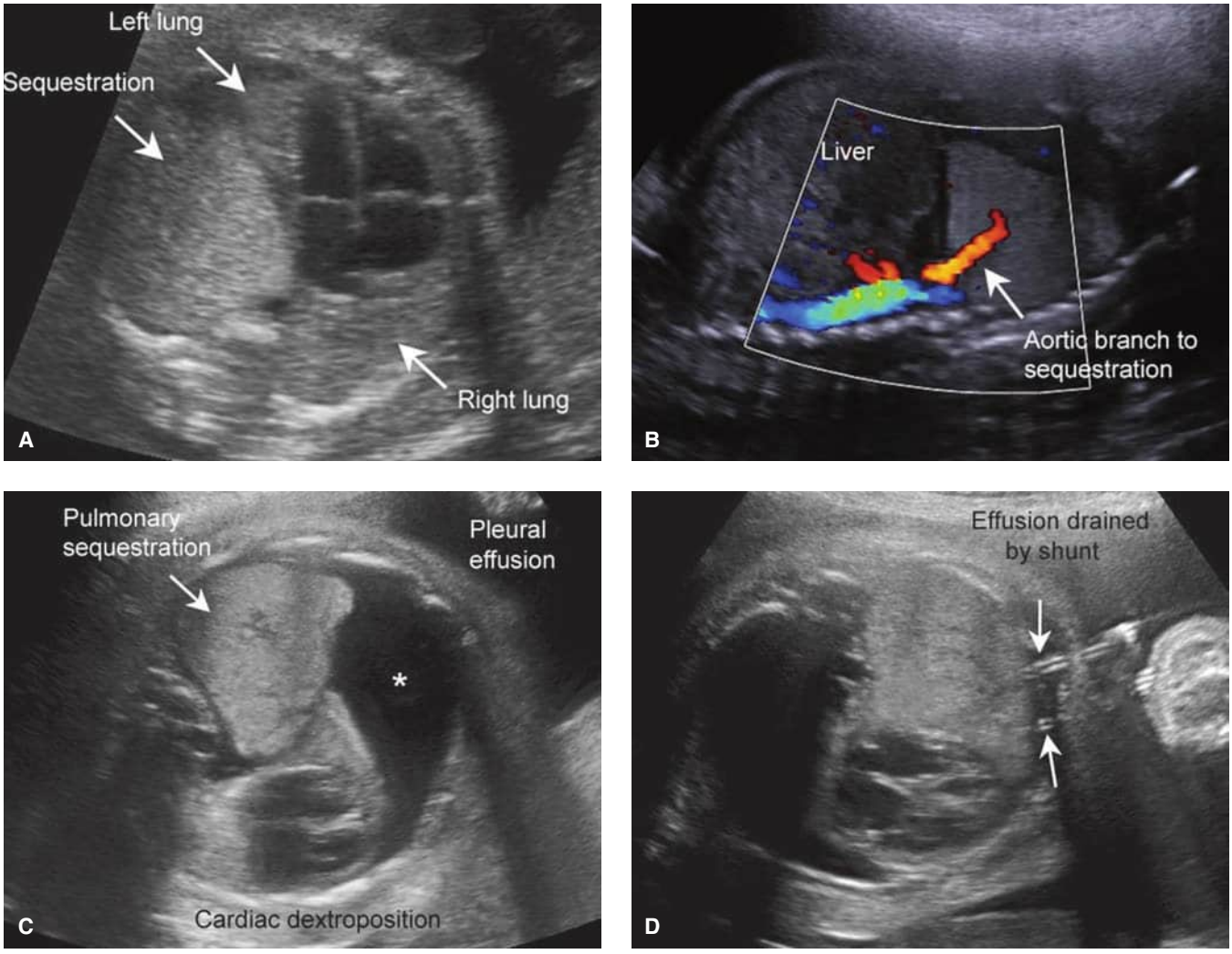

FIGURE 15-34 Pulmonary sequestration. **A.** Transverse image of the thorax depicts a left lower lobe pulmonary sequestration (*PS*) in this 25-week fetus. **B.** Sagittal image showing that blood supply to the mass is from a branch of the abdominal aorta, which confirms the diagnosis. **C.** Over the next 3 weeks, a large ipsilateral pleural effusion develops (*asterisk*), resulting in mediastinal shift and dextroposition of the heart to the far-right thorax. **D.** After placement of a double-pigtail shunt through the chest wall, which drains the effusion into the amniotic fluid, the lung significantly reexpanded. Arrows point to coils of the pigtail shunt. (Reproduced with permission from Dr. Elaine Duryea.)

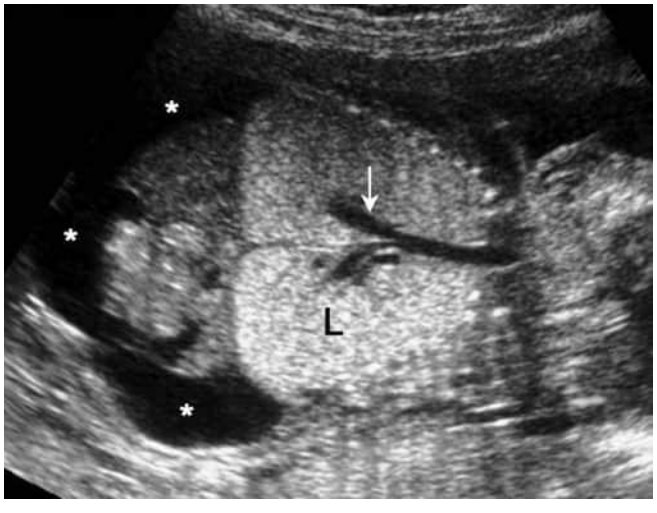

FIGURE 15-35 Congenital high airway obstruction sequence (CHAOS). The lungs (*L*) appear brightly echogenic, and the bronchi (*arrow*) are dilated with fluid. Flattening and eversion of the diaphragm is common, as is ascites (*asterisks*).

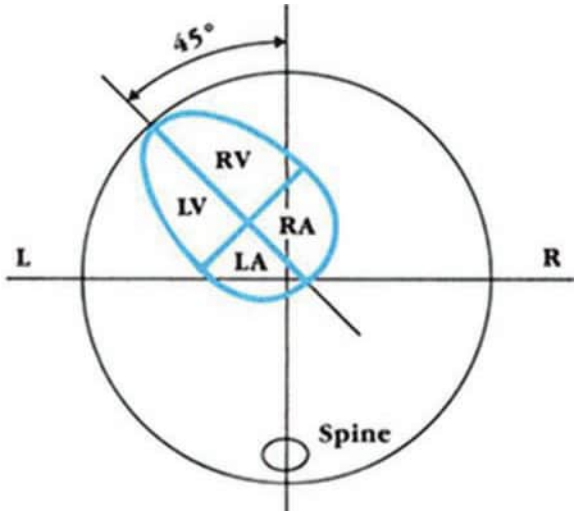

FIGURE 15-36 Diagram showing measurement of cardiac axis from the four-chamber view. LA = left atrium; LV = left ventricle; RA = right atrium; RV = right ventricle.

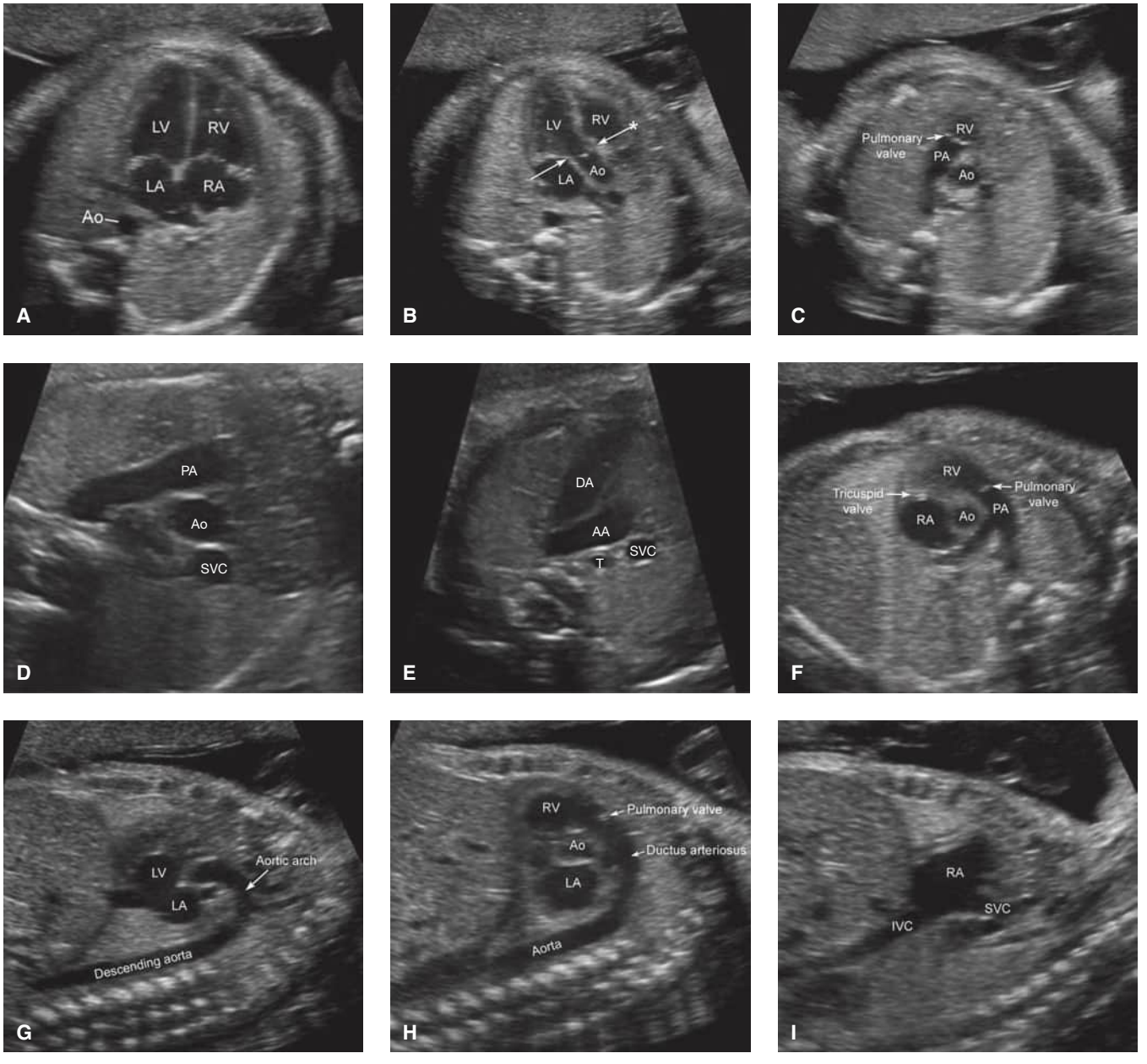

FIGURE 15-37 Standard and detailed examination cardiac views. **A.** Four-chamber view. **B.** Left ventricular outflow tract view. Arrow depicts mitral valve becoming the posterior wall of the aorta. The arrow with asterisk marks the interventricular septum becoming the anterior aortic wall. **C.** Right ventricular outflow tract view. **D.** Three-vessel view. **E.** Three-vessel trachea view **F.** High short-axis view (outflow tracts). **G.** Aortic arch view. **H.** Ductal arch view. **I.** Superior and inferior vena cavae views. AA = aortic arch; Ao = aorta; DA = ductal arch; IVC = inferior vena cava; LA = left atrium; LV = left ventricle; PA = pulmonary artery; RA = right atrium; RV = right ventricle; SVC = superior vena cava; T = trachea.

15-37). It is hoped that examination of the cardiac outflow tracts and 3-vessel views will improve detection of outflow tract abnormalities that may have a normal-appearing four-chamber view, such as tetralogy of Fallot and transposition of the great arteries. Centers with expertise have reported at least 90 percent detection of such anomalies with incorporation of these views (Brandt, 2015; Palatnik, 2016).

The *four-chamber view* is a transverse image of the fetal thorax at a level immediately above the diaphragm. It allows evaluation of cardiac size, position in the thorax, cardiac axis, atria and ventricles, foramen ovale, atrial septum primum, interventricular septum, and atrioventricular valves (Fig. 15-37A). The left ventricle is apex-forming, and two pulmonary veins are often visible entering the left atrium. The atria and ventricles should be similar in size, and the apex of the heart should form a 45-degree angle with the left anterior chest wall (see Fig. 15-36). Abnormalities of cardiac axis are encountered in more than one third of fetuses with structural cardiac anomalies (Shipp, 1995; Crane, 1997; Sinkovskaya, 2015).

The *left ventricular outflow tract view* demonstrates that the ascending aorta arises entirely from the left ventricle. The interventricular septum is shown to be in continuity with the anterior wall of the aorta, and the mitral valve in continuity with the posterior wall of the aorta (Fig. 15-37B). Ventricular septal

defects and outflow tract abnormalities are often visible in this view.

The *right ventricular outflow tract view* shows the right ventricle giving rise to the main pulmonary artery, which subsequently branches into the right and left pulmonary arteries. (Fig. 15-37C,F). Together, the left and right outflow tract views demonstrate the normal perpendicular orientation of the aorta and pulmonary artery and the comparable size of these great arteries.

The *3-vessel view* (3VV) is a transverse image obtained just above the base of the heart. The three vessels line up in a row: an oblique view of the pulmonary artery, which should appear long and cylindrical; a cross-sectional image of the ascending aorta; and a cross-sectional image of the superior vena cava (SVC) (Fig. 15-37D). The pulmonary artery and aorta should be similar in diameter. The 3-vessel trachea view (3VTV) also is a transverse image but is obtained further cephalad. It includes the pulmonary artery giving rise to the ductus arteriosus as it makes a V-shape with the aortic arch, along with the SVC and the trachea (Fig. 15-37E). The 3VTV can be helpful for identifying aortic arch abnormalities, particularly ductal-dependent lesions.

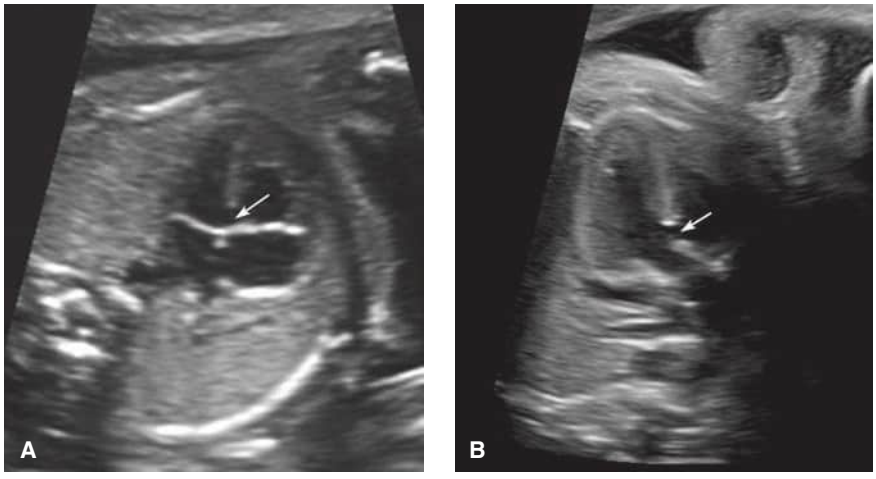

FIGURE 15-38 Ventricular septal defect. **A.** In this four-chamber view, a defect (*arrow*) is noted in the perimembranous portion of the interventricular septum. **B.** The left ventricular outflow tract view demonstrates a break in continuity (*arrow*) between the interventricular septum and the anterior wall of the aorta.

■ Specialized Cardiac Examination

The detailed ultrasound examination includes the five cardiac components of the standard examination plus the superior and inferior vena cavae and the aortic and ductal arch views (Fig. 15-37G–I). The examination also involves evaluation of the interventricular septum and cardiac situs, documentation of which may be facilitated with video clips.

Fetal echocardiography is a more extensive examination of cardiac structure and function designed to characterize abnormalities. In addition to grayscale imaging views, echocardiography includes evaluation of cardiac rate and rhythm, color Doppler ultrasound, pulsed-wave Doppler ultrasound, cardiac biometry, and if clinically relevant, cardiac function assessment (American Institute of Ultrasound in Medicine, 2020b). These components are beyond the scope of this text. Echocardiography indications are discussed in Chapter 14 (p. 252). Selected cardiac anomalies are reviewed next.

Ventricular Septal Defect

This is the most common congenital cardiac anomaly. It is found in approximately 1 in 300 births (Bjornard, 2013; Cragan, 2009; Dolk, 2010). A defect may be appreciated in the perimembranous or muscular portion of the interventricular septum in the four-chamber view, and imaging of the left ventricular outflow tract may show discontinuity of the interventricular septum as it becomes the wall of the aorta (Fig. 15-38). Color Doppler may demonstrate flow across the defect. Genetic abnormalities are diagnosed with chromosomal microarray analysis in approximately 1 percent of isolated cases but found in at least 15 percent if other structural abnormalities also are present (Maya, 2020). More than a third of prenatally diagnosed ventricular septal defects close in utero, and another third close in the first year of life (Cho, 2017; Paladini, 2002; Svirsky, 2019).

Endocardial Cushion Defect

This is also called an *atrioventricular (AV) septal defect* or *AV canal defect*. It has a birth prevalence of approximately 1 in 2500 and is associated with trisomy 21 in more than half of cases (Christensen, 2013; Cragan, 2009; Dolk, 2010). The endocardial cushions are the crux of the heart, and defects jointly involve the atrial septum primum, interventricular septum, and medial leaflets of the mitral and tricuspid valves (Fig. 15-39).

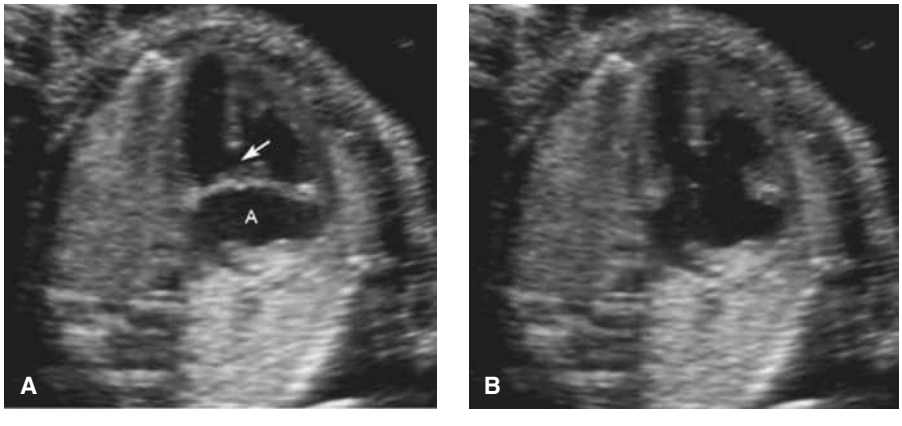

FIGURE 15-39 Endocardial cushion defect. **A.** During ventricular systole, the lateral leaflets of the mitral and tricuspid valves come together in the midline. But the atrioventricular valve plane is abnormal, a common atrium (*A*) is observed, and there is a visible defect (*arrow*) in the interventricular septum. **B.** During diastolic filling, opening of the atrioventricular valves more clearly demonstrates the absence of their medial leaflets.

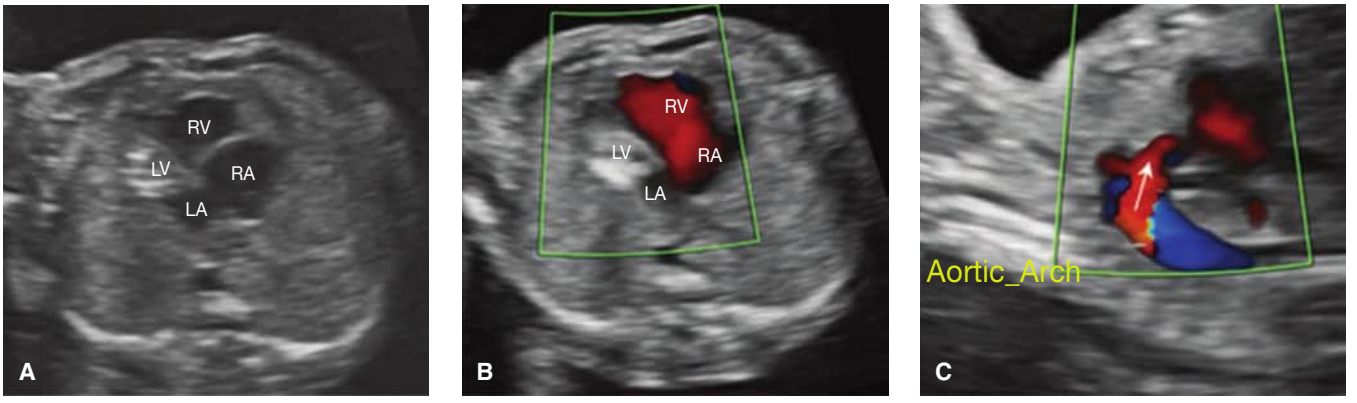

FIGURE 15-40 Hypoplastic left heart syndrome. **A.** In this four-chamber view, the left ventricle appears "filled in" and echogenic, due to endocardial fibroelastosis. **B.** Color Doppler depicts only flow from the right atrium into the right ventricle, and no left ventricular filling is visible. **C.** Color Doppler shows reversal of flow in the aortic arch (*arrow*), which is perfused retrograde via the ductus arteriosus. LA = left atrium; LV = left ventricle; RA = right atrium; RV = right ventricle.

The majority of defects are balanced–with ventricles comparable in size. Some are *unbalanced* however, with one side of the heart significantly smaller than the other. The endocardial cushion defect is considered *partial* if there is absence of the atrial septum primum and a more subtle AV valve plane abnormality, with no ventricular septal defect.

Endocardial cushion defects are a common finding in *heterotaxy*, also known as *cardiosplenic* or *isomerism syndromes*. Heterotaxy implies that thoraco-abdominal organs normally on one side of the body are on an incorrect side, on both sides, or absent, as in polysplenia or asplenia. Complex cardiac abnormalities are a common feature, particularly endocardial cushion defects. In a review of 632 pregnancies with fetal heterotaxy, an endocardial cushion defect was present in 60 percent (Buca, 2018). These endocardial cushion defects are a particularly at-risk group because of their association with third-degree heart block, which confers a poor prognosis.

Hypoplastic Left Heart Syndrome

This anomaly is found in approximately 1 in 4000 births (Bjornard, 2013; Cragan, 2009; Dolk, 2010;). During second-trimester ultrasound examination, the left ventricle may be so small that a chamber is difficult to appreciate (Fig. 15-40). Alternately, the left ventricle may be normal in size or dilated but have severely decreased contractility and an echogenic inner wall due to *endocardial fibroelastosis*. There may be no visible left ventricular inflow or outflow, and reversal of flow may be documented in the aortic arch in the 3-vessel trachea view. As gestation advances, the left ventricle and aorta become progressively smaller. Prenatal detection is nearly 90 percent in population-based registries.

Hypoplastic left heart syndrome is a ductal-dependent lesion for which neonatal administration of prostaglandin therapy is essential. Postnatal treatment consists of a three-staged palliative repair—*single ventricle palliation,* or cardiac transplantation. Rates of survival to adulthood may reach 70 percent (Feinstein, 2012). However, morbidity is high, and developmental delays are common (Lloyd, 2017; Paladini, 2017; Wilson, 2018). Fetal therapy for this condition is discussed in Chapter 19 (p. 378).

Coarctation of the Aorta

Coarctation refers to narrowing of the aortic arch. The birth prevalence approximates 1 in 2500 (Bjornard, 2013). Usually, the narrowing is focal and found just distal to the origin of the left subclavian artery at the aortic isthmus. Alternatively, a long segment of the aorta may be affected. Coarctation may be isolated or associated with other cardiac anomalies, such as hypoplastic left heart syndrome, unbalanced endocardial cushion defect, or double-outlet right ventricle. The most common sonographic finding is disproportion in ventricular size, with the left ventricle smaller than the right. However, only one third with this finding have coarctation (Ghi, 2018; van Nisselrooij, 2018). Other findings include narrowing of the aortic arch in the 3-vessel trachea view or narrowing of the isthmus in the aortic arch view–which may be challenging to image. Coarctation is associated with Turner syndrome (45,X), with the 22q11.2 deletion, and with autosomal trisomies.

Ebstein Anomaly

This rare anomaly is characterized by apical displacement of the tricuspid valve, such that the septal and posterior valve leaflets of the tricuspid valve attach closer to the cardiac apex (Fig. 15-41). The birth prevalence is approximately 1 in 20,000 (Boyle, 2017). Fetuses with Ebstein anomaly develop varying degrees of tricuspid regurgitation. In severe cases, right atrium becomes markedly dilated, and the fetus may develop cardiomegaly and hydrops. For many years, there was concern that lithium exposure predisposed to Ebstein anomaly. However, as discussed in Chapter 8 (p. 154), the absolute attributable risk is likely well below 1 percent.

Tetralogy of Fallot

This anomaly occurs in approximately 1 in 3000 births (Cragan, 2009; Dolk, 2010; Nelson, 2016). It includes a ventricular septal defect; an overriding aorta; a pulmonary valve or pulmonary artery abnormality, and right ventricular hypertrophy (Fig. 15-42). The last does not usually manifest before birth. Due to the location of the ventricular septal defect, the four-chamber view may appear normal.

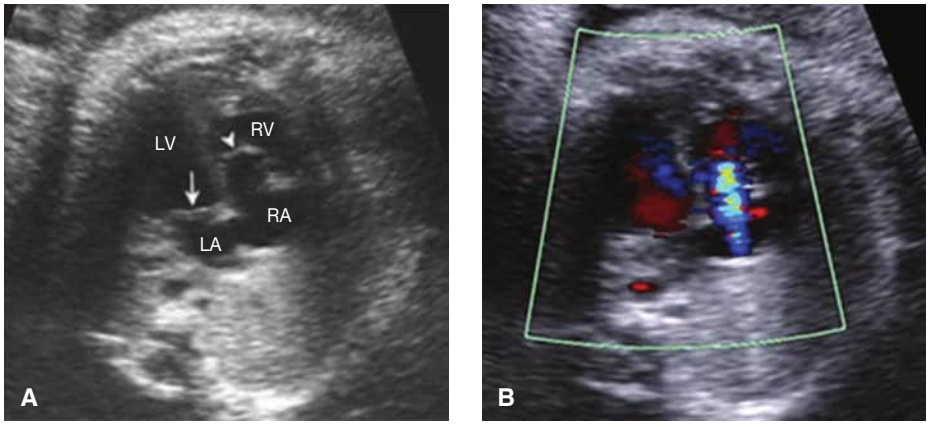

FIGURE 15-41 Ebstein anomaly. **A.** In this four-chamber view, the tricuspid valve's septal leaflet attaches closer to the cardiac apex (*arrowhead*) than the corresponding mitral valve leaflet (*arrow*). **B.** The color Doppler blue jet reflects tricuspid regurgitation. LA = left atrium; LV = left ventricle; RA = right atrium; RV = right ventricle.

The pulmonary artery abnormality is pulmonary stenosis in 60 percent of cases, pulmonary atresia in slightly more than 25 percent, and absent pulmonary valve in 10 to 15 percent (Zhao, 2016). Absence of the pulmonary valve leads to marked enlargement of the pulmonary artery and poses a risk for hydrops. The enlarged pulmonary artery can also compress the trachea and cause tracheomalacia.

Chromosomal abnormalities are identified in approximately one third of fetuses with tetralogy of Fallot. Of these, 22q11.2 deletions compose 15 to 20 percent, and autosomal trisomies constitute 10 percent (Zhao, 2016).

D-Transposition of the Great Arteries

This anomaly is characterized by outflow tracts that arise in parallel from the ventricles. The right ventricle gives rise to the aorta, and the left ventricle to the pulmonary artery (Fig. 15-43). Thus, there is *ventriculo-arterial discordance*. The birth prevalence approximates 1 in 4000 (Bjornard, 2013). The four-chamber view is often normal. Prenatal detection approximates 40 percent but is thought to improve with visualization of the outflow tracts (Ravi, 2018). Additionally, the 3-vessel views may demonstrate only two vessels, because the pulmonary artery is underneath the aorta.

D-transposition contrasts with *L-* or *corrected* transposition of the great arteries, in which there is atrioventricular discordance in addition to ventricular-arterial discordance. L-transposition is strongly associated with other cardiac anomalies and is much less likely to be diagnosed prenatally as an isolated finding.

Double-outlet Right Ventricle

With this anomaly, the majority of blood flow to both the pulmonary artery and the aorta comes from the right ventricle. Double-outlet right ventricle (DORV) is always associated with a ventricular septal defect. DORV has a spectrum of presentation. It is categorized according to the location of the ventricular septal defect and the relative proportion of blood flow from the right ventricle to the outflow tracts. The outflow tracts are often malposed, arising in parallel. The birth prevalence approximates 1 in 20,000 (Bjornard, 2013).

Truncus Arteriosus

This rare anomaly is characterized by a single, large outflow tract exiting the heart—a common arterial trunk—rather than a separate aorta and pulmonary artery. A prominent ventricular septal defect is usually identified, with an enlarged overriding outflow tract that gives rise to pulmonary arteries as well as head and neck vessels (Fig. 15-44). The differential diagnosis includes tetralogy of Fallot with pulmonary atresia. The birth prevalence of truncus arteriosus approximates 1 in 16,000 (Bjornard, 2013). In 1949, Collett and Edwards categorized four types of truncus arteriosus according to the origin of the

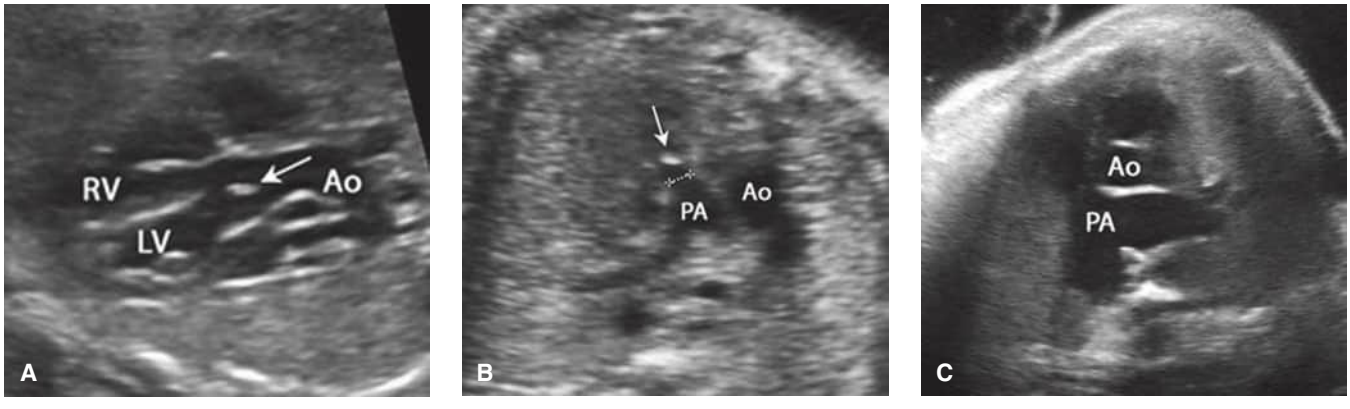

FIGURE 15-42 Tetralogy of Fallot. **A.** Left ventricular outflow tract view shows a ventricular septal defect with an overriding aorta. The arrow points to the aortic valve. **B.** Right ventricular outflow tract view demonstrating severe pulmonary artery stenosis. The arrow points to the pulmonary valve. **C.** In this fetus with tetralogy of Fallot with *absent pulmonary valve*, the pulmonary artery shows marked enlargement. Ao = aorta; LV = left ventricle; PA = pulmonary artery; RV = right ventricle.

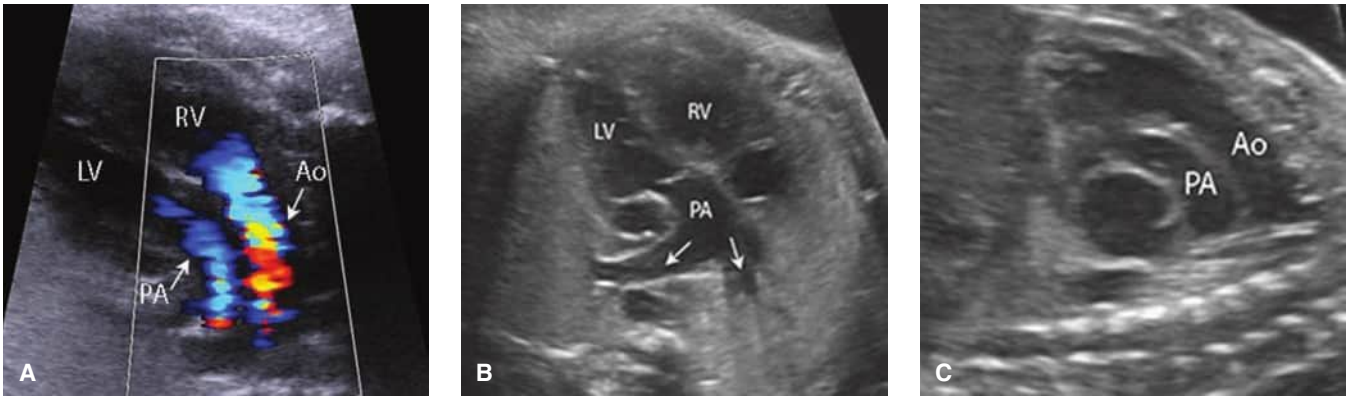

FIGURE 15-43 D-transposition of the great arteries. **A.** Transverse image with color Doppler depicting the outflow tracts arising in parallel. **B.** View of the left ventricle giving rise to the pulmonary artery, which subsequently branches (*arrows*). **C.** Sagittal image of the aorta arising anteriorly from the right ventricle and parallel to the pulmonary artery, which arises posteriorly. Ao = aorta; LV = left ventricle; PA = pulmonary artery; RV = right ventricle.

pulmonary arteries. Characterization of anatomic variants can often only be made postnatally.

Cardiac Rhabdomyoma

This is the most common cardiac tumor. Approximately 50 percent of cases are associated with tuberous sclerosis, an autosomal dominant disease with multiorgan system manifestations. Tuberous sclerosis is caused by mutations in the hamartin (*TSC1*) and tuberin (*TSC2*) genes.

Sonographically, cardiac rhabdomyomas are well-circumscribed echogenic masses, usually within the ventricles or outflow tracts (Fig. 15-45). They may be single or multiple, may grow in size during gestation, and may occasionally lead to inflow or outflow obstruction. In cases without obstruction or large tumor size, the prognosis is relatively good from a cardiac standpoint, because the tumors tend to regress after the neonatal period. Because extracardiac findings of tuberous sclerosis may not be apparent with prenatal sonography, MR imaging may be considered to evaluate fetal CNS anatomy (p. 266).

M-Mode

Motion-mode or M-mode imaging is a linear display of cardiac cycle events, with time on the x-axis and motion on the y-axis. It is often used to measure embryonic or fetal heart rate (Fig. 14-1, p. 248). If an abnormality of heart rate or rhythm is identified, M-mode imaging permits separate evaluation of atrial and ventricular waveforms. Thus, it is particularly useful for characterizing arrhythmias and their response to treatment (Chap. 19, p. 367). M-mode can also be used to assess ventricular function and atrial and ventricular outputs.

Premature Atrial Contractions

Also called atrial extrasystoles, these are the most common fetal arrhythmia and a frequent finding. They represent cardiac conduction system immaturity and often resolve with advancing gestation or in the neonatal period. Premature atrial contractions (PACs) may be conducted and thus sound like extra beats. However, they are more commonly blocked, and with handheld Doppler they sound like dropped beats. As shown

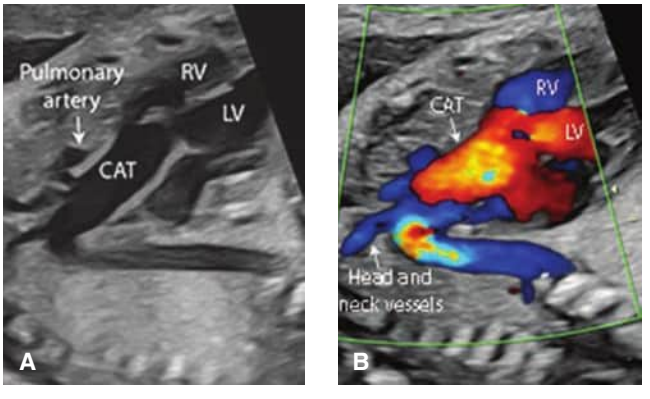

FIGURE 15-44 Truncus arteriosus. Grayscale **(A)** and color Doppler **(B)** images depict a single, large outflow tract. The common arterial trunk (*CAT*) overlies a ventricular septal defect (*arrowhead*) and gives rise to the head and neck vessels and pulmonary arteries. LV = left ventricle; RV = right ventricle. (Reproduced with permission from Paul Mallamaci, RDMS.)

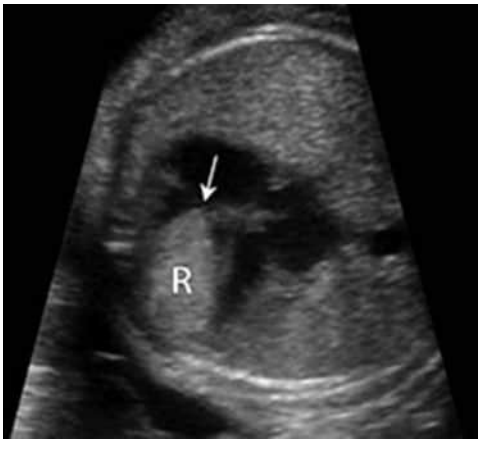

FIGURE 15-45 Rhabdomyoma. In this four-chamber view of the heart, a large, echogenic, well-circumscribed mass (*R*) fills the right ventricle and abuts the tricuspid valve (*arrow*). Despite its size, the mass did not obstruct flow, and the neonate did well.

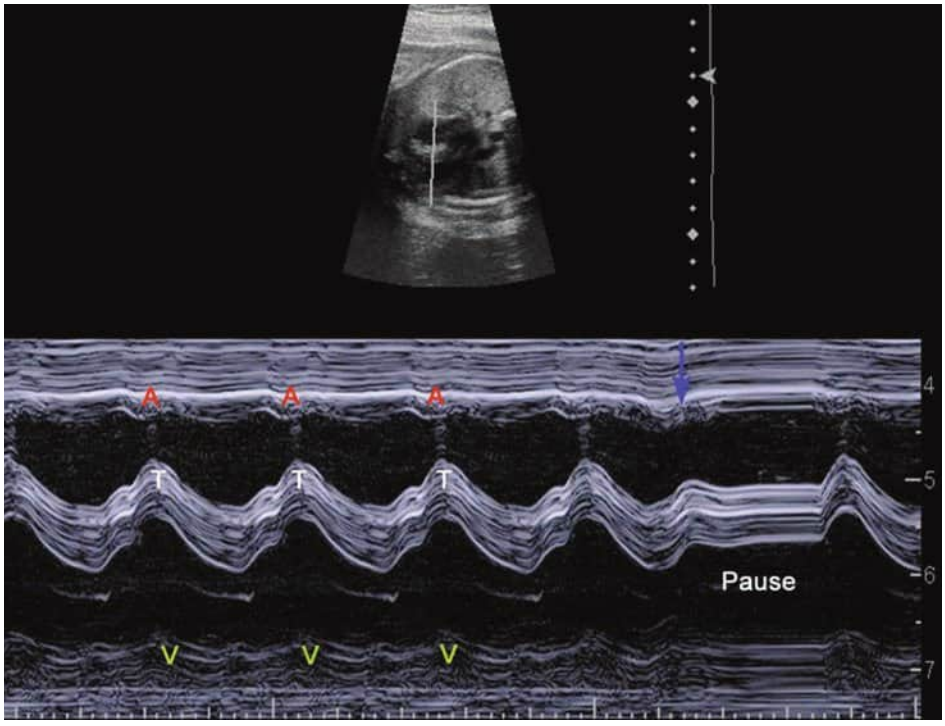

FIGURE 15-46 M-mode. This image demonstrates normal concordance between atrial (*A*) and ventricular (*V*) contractions. Movement of the tricuspid valve (*T*) is also shown. The blue arrow denotes a premature atrial contraction followed by a compensatory pause.

in Figure 15-46, the dropped beat may be demonstrated with M-mode evaluation as a compensatory pause that follows the premature contraction.

PACs are not associated with major structural cardiac abnormalities. Older case reports describe an association with maternal caffeine consumption and with hydralazine (Lodeiro, 1989; Oei, 1989). In approximately 2 percent of cases, affected fetuses are later identified to have *supraventricular tachycardia (SVT)*, which is an arrhythmia that requires urgent treatment (Copel, 2000). Accordingly, pregnancies with fetal PACs are often followed with fetal heart rate assessment as often as every 1 to 2 weeks until the ectopy resolves. Treatment of fetal SVT and other arrhythmias is discussed in Chapter 19 (p. 368).

ABDOMEN

Abdominal anatomy visible in the second and third trimester includes the stomach, liver, gallbladder, spleen, adrenal glands, kidneys, renal arteries, small and large bowel, and ventral wall. The stomach is nearly always identified after 14 weeks' gestation. Nonvisualization of the stomach may be secondary to impaired swallowing in the setting of oligohydramnios or to underlying causes such as esophageal atresia, a craniofacial anomaly, or a CNS or musculoskeletal abnormality. Fetuses with hydrops can also have impaired swallowing.

Both the liver and spleen may be viewed in a transverse image obtained at the level of the stomach and intrahepatic portion of the umbilical vein—the plane at which the abdominal circumference is measured (see Fig. 15-2B). Hepatosplenomegaly may occur with congenital infection or with hydrops. By convention, the liver is measured in the sagittal or coronal plane, from the top of the right hemidiaphragm to the inferior tip of the right lobe (Fig. 15-47). The spleen is posterior to the stomach in the transverse plane. The gallbladder may be imaged just inferior to the level at which the abdominal circumference is measured. It lies to the right of the intrahepatic portion of the umbilical vein and has a conical or teardrop shape (see Fig. 15-47B).

The appearance of fetal bowel changes with maturation. Increased bowel echogenicity may indicate a small amount of swallowed intraamnionic blood, especially if the maternal serum alpha-fetoprotein level is elevated. The bowel appears as bright as bone in approximately 0.5 percent of second-trimester fetuses. In such cases, the risk for fetal trisomy 21 is increased (Fig. 17-3, p. 340). Echogenic bowel is also associated with fetal cytomegalovirus infection and with cystic fibrosis, in which echogenicity represents inspissated meconium.

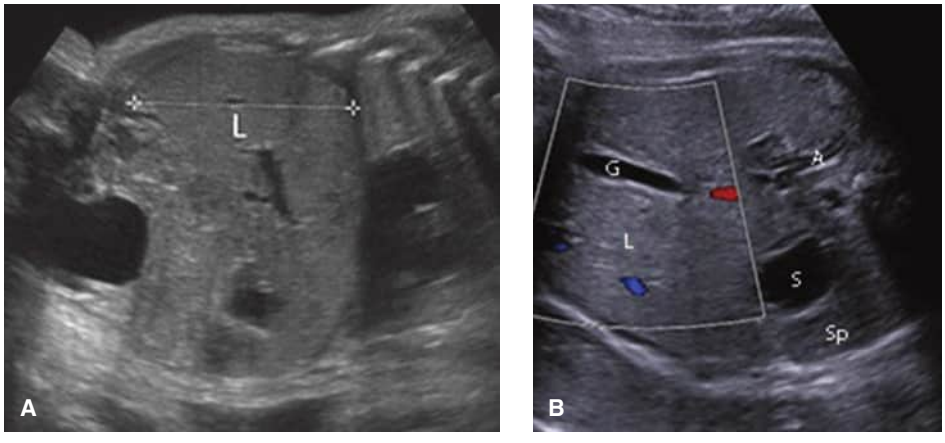

FIGURE 15-47 Abdominal organs. **A.** The liver is measured from the top of the right hemidiaphragm to the inferior tip of the right lobe in this coronal image. **B.** Transverse image of the abdomen just inferior to the level at which the abdominal circumference is measured, depicting the gallbladder (*G*), stomach (*S*), spleen (*Sp*), liver (*L*), and right adrenal gland (*A*).

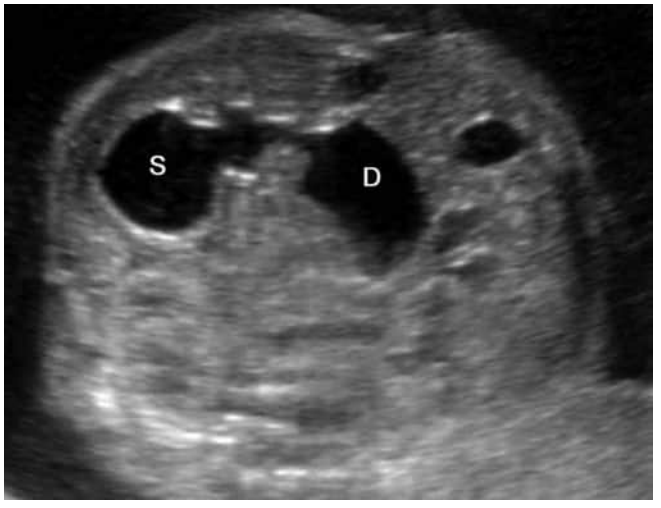

FIGURE 15-48 Duodenal atresia. Transverse image of the *double-bubble sign*, which represents distension of the stomach (*S*) and the first part of the duodenum (*D*). Continuity between these structures confirms that the second cystic structure is the duodenum.

Gastrointestinal Obstruction

Bowel atresia is characterized by obstruction and proximal bowel dilation. In general, the more proximal the obstruction, the more likely it is to lead to hydramnios. The degree of hydramnios from proximal small-bowel obstruction can be sufficiently severe to result in maternal respiratory compromise or preterm labor and may necessitate amnioreduction (Chap. 14, p. 258).

Esophageal Atresia

The birth prevalence of this anomaly approximates 1 in 4000 (Cragan, 2009; Pedersen, 2012). It may be suspected when there is no visible stomach bubble or when the stomach is contracted. However, because esophageal atresia is associated with a *tracheoesophageal fistula* in up to 90 percent of cases, fluid is often able to enter the stomach. More than 50 percent of those with esophageal atresia have other abnormalities or underlying genetic syndromes. Multiple malformations are present in 30 percent of cases, and aneuploidy such as trisomy 18 or 21, in 10 percent. Approximately 10 percent of cases of esophageal atresia is found as part of the VACTERL association (Pedersen, 2012).

Duodenal Atresia

This anomaly occurs in approximately 1 in 10,000 births (Best, 2012; Dolk, 2010). It is characterized by the sonographic *double-bubble sign,* which develops from distention of the stomach and the first part of the duodenum (Fig. 15-48). This finding may not be obvious before 24 weeks' gestation. Demonstrating continuity between the stomach and proximal duodenum confirms that the second "bubble" is the proximal duodenum. Approximately 30 percent of affected fetuses have an associated chromosomal abnormality or genetic syndrome, particularly trisomy 21. Of cases without a genetic abnormality, a third have associated anomalies, most commonly cardiac defects and other gastrointestinal abnormalities (Best, 2012).

Jejunoileal Atresia

This condition may present with dilated small-bowel loops that fill the abdomen or with *meconium peritonitis* from bowel perforation (Fig. 15-49). Associated gastrointestinal abnormalities are identified postnatally in 25 percent of cases, with malrotation in 10 to 15 percent (Stollman, 2009). Cystic fibrosis also is identified in approximately 10 percent.

In general, jejunal atresia is more strongly associated with bowel dilation and hyperperistalsis, and ileal atresia, with perforation. Bowel dilatation in jejunal atresia typically does not present until after 24 weeks' gestation and may be accompanied by hydramnios. Perforation is frequently associated with ascites, and bright echoes may be visible outside the bowel lumen, outlining the peritoneal cavity. Over time, the ascites resolves, and the extravasated meconium may form a pseudocyst. Fetal MR imaging can assist with identifying the level of the defect (Chap. 14, p. 267).

Anal Atresia

Also known as imperforate anus, this condition is less readily diagnosed by sonography. Hydramnios is not a typical feature, and the bowel may not be significantly dilated. A transverse view through the pelvis may show an enlarged rectum as an anechoic structure between the bladder and the sacrum. Anal atresia is a feature of the VACTERL association.

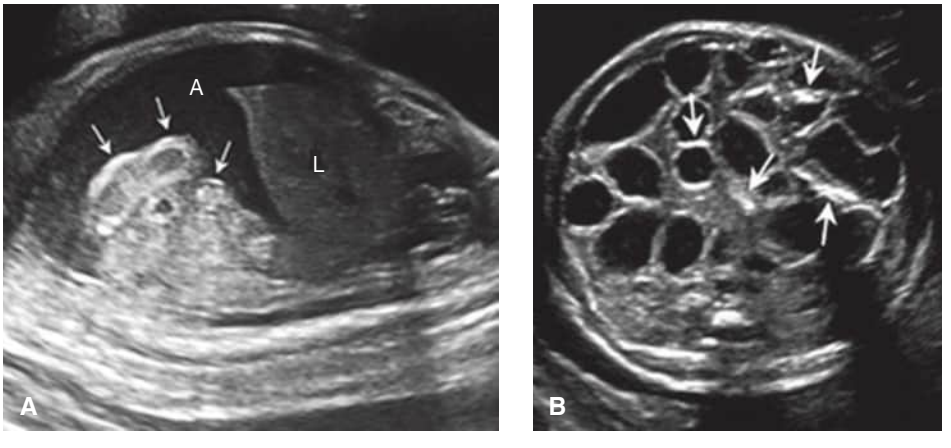

FIGURE 15-49 Jejunoileal atresia with meconium peritonitis. **A.** Sagittal image of the fetal abdomen at 26 weeks' gestation with severe ascites following bowel perforation. Arrows point to the bowel, which is considerably more echogenic than the liver. **B.** Transverse image at 30 weeks demonstrates resolution of ascites. The abdomen is now filled with dilated loops of small bowel. Focal bright echoes (*arrows*) represent extraluminal meconium. A = ascites; L = liver.

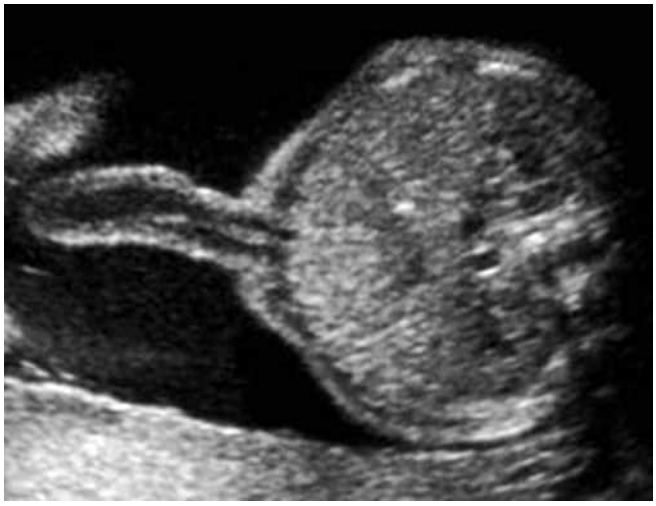

FIGURE 15-50 Normal ventral wall. Transverse view of the abdomen demonstrating normal umbilical cord insertion and integrity of the anterior abdominal wall.

Ventral Wall Defects

The integrity of the abdominal wall is assessed at the level of the cord insertion during the standard examination (Fig. 15-50). Ventral wall defects include gastroschisis, omphalocele, and body stalk anomaly.

Gastroschisis

This is a full-thickness abdominal wall defect located to the right of the umbilical cord insertion. Bowel herniates through the defect into the amnionic cavity. Gastroschisis may be diagnosed as early as the late first trimester (Fig. 15-51). The prevalence is approximately 1 in 2000 births (Jones, 2016; Nelson, 2015). Gastroschisis is the one major anomaly more common in fetuses of younger mothers, and the average maternal age is 20 years (Santiago-Muñoz, 2007). Coexisting bowel abnormalities such as *jejunal atresia* are found in approximately 15 percent of cases (Overcash, 2014). Gastroschisis is not associated with aneuploidy, and the survival rate is 90 to 95 percent (Nelson, 2015; Raitio, 2020).

Fetal-growth restriction complicates gastroschisis in 15 to 40 percent of cases (Overcash, 2014; Santiago-Muñoz, 2007). Growth restriction does not appear to confer increased mortality (Nelson, 2015; Overcash, 2014). However, earlier gestational age at delivery does pose a risk for adverse outcome, and planned delivery at 36 to 37 weeks' gestation has not been found to benefit the neonate (Al-Kaff, 2016; South, 2013).

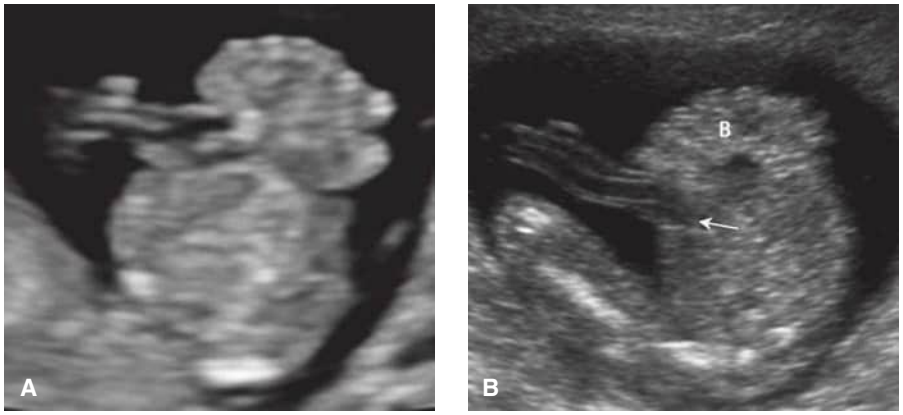

FIGURE 15-51 Gastroschisis. Transverse views of the lower abdomen at 13 weeks' gestation **(A)** and 18 weeks **(B)** depict multiple small bowel loops (*B*) that have herniated into the amnionic cavity through a defect to the right of the cord insertion (*arrow*).

Omphalocele

The birth prevalence of this anomaly approximates 1 in 3000 to 5000 (Canfield, 2006; Dolk, 2010). It develops when the lateral ectomesodermal folds fail to meet in the midline. Abdominal organs herniate into the base of the umbilical cord, covered only by a two-layered sac of amnion and peritoneum (Fig. 15-52). More than half of cases are associated with other major anomalies or aneuploidy. Aneuploidy is particularly common with smaller defects (De Veciana, 1994). Omphalocele is also a component of several syndromes, including *Beckwith–Wiedemann*, *cloacal exstrophy*, and *pentalogy of Cantrell*. Neonatal survival approximates 90 percent for isolated cases and 80 percent in those with other structural abnormalities (Raitio, 2021; Springett, 2014). Isolated defects containing liver are typically delivered via cesarean to decrease the risk for fetal trauma and bleeding.

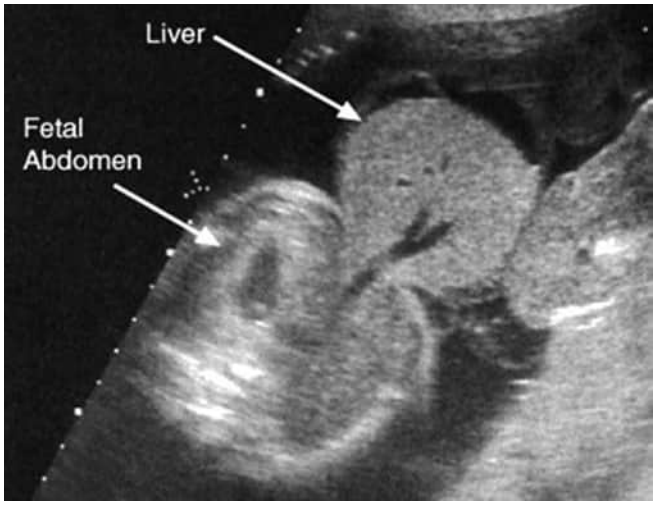

FIGURE 15-52 Omphalocele. Transverse view of the abdomen showing a large, round, membrane-covered ventral wall defect containing exteriorized liver.

Body Stalk Anomaly

Also known as *limb-body-wall complex* or *cyllosoma*, this rare, lethal anomaly is characterized by abnormal body wall formation. Typically, *no* abdominal wall is visible, and the abdominal organs extrude into the extraamnionic coelom (Fig. 15-53). The body and placenta are closely approximated or fused, and

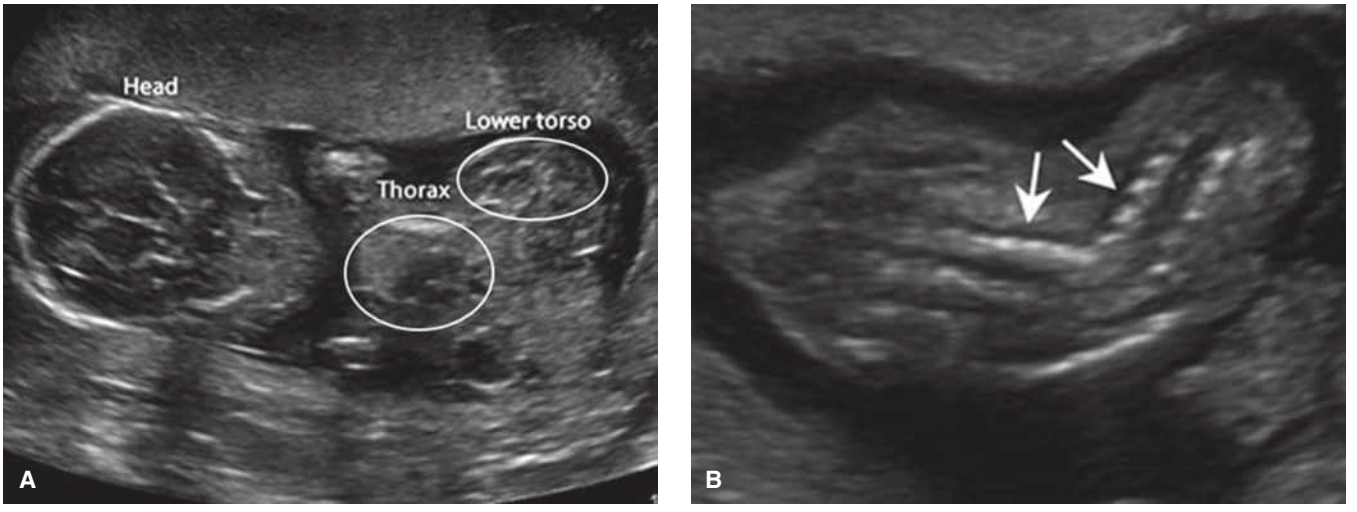

FIGURE 15-53 Body-stalk anomaly. **A.** This 15-week fetus has no visible abdominal wall. The thorax is disproportionately small compared with the head, and the small lower torso is deviated to the side. Arrows point to the large mass of extruded abdominal organs. **B.** Acute-angle scoliosis. Arrows depict the abnormal curvature of the spine. (Reproduced with permission from Deirdre Snelson, RDMS.)

the umbilical cord is extremely short. Acute-angle scoliosis is another feature, and amnionic bands are often identified.

Kidneys and Genitourinary Tract

The fetal kidneys are visible adjacent to the spine, frequently in the first trimester and routinely by 18 weeks' gestation (Fig. 15-54). The length of the kidney approximates 20 mm at 20 weeks and grows about 1.1 mm each week thereafter (Chitty, 2003).

The fetal bladder is also readily seen in the second trimester as a round, anechoic structure in the anterior midline of the pelvis. With application of Doppler, the bladder is outlined by the two superior vesical arteries as they become the umbilical arteries of the umbilical cord (Chap. 6, p. 114). The fetal ureters and urethra are not visible sonographically unless abnormally dilated.

After 18 weeks' gestation, the kidneys are the major source of amnionic fluid (Chap. 14, p. 256). Normal amnionic fluid volume in the second half of pregnancy suggests urinary tract patency and at least one functioning kidney.

External genitalia are a component of the detailed examination and are part of the standard examination in multifetal gestations and when medically indicated (American Institute of Ultrasound in Medicine, 2019). Identification may aid counseling in pregnancies at risk for an X-linked genetic condition. Examples of normal and ambiguous genitalia are shown in Figure 15-55. Disorders of sexual development are discussed in Chapter 3 (p. 35).

Renal Pelvis Dilatation

Present in 1 to 5 percent of fetuses, this finding is also called urinary tract dilatation or hydronephrosis. In 40 to 90 percent of cases, and particularly when mild, renal pelvis dilatation is transient or physiological and does not represent an underlying abnormality (Ismaili, 2003; Nguyen, 2010). In approximately one third of cases, a urinary tract abnormality is confirmed in the neonatal period. Of these, *ureteropelvic junction (UPJ) obstruction* and *vesicoureteral reflux (VUR)* are the most frequent.

The fetal renal pelvis diameter is measured anterior-to-posterior in a transverse plane. Calipers are placed on the inner border of the fluid collection (Fig. 15-56). Although various thresholds have been defined, the pelvis is typically considered dilated if it exceeds 4 mm in the second trimester or 7 mm at approximately 32 weeks' gestation (Nguyen, 2014; Reddy, 2014). The second-trimester threshold is used to identify pregnancies that warrant subsequent third-trimester evaluation.

The Society for Fetal Urology categorized renal pelvis dilatation based on a metaanalysis of more than 100,000 screened pregnancies (Table 15-2) (Lee, 2006; Nguyen, 2010). Provided that the finding is isolated, the degree of dilation correlates with

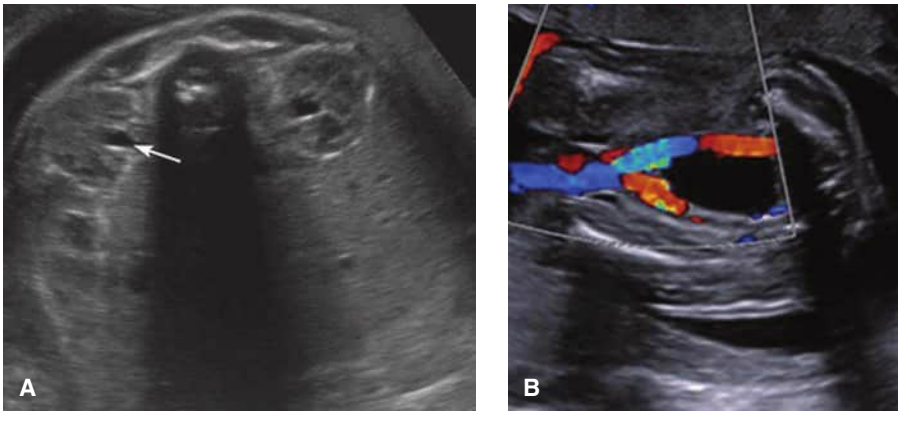

FIGURE 15-54 Normal fetal kidneys and bladder. **A.** The kidneys are visible adjacent to the spine in this 29-week fetus. A small amount of urine is often visible within the renal pelvis (*arrow*). **B.** Normal fetal bladder, outlined by the two superior vesical arteries as they become the umbilical arteries.

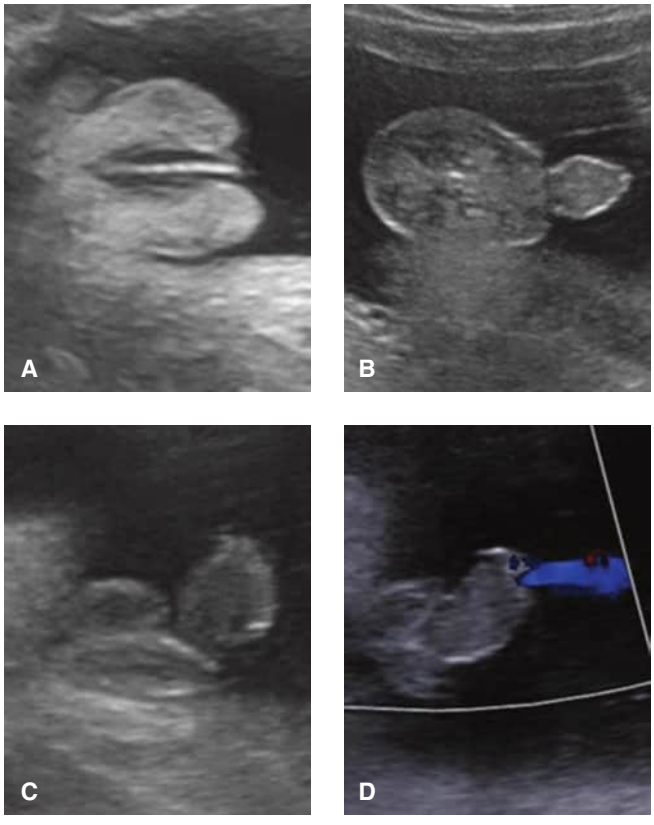

FIGURE 15-55 Normal and ambiguous genitalia. **A.** Female labia. **B.** Male penis and scrotum. **C.** Ambiguous genitalia with a phallus and bifid scrotum. **D.** With this condition, color Doppler can assist locating the urethral meatus, which is pinpointed here by the urine stream (*blue*).

the likelihood of an underlying abnormality. Associated calyceal dilation, cortical thinning, or dilation elsewhere along the urinary tract confer increased risk (Nguyen, 2014). Mild pyelectasis in the second trimester is a minor aneuploidy marker associated with a slightly increased risk for trisomy 21, particularly when other findings or risk factors are also present (Fig. 17-3, p. 340).

Ureteropelvic Junction Obstruction. This condition is the most common abnormality associated with renal pelvis dilatation. The birth prevalence is 1 in 1000 to 2000, and males are affected three times more often than females (Williams, 2007; Woodward, 2002). Obstruction is generally functional rather than anatomical, and it is bilateral in up to a fourth of cases. The likelihood of UPJ obstruction ranges from 5 percent with mild renal pelvis dilatation to more than 50 percent with severe dilatation (Lee, 2006).

TABLE 15-2. Risk for Postnatal Urinary Abnormality According to Degree of Renal Pelvis Dilation

Dilation	Second Trimester	Third Trimester	Postnatal Abnormality
Mild	4 to <7 mm	7 to <9 mm	12%
Moderate	7 to ≤10 mm	9 to ≤15 mm	45%
Severe	>10 mm	>15 mm	88%

Modified from Lee, 2006; Nguyen, 2010.

Duplicated Renal Collecting System. In this anatomical anomaly, the upper and lower poles of the kidney—called moieties—are each drained by a separate ureter (Fig. 15-57). Duplication is found in approximately 1 in 4000 pregnancies, is more common in females, and is bilateral in 15 to 20 percent of cases (James, 1998; Vergani, 1998; Whitten, 2001). Sonographically, an intervening tissue band separates two distinct renal pelves. Hydronephrosis or ureteral dilation may develop due to abnormal implantation of one or both ureters within the bladder—a relationship that reflects the anatomical *Weigert-Meyer* rule. The upper pole ureter tends to develop obstruction from a ureterocele within the bladder, whereas the lower pole ureter has a shortened intravesical segment that predisposes to VUR (see Fig. 15-57). Thus, both moieties may become dilated from different etiologies, and both are at risk for loss of function.

Renal Agenesis

The estimated prevalence of bilateral renal agenesis is 1 in 8000 births, whereas that of unilateral renal agenesis is 1 in 1000 births (Cragan, 2009; Dolk, 2010; Sheih, 1989; Wiesel, 2005). With an absent kidney, color Doppler imaging of the descending aorta demonstrates absence of the ipsilateral renal artery (Fig. 15-58). In addition, the ipsilateral adrenal gland typically enlarges to fill the renal fossa, termed the *lying down adrenal sign* (Hoffman, 1992).

If renal agenesis is bilateral, no urine is produced, and the resulting anhydramnios leads to pulmonary hypoplasia, limb contractures, and distinctive facies. When this combination results from renal agenesis, it is called *Potter syndrome*, after Dr. Edith Potter, who described it in 1946. When these abnormalities result from severely decreased amniotic fluid volume from another etiology, such as bilateral multicystic dysplastic kidney or autosomal

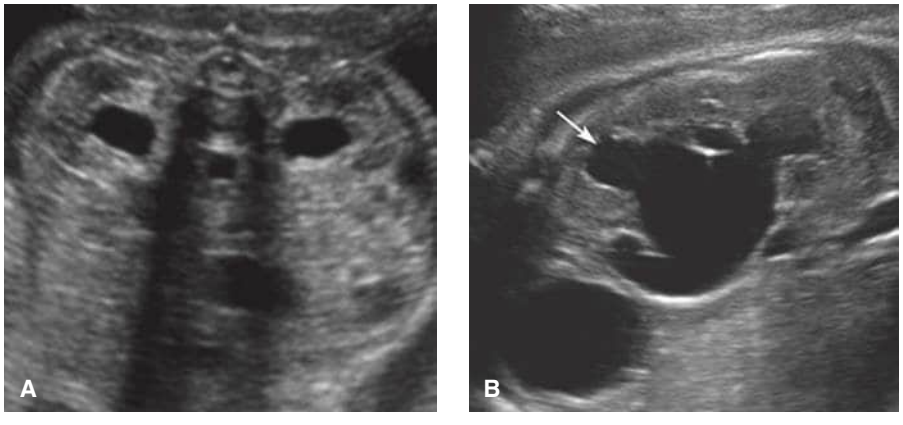

FIGURE 15-56 Renal pelvis dilatation. **A.** The anterior-posterior diameter of the renal pelves measured 7 mm in the transverse plane in this 34-week fetus. **B.** Sagittal image at 32 weeks depicts renal pelvis dilatation with rounded calyces (*arrow*) in the setting of ureteropelvic junction obstruction.

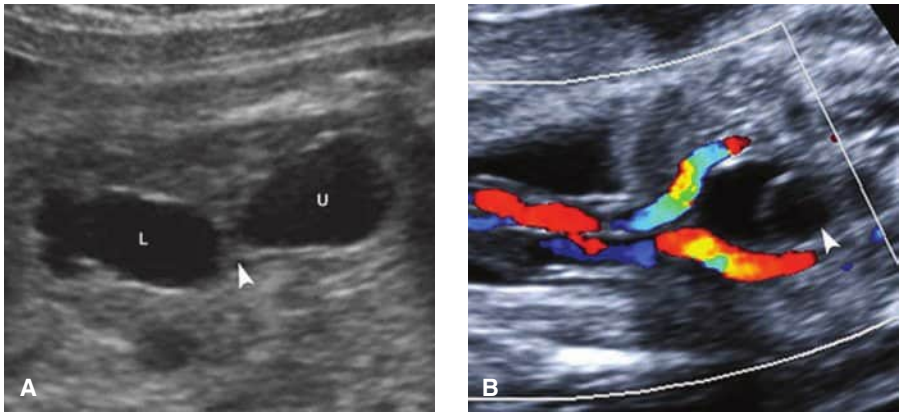

FIGURE 15-57 Duplicated renal collecting system. **A.** Renal pelvis dilatation is visible in both the upper (*U*) and lower (*L*) pole moieties, which are separated by an intervening band of renal tissue (*arrowhead*). **B.** A ureterocele (*arrowhead*) is visible within the bladder. Color Doppler depicts the superior vesical arteries.

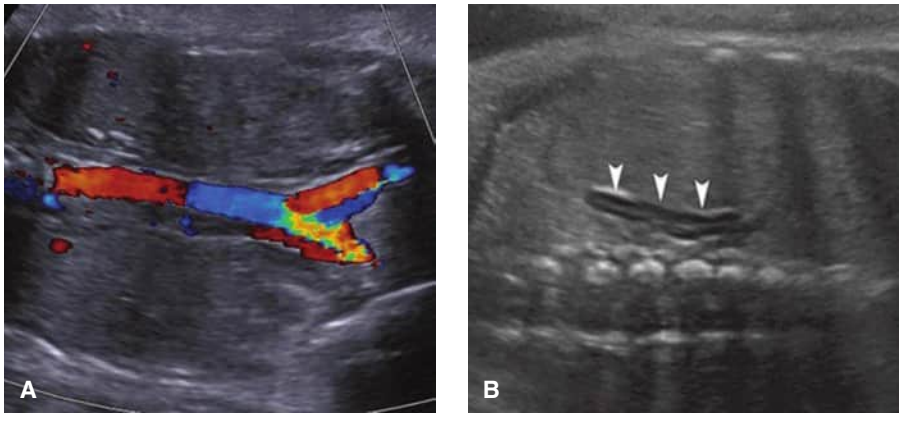

FIGURE 15-58 Renal agenesis. **A.** Coronal image of a fetus with bilateral renal agenesis in which color Doppler of the abdominal aorta is used to demonstrate absence of the renal arteries. **B.** In this fetus with unilateral renal agenesis, arrowheads point to the adrenal gland (*arrowheads*) filling the renal fossa, which is the "lying-down" adrenal sign.

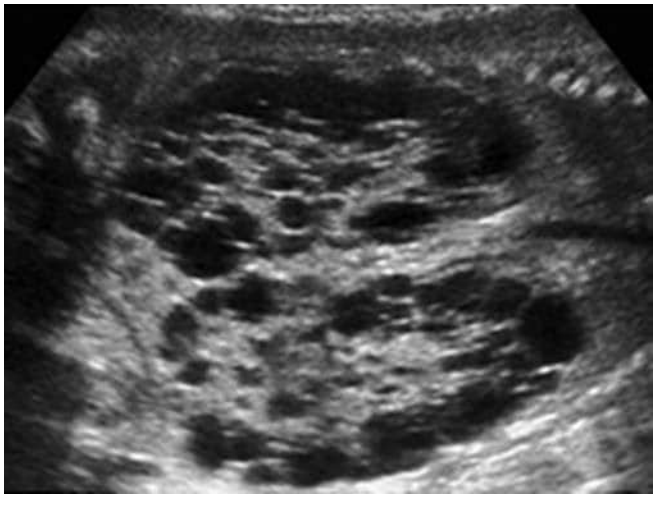

FIGURE 15-59 Multicystic dysplastic kidneys. Coronal view of the fetal abdomen demonstrates enlarged kidneys that are filled with cysts of varying size and contain no visible renal pelvis or normal-appearing renal tissue.

recessive polycystic kidney disease, it is called *Potter sequence.* The prognosis for these abnormalities is extremely poor.

Multicystic Dysplastic Kidney

This severe form of renal dysplasia results in a nonfunctioning kidney. The nephrons and collecting ducts form abnormally, such that primitive ducts are surrounded by fibromuscular tissue, and the ureter is atretic (Hains, 2009). Sonographically, the kidney contains numerous, variably sized, smooth-walled cysts that do not communicate with the renal pelvis and are surrounded by echogenic cortex (Fig. 15-59).

Unilateral multicystic dysplastic kidney (MCDK) has a prevalence of 1 in 4000 births. Contralateral renal abnormalities are present in 30 to 40 percent—most frequently VUR or UPJ obstruction (Schreuder, 2009). Nonrenal anomalies have been reported in 25 percent of cases. Cystic dysplasia may occur as a component of many genetic syndromes (Lazebnik, 1999; Schreuder, 2009). If MCDK is isolated and unilateral, the prognosis is generally good. Bilateral MCDK is found in approximately 1 in 12,000 births. It is associated with severely decreased amnionic fluid volume starting early in gestation. This leads to Potter sequence and a poor prognosis.

Polycystic Kidney Disease

Of the hereditary polycystic diseases, only the infantile form of *autosomal recessive polycystic kidney disease (ARPKD)* may be reliably diagnosed prenatally. ARPKD is a chronic, progressive disease of the kidneys and liver that results in cystic dilation of the renal collecting ducts and in congenital hepatic fibrosis (Turkbey, 2009). The carrier frequency of a disease-causing mutation in the *PKHD1* gene approximates 1 in 70, and the birth prevalence is 1 in 20,000 (Zerres, 1998). The phenotypes of ARPKD range from lethal pulmonary hypoplasia at birth to a presentation in late childhood or even adulthood with predominantly hepatic manifestations. Sonographically, ARPKD displays abnormally large kidneys that may fill or even distend the fetal abdomen and have a solid, ground-glass texture (Fig. 15-60). Severe oligohydramnios confers a poor prognosis.

Autosomal dominant polycystic kidney disease (ADPKD), which is far more common, usually does not manifest until adulthood (Chap. 56, p. 1001). Even so, some fetuses with ADPKD have mild renal enlargement and enhanced renal echogenicity in the setting of normal amnionic fluid volume.

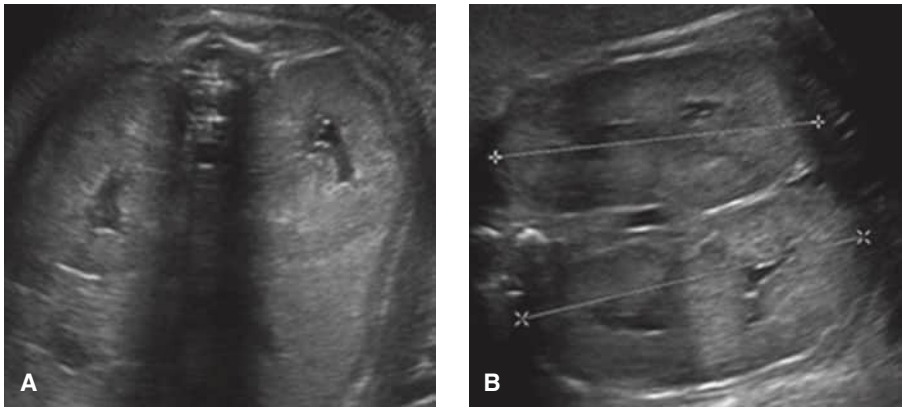

FIGURE 15-60 Autosomal recessive polycystic kidney disease (ARPKD). Transverse **(A)** and coronal **(B)** images of a 29-week fetus with marked renal enlargement. The kidneys measure 7 cm in length and have a ground-glass appearance. There is anhydramnios.

The differential diagnosis for these findings includes several genetic syndromes, aneuploidy, or normal variant.

Bladder Outlet Obstruction

Distal obstruction of the urinary tract is more frequent in male fetuses, and the most common etiology is *posterior urethral valves*. It may be diagnosed as early as the first trimester in some cases (Fig. 15-61). The bladder is markedly dilated, with accompanying dilation of the proximal urethra, which is termed the "keyhole" sign. Oligohydramnios, particularly before midpregnancy, portends pulmonary hypoplasia and poor prognosis. The kidneys may initially manifest severe hydroureteronephrosis but later develop cystic renal dysplasia or become small and echogenic. Outcome may be poor even with normal amnionic fluid volume. Associated anomalies occur in 40 percent of cases, and aneuploidy has been reported in 5 to 8 percent (Hayden, 1988; Hobbins, 1984; Mann, 2010). Evaluation and potential fetal therapy for bladder outlet obstruction is discussed in Chapter 19 (p. 376).

SKELETON

The standard examination includes demonstrating the presence of the arms, legs, hands, and feet (American Institute of Ultrasound in Medicine, 2018). The detailed examination includes, in addition, the number and position of the digits—fingers and toes (Fig. 15-62).

The Nosology and Classification of Genetic Skeletal Disorders includes 461 skeletal anomalies in 42 groups, characterized according to their molecular phenotype, clinical features, or radiographic findings (Mortier, 2019). More than 90 percent of skeletal disorders now have a known genetic basis, with pathogenic variants identified in more than 400 genes. The two types of skeletal dysplasias are *osteochondrodysplasias*—the generalized abnormal development of bone and/or cartilage, and *dysostoses*—which are abnormalities of individual bones. In addition to these *malformations*, skeletal abnormalities include *deformations*, as with some cases of clubfoot, and *disruptions* such as limb-reduction defects.

■ Skeletal Dysplasias

The prevalence of skeletal dysplasias approximates 3 in 10,000 births. Two groups account for more than half of all cases: the *fibroblast growth factor 3 (FGFR3) chondrodysplasia* group and the *osteogenesis imperfecta* and decreased bone density group. Each occurs in 0.8 in 10,000 births (Stevenson, 2012).

Evaluation of a pregnancy with suspected skeletal dysplasia includes a survey of every long bone, as well as the hands and feet, skull size and shape, clavicles, scapulae, thorax, and spine. Reference tables are used to determine which long bones are affected and ascertain the degree of shortening (Appendix, p. 1239). Involvement of all long bones is termed *micromelia*, whereas predominant involvement of only the proximal, intermediate, or distal long bone segments is termed *rhizomelia*, *mesomelia*, and *acromelia*, respectively. The degree of ossification should be noted, as should presence of bowing or fractures.

Although precise characterization may elude prenatal diagnosis, it is frequently possible to determine whether a skeletal dysplasia is lethal. Lethal dysplasias show profound long bone

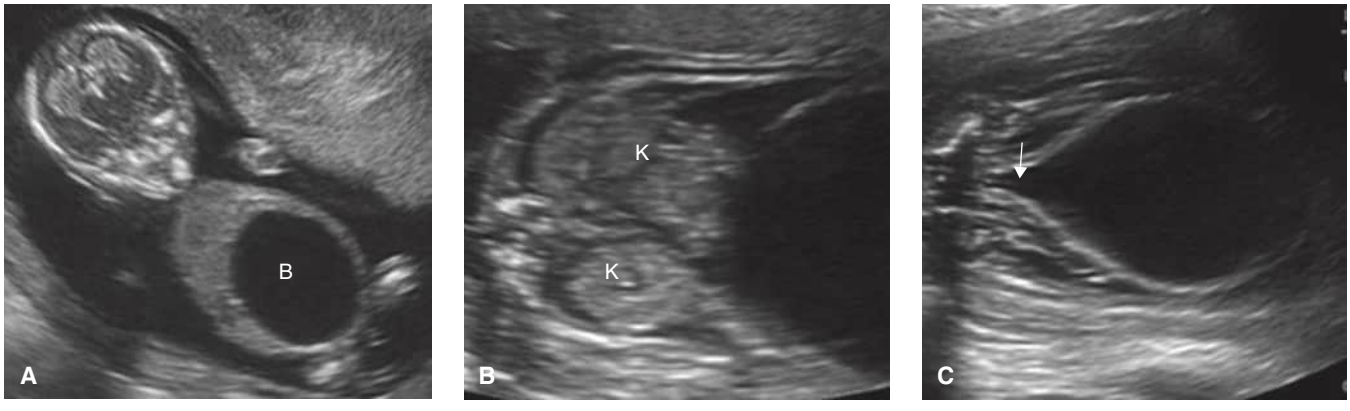

FIGURE 15-61 Bladder outlet obstruction. **A.** The bladder (*B*) is so large that it fills the abdomen in this 13-week fetus. **B.** By 18 weeks, the kidneys (*K*) have become brightly echogenic. **C.** The bladder is markedly dilated and thick-walled, with dilation of the proximal urethra, termed the "keyhole" sign (*arrow*).

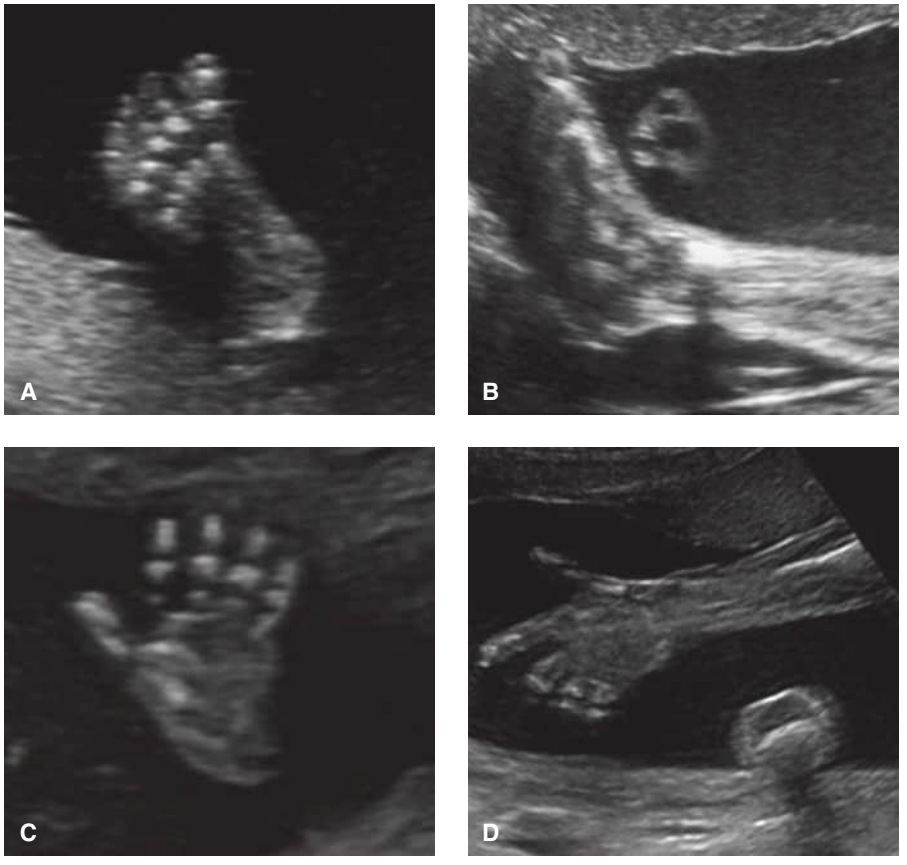

FIGURE 15-62 Normal extremities. **A.** Footprint with toes identified. **B.** Normal ankle position. **C.** Hand with fingers identified. **D.** Normal hand and forearm position.

shortening, often with measurements far below the 5th percentile, and display femur length-to-abdominal circumference ratios <16 percent (Nelson, 2014; Rahemtullah, 1997; Ramus, 1998). Other sonographic abnormalities are generally evident. Pulmonary hypoplasia is suggested by a thoracic circumference <80 percent of the abdominal circumference value, a thoracic circumference <2.5th percentile, and a cardiac circumference >50 percent of the thoracic circumference value (Appendix, p. 1238). Affected pregnancies may also develop hydramnios and/or hydrops.

The FGFR3 chondrodysplasias include *achondroplasia*, *hypochondroplasia*, and *thanatophoric dysplasia*. Achondroplasia is the most common nonlethal skeletal dysplasia. An impressive 98 percent of cases are due to a specific point mutation in the *FGFR3* gene. Inheritance is autosomal dominant, and 80 percent of cases result from a new mutation. Achondroplasia is characterized by long bone shortening that is predominantly *rhizomelic*, an enlarged head with frontal bossing, depressed nasal bridge, exaggerated lumbar lordosis, and a trident configuration of the hands. Intelligence is usually normal. The femur and humerus measurements may not fall below the 5th percentile until the early third trimester. In homozygotes, who represent 25 percent of the offspring of heterozygous parents, the condition is characterized by greater long bone shortening and is lethal.

The other major class of FGFR3 dysplasias, *thanatophoric dysplasia*, is the most common lethal skeletal disorder. It is characterized by severe micromelia, and affected fetuses—particularly those with type II—may develop a characteristic cloverleaf skull deformity (*Kleeblattschädel*) due to craniosynostosis. Genetic testing is confirmatory.

Osteogenesis imperfecta represents a group of skeletal dysplasias typified by hypomineralization. There are multiple types, and more than 90 percent of cases are characterized by a mutation in the *COL1A1* or *COL1A2* gene. Type II, also called the perinatal form, is lethal. The skull displays a profound lack of ossification, and gentle pressure on the maternal abdomen from the ultrasound transducer results in visible skull deformation (Fig. 15-63). Other features include multiple in-utero fractures and ribs that appear "beaded." Inheritance is autosomal dominant, such that all cases result from either new mutations or gonadal mosaicism. Another skeletal dysplasia that creates severe hypomineralization is *hypophosphatasia*, which has an autosomal recessive inheritance.

Polydactyly

The most common skeletal abnormality is polydactyly, which occurs in approximately 1 in 1000 births. It is *post-axial* if on the side of the ulna or fibula and *pre-axial* if on the side of the

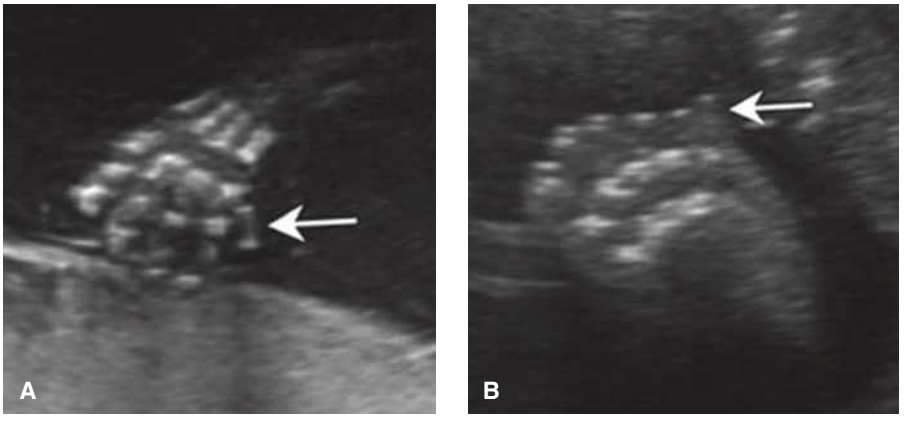

FIGURE 15-63 Post-axial polydactyly. **A.** In this image of the hand, the arrow points to a rudimentary digit adjacent to the little finger. **B.** Foot with 6 toes in a fetus with trisomy 13. The arrow points to the extra digit.

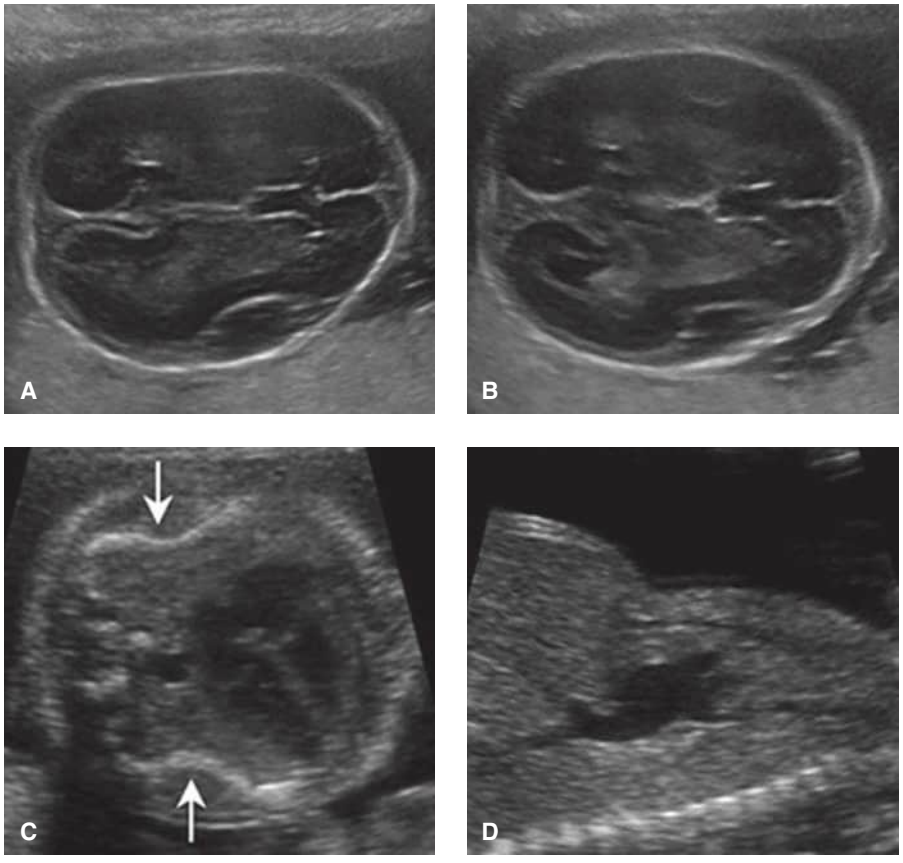

FIGURE 15-64 Osteogenesis imperfecta, Type IIa. **A.** Due to lack of skull ossification, gentle ultrasound transducer pressure on the maternal abdomen results in visible deformation (flattening) of the skull in this 24-week fetus. **B.** When the transducer pressure is removed, the skull shape returns to normal. **C.** In the four-chamber view of the heart, in-utero fractures lead to abrupt angulation of the ribs (*arrows*). **D.** The thorax is markedly smaller than the abdomen in this sagittal image.

radius or tibia (Fig. 15-64). The extra digit is often rudimentary, and in the absence of a bony component, prenatal detection may be limited. Post-axial polydactyly is more common and is frequently inherited in an autosomal dominant fashion. Polydactyly is also a feature of syndromes such as Meckel-Gruber and trisomy 13.

■ Clubfoot—Talipes Equinovarus

This disorder is notable for a deformed talus and shortened Achilles tendon. The affected foot is abnormally fixed and positioned with *equinus* (downward pointing), *varus* (inward rotation), and forefoot adduction. Most cases are considered malformations, with a multifactorial genetic component. However, an association with environmental factors and with early amniocentesis suggests that deformation also plays a role (Tredwell, 2001). Sonographically, the footprint is visible in the same plane as the tibia and fibula (Fig. 15-65).

The prevalence of clubfoot approximates 1 in 1000 births, and the male:female ratio is 2:1 (Carey, 2003; Pavone, 2012). Clubfoot is bilateral in approximately 50 percent of cases. At least 50 percent of affected individuals have associated abnormalities, such as neural-tube defects, arthrogryposis, and myotonic dystrophy and other genetic syndromes (Mammen, 2004; Sharma, 2011). If there are other abnormalities, aneuploidy is present in 30 percent. In contrast, the aneuploidy rate is <4 percent when clubfoot appears isolated (Lauson, 2010; Sharma, 2011). Thus, a careful search for associated abnormalities is warranted, and chromosomal microarray analysis may be considered.

■ Limb-Reduction Defects

Documentation of the arms and legs is a component of the standard examination. The absence or hypoplasia of all or part of one or more extremities is a *limb-reduction defect*. The birth prevalence is 4 to 8 in 10,000 (Kucik, 2012; Stoll, 2010; Vasluian, 2013). Approximately half of these are isolated defects, up to one third occur as part of a recognized syndrome, and individuals in the remaining cases have other coexisting anomalies (Stoll, 2010; Vasluian, 2013). Upper extremities are affected more frequently than lower ones. A terminal *transverse limb defect* lacks part or all of a distal limb to create a stump (Fig. 15-66). This is more common than a *longitudinal defect*, which is complete or partial absence of the long bone(s) on only one side of a given extremity.

Absence of an entire extremity is termed *amelia*. *Phocomelia*, associated with thalidomide exposure, is an absence of one or more long bones with the hands or feet attached to the trunk (Chap. 8, p. 155). Limb-reduction defects are associated with numerous genetic syndromes, such

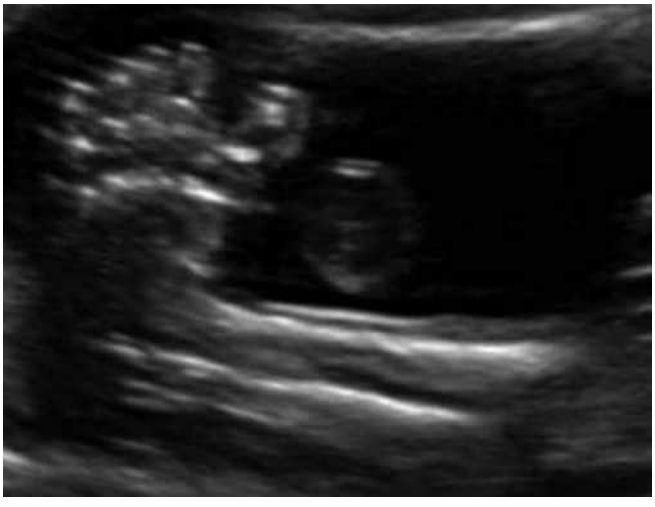

FIGURE 15-65 Talipes equinovarus or clubfoot. This condition is diagnosed by visualizing the "footprint" in the same plane as the tibia and fibula.

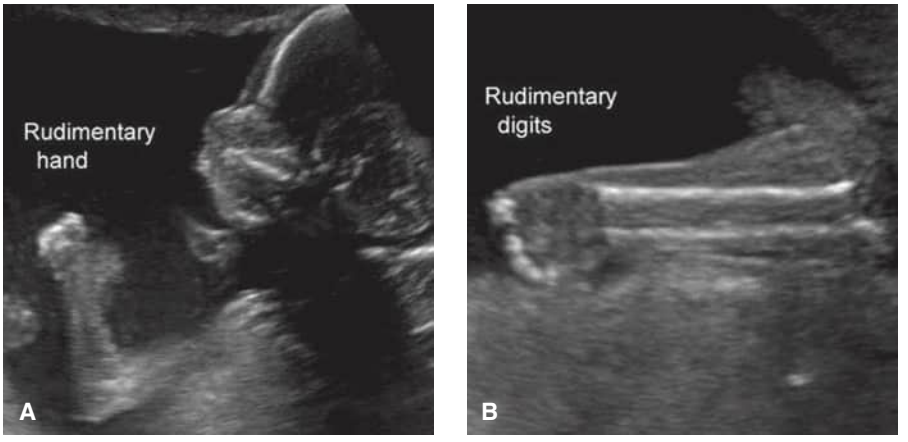

FIGURE 15-66 Transverse limb-reduction defect. **A.** At 18 weeks' gestation, only a rudimentary hand was visible. **B.** By 24 weeks, the radius and ulna were normal in size and appearance, and small rudimentary digits were evident.

as *Roberts syndrome*, an autosomal recessive condition characterized by *tetraphocomelia.* A *clubhand deformity*, usually from an absent radius, is a component of the *thrombocytopenia-absent radius syndrome* and is also associated with trisomy 18 (Fig. 16-5, p. 312). Limb-reduction defects may occur in the setting of a disruption such as amnionic-band sequence (Chap. 6, p. 113). They have also been associated with chorionic villus sampling when performed before 10 weeks' gestation (Fig. 17-5, p. 346).

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CHAPTER 16

Genetics

Genetics is the study of genes, heredity, and the variation of inherited characteristics. Medical genetics addresses the etiology and pathogenesis of human diseases that are at least partially genetic in origin, as well as their prediction and prevention. Whereas a gene is a specific sequence of deoxyribonucleic acid (DNA) on a single chromosome that codes for a particular protein, a *genome* is the entirety of all genes that make up an organism. *Genomics* is the study of how genes function and interact with one other. Chromosomal, mendelian, and nonmendelian genetic conditions are reviewed in this chapter. Prenatal and preimplantation genetic testing and newborn genetic screening are discussed in Chapters 17 and 32, respectively.

Genetic disease is common. Two to 3 percent of newborns have a recognized structural abnormality, another 3 percent are diagnosed with an abnormality by age 5 years, and yet another 8 to 10 percent are found to have a functional or developmental abnormality before reaching adulthood.

GENOMICS IN OBSTETRICS

The Human Genome Project was an international research program that sequenced the 3 billion base pairs and more than 20,000 genes that make up the human genome. It paved the way for research into gene organization and function in an effort to understand the molecular basis of disease. More than 99 percent of our DNA is identical. The coding regions of DNA—*exons*—constitute only 1.5 percent of the genome. An *exome* is the entirety of all the exons that an organism contains. *Introns* are DNA sequences involved in coding regulation and make up 24 percent of the genome. Intergenic DNA composes the remainder.

Our genetic code varies once every 200 to 500 base pairs, usually as a single-nucleotide polymorphism (SNP). Thus, whole genome sequencing and whole exome sequencing, described later (p. 327), hold tremendous potential to further elucidate genetic variants in disease.

Toward this goal, genetic and genomic databases are maintained by the National Center for Biotechnology Information (2021). These are freely accessible and can be indispensable to providers who offer counseling and testing for genetic conditions. The *GeneReviews* database has in-depth clinical information for more than 800 genetic conditions, including diagnostic criteria and management considerations. The *Genetic Testing Registry (GTR)* database contains information for nearly 80,000 genetic tests and instructions for specimen collection and transport to individual laboratories throughout

the world (National Center for Biotechnology Information, 2021). The National Library of Medicine (2021) has also established a genetic information database, the *MedlinePlus Genetics,* which is intended for the lay population. It provides explanations of more than 1300 genetic conditions, a glossary of genetic concepts, and links to more comprehensive medical resources.

CHROMOSOMAL ABNORMALITIES

Chromosomal abnormalities figure prominently in genetic disease. They account for >50 percent of first-trimester miscarriages, approximately 20 percent of second-trimester losses, and 6 to 8 percent of stillbirths and early-childhood deaths (Reddy, 2012; Stevenson, 2004; Wou, 2016). Based on data from population-based registries, chromosomal abnormalities are identified in 0.4 percent of recognized pregnancies (Wellesley, 2012). Most of these are aneuploidies. Trisomy 21 accounts for >50 percent, trisomy 18 for nearly 15 percent, and trisomy 13 for 5 percent of cases (Fig. 16-1). If no karyotypic abnormality is identified in a fetus with a structural anomaly, additional testing with chromosomal microarray analysis is anticipated to detect a chromosomal deletion or duplication—a *copy number variant*—in approximately 6.5 percent of cases (American College of Obstetricians and Gynecologists, 2020c).

Standard Nomenclature

Chromosomal abnormalities are described using the International System for Human Cytogenomic Nomenclature (McGowan-Jordan, 2020). Abnormalities fall into two broad categories: *abnormal chromosome number*, such as trisomy, and *abnormal chromosome structure*, such as a DNA segment deletion or duplication. Each chromosome has a short arm, termed the "p" or petit arm, and a long arm, known as the "q" arm, selected because it is the next letter in the alphabet. The two arms are separated by the centromere.

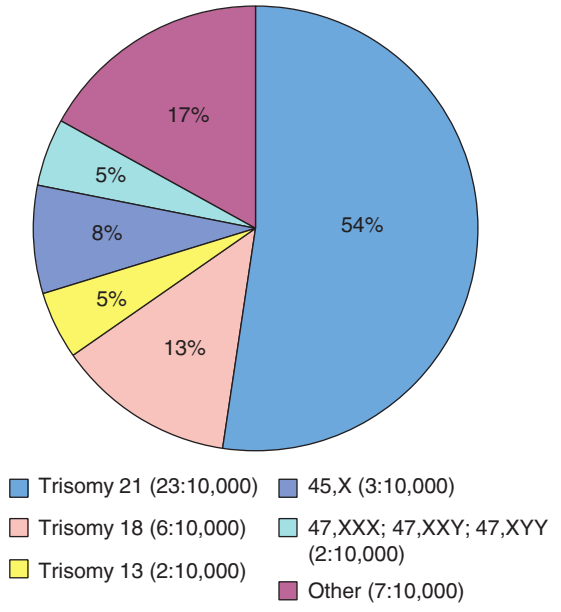

FIGURE 16-1 Prevalence and relative proportion of selected chromosomal abnormalities from EUROCAT (European Surveillance of Congenital Anomalies) population-based registries that included >10,000 aneuploid live births, fetal deaths, and pregnancy terminations, 2000–2006.

When reporting a karyotype, the total number of chromosomes is listed first, corresponding to the number of centromeres. This is followed by the sex chromosomes, XX or XY, and then by a description of any structural variation. Specific chromosomal abnormalities are indicated by standard abbreviations, such as del (deletion), inv (inversion), and t (translocation). The affected region or bands of the arms are then reported, so that the reader will know the exact location. Examples are shown in Table 16-1.

Nomenclature is similar for fluorescence in situ hybridization (FISH), a technique used to rapidly identify a specific chromosome abnormality (p. 325). The abbreviation *ish* applies when in situ hybridization is performed on metaphase cells and *nuc ish* when performed on interphase nuclei. If the result is normal, ish is followed by the probe's specific chromosomal region, such as 22q11.2, and then the name of the probe and the number of signals visualized—for example, HIRAx2. If a deletion is identified, *del* is included before the chromosomal region, and the name of the probe is followed by a minus sign (HIRA–), as shown in Table 16-1. The 22q11.2 deletion syndrome is discussed later (p. 315).

For chromosomal microarray analysis (CMA), the designation begins with the abbreviation *arr* (p. 348). This is followed by the version of the genome build to which the nucleotide designations are aligned, such as GRCh38 for Genome Reference Consortium human build 38. Next, the number of the chromosome containing the abnormality is listed, followed by the p or q arm, and then the specific bands in question. CMA reports also include the affected base pair coordinates and thus convey the exact size and location for every abnormality identified (see Table 16-1). The information is reported in the same way whether the alteration is pathogenic or is of uncertain clinical significance.

Abnormalities of Chromosome Number

The most easily recognized chromosomal abnormalities are numerical. *Aneuploidy* is the inheritance of either an extra chromosome—resulting in trisomy, or loss of a chromosome—*monosomy*. This differs from *polyploidy*, which is an abnormal number of whole haploid chromosome sets. For example, triploidy has 69 chromosomes. The estimated incidence of various numerical chromosomal abnormalities is shown in Figure 16-1 (Wellesley, 2012).

Autosomal Trisomies

Trisomy usually results from nondisjunction, which is the failure of normal chromosomal pairing and separation during meiosis. Nondisjunction may occur if the chromosomes: (1) fail to pair up, (2) pair up properly but separate prematurely, or (3) fail to separate. Although each chromosome pair is equally likely to have a segregation error, trisomies other than 21, 18, or 13 rarely result in term pregnancies. Each of these autosomal

TABLE 16-1. Examples of Karyotype Designations Using the 2020 International System for Human Cytogenomic Nomenclature

Karyotype	Description
46,XX	Normal female chromosome constitution
47,XY,+21	Male with trisomy 21
47,XX,+21/46,XX	Female who is a mosaic of trisomy 21 cells and cells with normal constitution
46,XY,del(4)(p14)	Male with terminal deletion (del) of the short arm of chromosome 4 at band p14
46,XX,dup(5)(p14p15.3)	Female with duplication (dup) of the short arm of chromosome 5 from band p14 to band p15.3
45,XY,der(13;14)(q10;q10)	Male with balanced robertsonian translocation (der) of the long arms of chromosomes 13 and 14—the karyotype now has one normal 13, one normal 14, and the translocation chromosome, reducing the normal 46 chromosome complement to 45
46,XX,t(11;22)(q23;q11.2)	Female with a balanced reciprocal translocation (t) between chromosomes 11 and 22, with breakpoints at 11q23 and 22q11.2
46,XY,inv(3)(p21q13)	Male with inversion (inv) of chromosome 3 that extends from p21 to q13—a pericentric inversion because it includes the centromere
46,X,r(X)(p22.1q27)	Female with one normal X and one ring (r) X chromosome, with the regions distal to p22.1 and q27 deleted from the ring
46,X,i(X)(q10)	Female with one normal X chromosome and an isochromosome (i) of the long arm of the other X
ish 22q11.2(HIRAx2)	FISH of metaphase cells using a probe for the HIRA locus of the 22q11.2 region, with 2 signals identified (no evidence of microdeletion)
ish del(22)(q11.2q11.2) (HIRA-)	FISH of metaphase cells using a probe for the HIRA locus of the 22q11.2 region, with only one signal identified, consistent with the microdeletion
arr[GRCh38] 18p11.32q23 (102328_79093443)x3	Microarray analysis (arr), genome build GRCh38, showing a single copy gain on chromosome 18 from band p11.32 to band q23 (essentially the entire chromosome), consistent with trisomy 18
arr[GRCh38] 4q32.2q35.1 (163146681_183022312)x1	Microarray analysis (arr), genome build GRCh38, showing a copy loss on the long arm of chromosome 4 at bands q32.2 through q35.1 (19.9 Mb)
arr[GRCh38] 15q11.2q26 (23123715_101888908)x2 hmz	SNP microarray analysis (arr), genome build GRCh 38, showing homozygosity for the entire long arm of chromosome 15

FISH = fluorescence in situ hybridization; GRCh38 = Genome Reference Consortium human build 38; HIRA = histone cell cycle regulator; SNP = single nucleotide polymorphism.
Used with permission from Dr. Kathleen S. Wilson.

trisomies has a spectrum of phenotypic severity. Some fetuses come to attention earlier in a pregnancy due to multiple major organ abnormalities or hydrops fetalis (p. 328). Others have more subtle findings or are detected only through prenatal screening tests (Chap. 17, p. 337). Survival data are based on cases with better prognosis, and this factors into counseling.

The likelihood that a pregnancy will be complicated by an autosomal trisomy rises steeply with maternal age and particularly after age 35 (Fig. 16-2) (Mai, 2013). From birth until ovulation, oocytes are suspended in midprophase of meiosis I. If nondisjunction occurs after completion of meiosis, one gamete will have two copies of the affected chromosome, which leads to trisomy if fertilized. The other gamete, receiving no copy of the affected chromosome, is nullisomic and will be monosomic if fertilized. It is estimated that 10 to 20 percent of oocytes are aneuploid secondary to meiotic errors compared with 3 to 4 percent of sperm. After a pregnancy with an autosomal trisomy, the risk for any autosomal trisomy in a future pregnancy approximates 1 percent until the woman's age-related risk exceeds this. Screening and prenatal diagnosis of autosomal trisomies are discussed in Chapter 17 (p. 333). Parental chromosomal studies are not indicated unless the abnormality was caused by an unbalanced translocation or other structural rearrangement (p. 315).

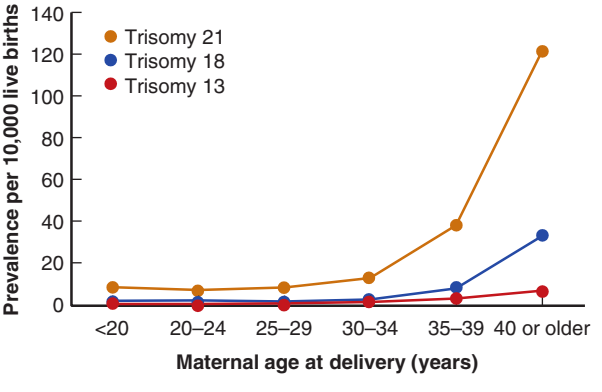

FIGURE 16-2 Prevalence of autosomal trisomies according to maternal age found in population-based birth defect surveillance programs in the United States, 2006–2010.

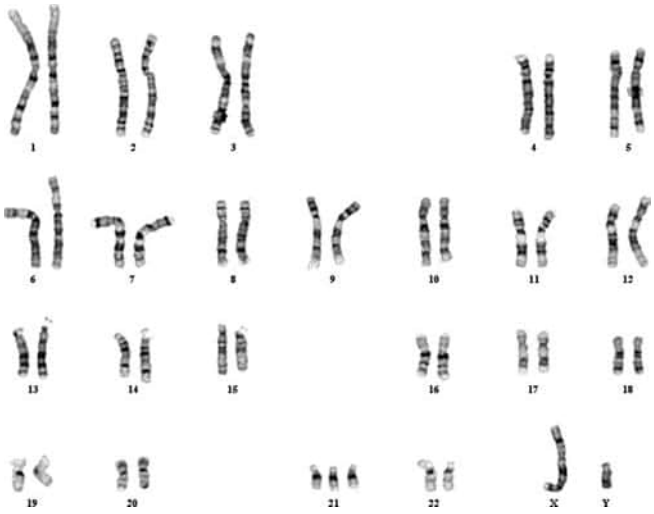

FIGURE 16-3 Male karyotype with trisomy 21 (47,XY,+21), consistent with Down syndrome. (Reproduced with permission from Dr. Prasad Koduru.)

Trisomy 21—Down Syndrome. In 1866, J. L. H. Down described a group of intellectually disabled children with distinctive physical features. Nearly 100 years later, Lejeune (1959) demonstrated that Down syndrome stems from an autosomal trisomy (Fig. 16-3). Trisomy 21 causes 95 percent of Down syndrome cases. The nondisjunction event occurs during meiosis I in approximately 75 percent of cases and in meiosis II in the remainder. Because chromosome 21 is acrocentric, a robertsonian translocation (p. 315) may occur, and this accounts for 3 to 4 percent of Down syndrome births. The remaining 1 to 2 percent are caused by isochromosome 21 or mosaicism for chromosome 21 (p. 317).

Down syndrome is the most common nonlethal trisomy. It is identified in approximately 1 in 450 pregnancies (Loane, 2013). In the United States, fetal losses and pregnancy terminations yield an estimated prevalence of 1 case per 740 live births (Mai, 2013; Parker, 2010). The fetal death rate beyond 20 weeks' gestation approximates 5 percent. Coinciding with the rise in overall number of pregnancies in women aged 35 years and older, the proportion of pregnancies with Down syndrome has increased approximately 33 percent during the past four decades (Loane, 2013; Parker, 2010; Shin, 2009). Most Down syndrome births at Parkland Hospital now occur in women in this age group (Hussamy, 2019).

If major anomalies and minor aneuploidy markers are considered, 50 to 75 percent of pregnancies affected by Down syndrome are found to have a sonographic abnormality (Chap. 17, p. 340) (American College of Obstetricians and Gynecologists, 2020d; Hussamy, 2019). A major structural malformation is detected in the second trimester in approximately one third of cases. The most prevalent anomalies in affected children are cardiac and gastrointestinal. Cardiac abnormalities occur in approximately 50 percent, particularly endocardial cushion defects and ventricular septal defects (Figs. 15-39A and 15-39B, p. 291) (Bergstrom, 2016; Freeman, 2008; Stoll, 2015). Gastrointestinal abnormalities are identified in 6 to 12 percent and include esophageal atresia, duodenal atresia, and Hirschsprung disease (Fig. 15-48, p. 296) (Bull, 2011; Stoll, 2015).

Other health problems are also common with Down syndrome. These include hearing loss in 75 percent, optical refractive errors in 50 percent, cataracts in 15 percent, obstructive sleep apnea in 60 percent, thyroid disease in 15 percent, transient myeloproliferative disorder in 10 percent of newborns, early-onset Alzheimer's disease in 70 percent of adults, and a higher incidence of leukemia (Bull, 2011; Hartley, 2015). Women with Down syndrome are fertile, and nearly one third of their offspring will have Down syndrome. Males with Down syndrome have markedly reduced spermatogenesis and are almost always sterile. The average intelligence quotient (IQ) score is 35 to 70. Social skills in affected children are usually higher than predicted by their IQ scores.

Characteristic features of Down syndrome are shown in Figure 16-4. Typical findings include brachycephaly; epicanthal folds and up-slanting palpebral fissures; Brushfield spots, which are whitish spots on the periphery of the iris; a flat nasal bridge; and hypotonia. Infants often have loose skin at the

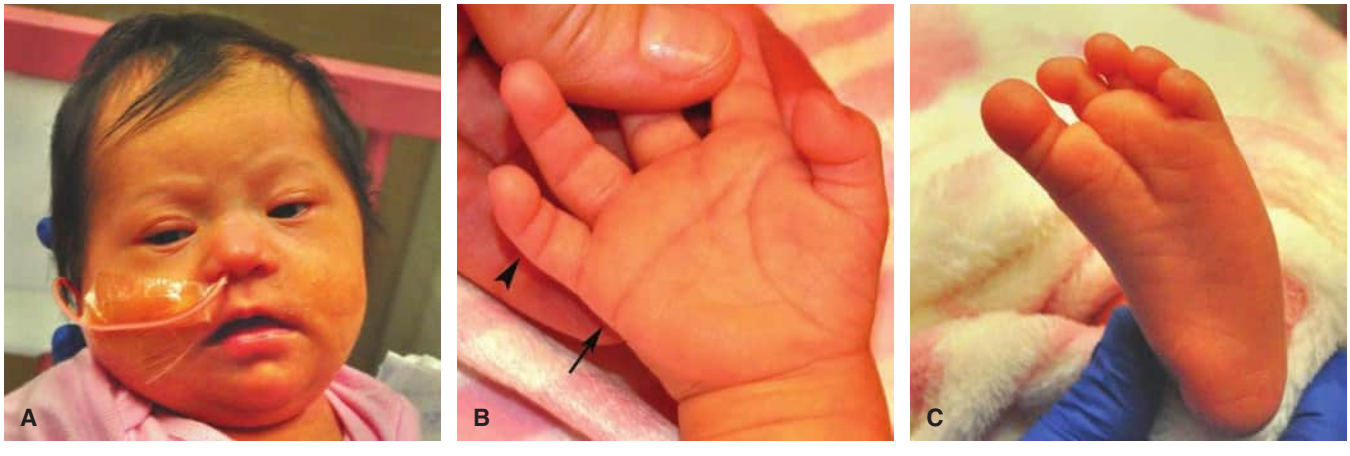

FIGURE 16-4 Newborn with Down syndrome, karyotype 47,XX,+21 (trisomy 21). **A.** Characteristic facial features include epicanthal folds and a flattened nasal bridge. **B.** The hand has a single palmar crease (*arrow*) and hypoplasia of the middle phalanx of the fifth digit (*arrowhead*). **C.** The "sandal gap" between the first and second toes is also known as hallux varus. (Reproduced with permission from Dr. Aldeboran N. Rodriguez.)

nape of the neck, a prominent space or "sandal-gap" between the first and second toes, short fingers, a single palmar crease, and clinodactyly of the fifth digit, in which hypoplasia of the middle phalanx causes inward curvature. Discussed in Chapter 17, some of these findings are seen during prenatal ultrasound examination.

Data suggest that approximately 95 percent of liveborn infants with Down syndrome survive the first year. The 10-year survival rate is at least 90 percent overall and is 99 percent if major malformations are absent (Rankin, 2012; Vendola, 2010). Average life expectancy is 55 to 60 years. Several organizations offer education and support for prospective parents faced with prenatal diagnosis of Down syndrome. These include the March of Dimes, National Down Syndrome Congress (www.ndsccenter.org), and National Down Syndrome Society (www.ndss.org).

Trisomy 18—Edwards Syndrome. The association between this constellation of abnormalities and an autosomal trisomy was first described by Edwards (1960). In population-based series of abortuses, stillbirths, and live births, trisomy 18 approximates 1 per 2000 recognized pregnancies (Goel, 2019; Loane, 2013; Parker, 2010). High in-utero lethality and termination of many affected pregnancies explains a live birth prevalence of just 1 per 6600 to 10,000. Unlike Down syndrome and Patau syndrome, which may result from a robertsonian translocation because they involve acrocentric chromosomes, Edwards syndrome uncommonly stems from a chromosomal rearrangement.

Virtually every organ can be affected by trisomy 18. Common major anomalies include heart defects in more than 90 percent, particularly ventricular septal defects. Cerebellar vermian agenesis, myelomeningocele, diaphragmatic hernia, omphalocele, imperforate anus, and renal anomalies such as horseshoe kidney are others (Rosa, 2011; Springett, 2015; Watson, 2008). Sonographic images of these abnormalities are shown in Chapter 15. Frequent cranial and extremity abnormalities in affected fetuses include a "strawberry-shaped" cranium, abnormally wide cavum septum pellucidum, choroid plexus cysts, micrognathia, clenched hands with overlapping digits, radial aplasia with hyperflexed wrists, and rockerbottom or clubbed feet (Fig. 16-5) (Abele, 2013). Importantly, choroid plexus cysts only raise the risk for trisomy 18 in the setting of other risk factors, such as fetal structural abnormalities or an abnormal aneuploidy screening test result (Reddy, 2014).

Pregnancies with trisomy 18 that reach the third trimester often develop fetal-growth restriction, and the mean birthweight is <2500 g (Lin, 2006; Rosa, 2011). When undiagnosed, trisomy 18 has resulted in emergency cesarean for "fetal distress" in nearly 50 percent of cases (Schneider, 1981; Houlihan, 2013). Mode of delivery and management of heart rate abnormalities should be discussed in advance. Discussed in Chapter 35 (p. 628), perinatal palliative care consultation should be offered (American College of Obstetricians and Gynecologists, 2019).

In the National Birth Defects Prevention Study, median neonatal survival with trisomy 18 was 8 days, and the 5-year survival rate was 12 percent (Meyer, 2016). Not unexpectedly, major anomalies lower survival rates. Data from the Society of Thoracic Surgeons indicate that infants with trisomy 18 who undergo cardiac surgery have mortality rates 3 to 5 times higher than those without trisomy 18 (Cooper, 2019). Thus, among the minority with trisomy 18 who survive until birth, the condition is severely life limiting.

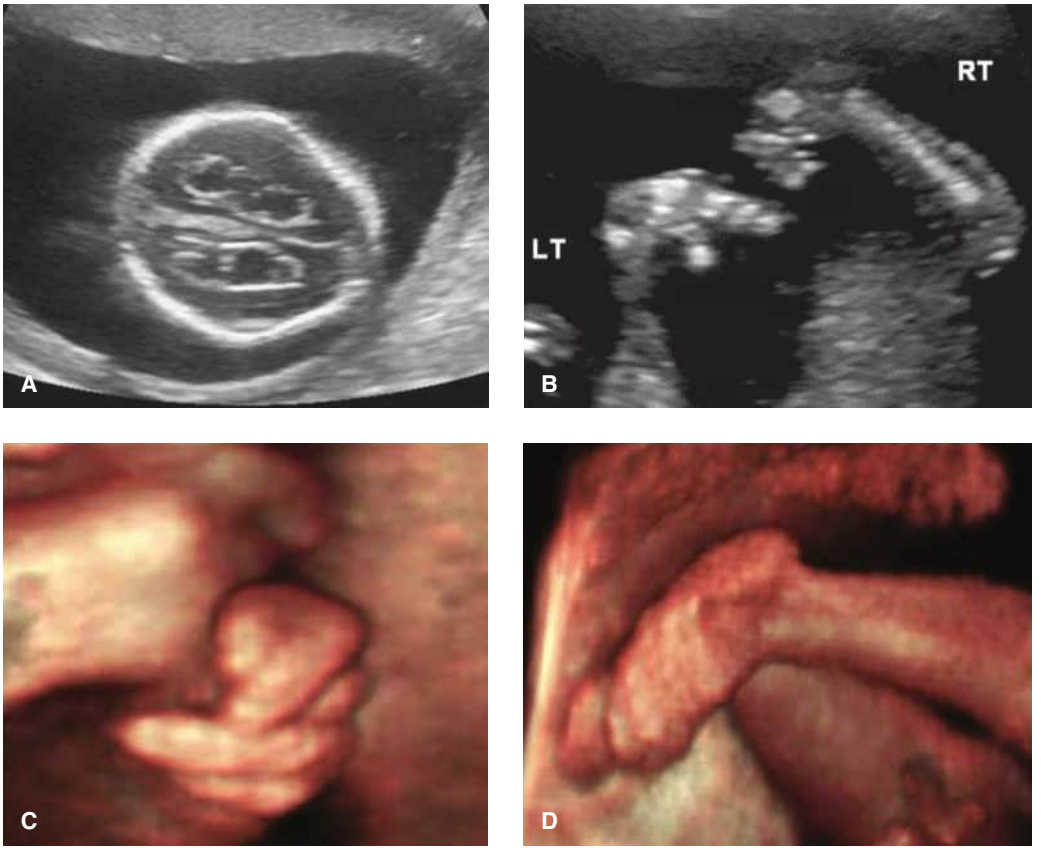

FIGURE 16-5 Trisomy 18—Edwards Syndrome. **A.** This transventricular sonographic view shows fetal choroid plexus cysts and an angulated "strawberry-shaped" skull. **B.** Radial clubhand is manifested as a single forearm bone (radius), with the hands in a fixed, hyperflexed position at right angles to the forearms. **C.** This three-dimensional (3-D) sonographic image shows the characteristic hand position of clenched fist with overlapping digits. **D.** 3-D sonographic image displays a rockerbottom foot (vertical talus).

Trisomy 13—Patau Syndrome. This constellation of fetal abnormalities and their association with an autosomal trisomy was first described by Patau and colleagues (1960). The incidence of trisomy 13 approximates 1 case in 5000 recognized pregnancies, which includes abortuses and stillbirths. Most affected fetuses are lost or terminated. The live birth prevalence is 1 per 12,000 to 18,000 (Goel, 2019; Loane, 2013; Parker, 2010).

At least 80 percent of pregnancies with Patau syndrome result from trisomy 13. With rare exception, the remainder are caused by a robertsonian translocation involving chromosome 13. The most common translocation involves chromosomes 13 and 14, der(13;14)(q10;q10), which is carried by approximately 1 in 1300 phenotypically normal individuals. Among translocation carriers, fewer than 2 percent give birth to a live infant with Patau syndrome.

Trisomy 13 may be associated with abnormalities of any organ system. Abnormalities of the brain, heart, kidneys, and extremities are the most frequent. Holoprosencephaly, usually the alobar type, is present in two thirds of cases and often is accompanied by severe facial abnormalities (Fig. 15-13, p. 279). These may include hypotelorism or cyclopia, microphthalmia, and nasal abnormalities that range from a single nostril to a proboscis. Cardiac defects are found in up to 90 percent (Shipp, 2002). Other abnormalities that suggest trisomy 13 include cephalocele, microcephaly, omphalocele, cystic renal dysplasia, polydactyly, rockerbottom feet, aplasia cutis, and cleft lip-palate, which may be median (Lin, 2007; Springett, 2015). Sonographic images of several of these are shown in Chapter 15. Affected fetuses often also have bilateral echogenic intracardiac foci. For the fetus or newborn with a cephalocele, cystic kidneys, and polydactyly, the differential diagnosis includes trisomy 13 and the autosomal-recessive Meckel–Gruber syndrome.

Trisomy 13 is life limiting, even more so than trisomy 18 (Domingo, 2019). In the National Birth Defects Prevention Study, median survival of neonates with trisomy 13 was 5 days, and the 5-year survival rate was below 10 percent (Meyer, 2016). Occasionally children with trisomy 13 have been candidates for palliative surgical procedures. Most of these have a milder phenotype that lacks brain, cardiac, gastrointestinal, or genitourinary abnormalities (Nelson, 2016). Counseling regarding prenatal diagnosis and management options is similar to that described for trisomy 18.

Unlike other aneuploidies, fetal trisomy 13 confers risk to the pregnant woman. Continuing pregnancies have at least a 25-percent risk for hypertensive complications (Dotters-Katz, 2018; Tuohy, 1992). The risk for preeclampsia with severe features is increased more than tenfold and often develops prior to 32 weeks' gestation. Chromosome 13 contains the gene for soluble fms-like tyrosine kinase-1 (sFlt-1), which is an antiangiogenic protein associated with preeclampsia (Chap. 40, p. 694). Investigators have documented overexpression of the sFlt-1 protein by trisomic 13 placentas and in serum of women with preeclampsia (Bdolah, 2006; Silasi, 2011).

Other Trisomies. Live births are extremely rare with any other autosomal trisomy. Trisomy 22 has been described in case reports and series (Heinrich, 2013; Kehinde, 2014). Affected fetuses have severe growth restriction, microcephaly with an abnormal-shaped cranium, midface hypoplasia, and cardiac and genitourinary abnormalities. Trisomy 16 is the most prevalent trisomy among first-trimester losses, accounting for 16 percent. Trisomies 21 and 22 are also common among first trimester losses. Trisomy 1 has never been reported.

Monosomy

Nondisjunction creates an equal number of nullisomic and disomic gametes. As a rule, missing chromosomal material is more devastating than extra chromosomal material, and almost all monosomic conceptuses are lost before implantation. The one exception is monosomy for the X chromosome (45,X), Turner syndrome, which is discussed subsequently. Unlike autosomal trisomies, which increase in incidence with maternal age, monosomy and maternal age lack an association.

Polyploidy

This is defined as more than two complete haploid chromosomal sets. Polyploidy accounts for approximately 20 percent of spontaneous abortions but is rarely found later in gestation.

Triploid pregnancies have three haploid sets, 69 chromosomes. If extra set of chromosomes is paternal, the result is *diandric triploidy*, and if maternal, *digynic triploidy*, relevant because the phenotype reflects the parent of origin. This is an example of *imprinting* (p. 322). Diandric or type I triploidy occurs after fertilization of one egg by two sperm or by one abnormal diploid sperm. Diandric triploidy produces a partial molar pregnancy, discussed in Chapter 13 (p. 237). With digynic or type II triploidy, the extra chromosomal set is maternal, and the egg fails to undergo the first or second meiotic division before fertilization. Digynic triploid placentas do not develop molar changes. However, the fetus usually develops asymmetrical growth restriction. Although diandric triploidy accounts for the majority of triploid conceptions, the early loss rate is so high that two thirds of triploid pregnancies identified beyond the first trimester are digynic (Jauniaux, 1999).

Triploidy is recognized in 1 per 5000 pregnancies (Zalel, 2016). It is considered lethal, and fetuses with either the diandric or digynic form typically have multiple structural anomalies. The brain, heart, kidneys, and extremities are commonly affected (Massalska, 2017; Zalel, 2016). Counseling, prenatal diagnosis, and delivery management are similar to those for trisomies 18 and 13. The recurrence risk for a woman whose triploid fetus survived past the first trimester is 1 to 1.5 percent, and thus prenatal diagnosis is offered in future pregnancies.

Tetraploid pregnancies have four haploid sets of chromosomes, resulting in either 92,XXXX or 92,XXYY. This suggests a postzygotic failure to complete an early cleavage division. The conceptus invariably succumbs, and the recurrence risk is minimal.

Sex Chromosome Abnormalities

45,X—Turner Syndrome. First described by Turner (1938), this syndrome later was found to be caused by monosomy X (Ford, 1959). The birth prevalence of Turner syndrome is approximately 1 in 2500 girls (Cragan, 2009; Dolk, 2010). The missing X chromosome is paternally derived in 80 percent of cases (Cockwell, 1991; Hassold, 1990).

Turner syndrome is the only monosomy compatible with life, but it is also the most common aneuploidy in first-trimester losses, accounting for 20 percent. This is explained by its wide range in phenotype. Approximately 98 percent of affected conceptuses are so abnormal that they abort early in the first trimester. Of the remainder, many manifest large, septated cystic hygromas in the late first or early second trimester, often in the setting of edema that progresses to hydrops fetalis. When cystic hygromas are accompanied by hydrops, the prognosis is extremely poor (Chap. 15, p. 286).

Fewer than 1 percent of pregnancies with Turner syndrome result in a liveborn neonate. Of these, only half are actually monosomy X—approximately a fourth have mosaicism for monosomy X, such as 45,X/46,XX or 45,X/46,XY, and another 15 percent have isochromosome X. It is thought that surviving individuals with 45,X may have had the benefit of "rescue" by an additional cell line containing 46,XX during critical phases of development that was subsequently lost (Hook, 2014).

Abnormalities associated with Turner syndrome include left-sided cardiac defects—such as coarctation of the aorta, hypoplastic left heart syndrome, or bicuspid aortic valve—in 30 to 50 percent; renal anomalies, particularly horseshoe kidney; and hypothyroidism. Other features are short stature, broad chest with widely spaced nipples, congenital lymphedema—puffiness over the dorsum of hands and feet, and a "webbed" posterior neck resulting from cystic hygromas. Intelligence scores are generally in the normal range, but there may be impairments in visual-spatial organization, nonverbal problem solving, and interpretation of social cues. A consensus guideline is available that addresses screening and treatment for the range of health problems affected individuals face (Graveholt, 2017). Growth hormone is typically administered in childhood to ameliorate short stature. More than 90 percent have ovarian dysgenesis and require estrogen repletion at puberty. An exception is mosaicism involving the Y chromosome, as this confers risk for germ cell neoplasm—regardless of whether the child is phenotypically male or female. Accordingly, eventual prophylactic bilateral gonadectomy is indicated (Cools, 2011; Schorge, 2020).

47,XXX. Approximately 1 in 1000 female newborns has an additional X chromosome—47,XXX (Berglund, 2020). The extra X is maternally derived in more than 90 percent of cases. The prevalence of 47,XXX is weakly associated with maternal age, and cell-free DNA screening has resulted in increased diagnoses. No specific pattern of malformations has been described, but genitourinary problems and seizure disorders are more common (Wigby, 2016). Affected infants do not have a characteristic appearance. When children do come to attention, features may include tall stature, hypertelorism, epicanthal folds, kyphoscoliosis, clinodactyly, and hypotonia (Tartaglia, 2010; Wigby, 2016). More than one third are diagnosed with a learning disability, half have attention deficit disorder, and overall cognitive scores are in the low-average range. Pubertal development is unaffected. Primary ovarian insufficiency has been reported. In the absence of prenatal diagnosis, it is estimated that 47,XXX is ascertained in only 10 percent of affected children (Tartalgia, 2010).

Females with two or more extra X chromosomes—48,XXXX or 49,XXXXX—are likely to have physical abnormalities apparent at birth. These abnormal X complements are associated with intellectual disability. For both males and females, the IQ score is lower with each additional X chromosome.

47,XXY—Klinefelter Syndrome. This is the most common sex chromosome abnormality. It occurs in approximately 1 in 700 male infants (Radicioni, 2010). The additional X chromosome is maternally or paternally derived with equal propensity (Jacobs, 1995; Lowe, 2001). There is a weak association with advanced maternal and paternal age.

Like 47,XXX, newborns with 47,XXY usually appear phenotypically normal and do not have a higher incidence of anomalies. As children, boys are typically taller than average and have normal prepubertal development. However, they have gonadal dysgenesis, do not undergo normal virilization, and require testosterone supplementation. They may develop gynecomastia. IQ scores usually lie in the average to low-average range, with increased rates of delayed language development (Boada, 2009; Girardin, 2011). Initiation of hormone replacement was previously recommended to begin in adolescence. However, more recent research suggests that therapy earlier in childhood results in improved working memory and executive functioning and a decrease in anxiety disorders (Samango-Sprouse 2019; Tran, 2019).

47,XYY. This aneuploidy occurs in approximately 1 in 1000 male newborns (Berglund, 2020). As with 47,XXX and XXY individuals, affected boys tend to be tall. A third have macrocephaly, nearly two thirds demonstrate hypotonia, and tremors are common (Bardsley, 2013). Rates of major anomalies are not elevated, although hypertelorism and clinodactyly may be identified in more than half. Pubertal development is normal, and fertility is unimpaired. Affected individuals do have increased rates of oral and written language impairments, attention deficit disorder, developmental delays, and autism spectrum disorder (Bardsley, 2013; Joseph, 2018).

Males with more than two Y chromosomes—48,XYYY—or with both additional X and Y chromosomes—48,XXYY or 49,XXXYY—are more likely to have congenital abnormalities, medical problems, and intellectual disability (Tartaglia, 2011).

■ Abnormalities of Chromosome Structure

Structural chromosomal abnormalities include deletions, duplications, translocations, isochromosomes, inversions, ring chromosomes, and mosaicism (see Table 16-1). Identification of a structural chromosomal abnormality in offspring raises two primary questions. First, what phenotypic or later developmental abnormalities are associated with the finding? Second, is parental karyotype evaluation indicated? In other words, are the parents at increased risk of carrying this abnormality, and if so, what is their risk of having future affected offspring?

Deletions and Duplications

A chromosome with a deletion has a stretch of DNA that is missing, whereas one with a duplication has a region that is included twice. Most deletions and duplications occur during

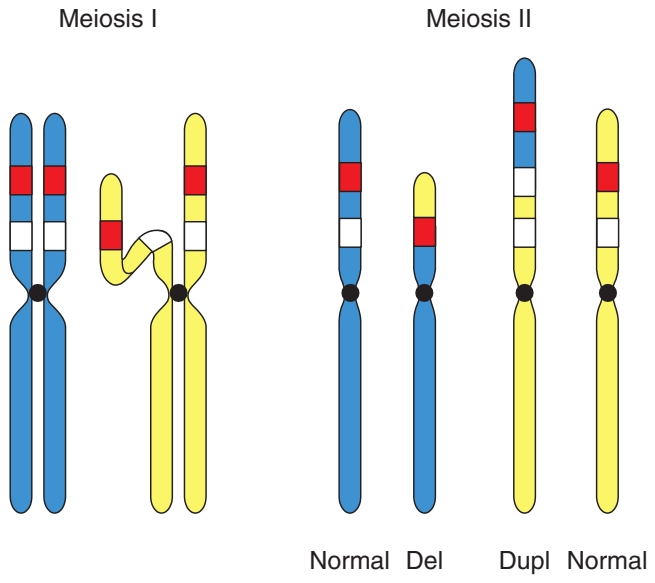

FIGURE 16-6 A mismatch during pairing of homologous chromosomes may lead to a deletion in one chromosome and a duplication in the other. Del = deletion; Dupl = duplication.

meiosis and result from malalignment or mismatching during the pairing of homologous chromosomes. The misaligned segment may then be deleted, or if the mismatch remains when the two chromosomes recombine, it may result in a deletion in one chromosome and duplication in the other (Fig. 16-6). When a deletion or duplication is identified in a fetus or infant, parental karyotyping should be offered, because if either parent carries a balanced translocation, the recurrence risk in subsequent pregnancies is significantly increased. Deletions involving DNA segments large enough to be seen with standard cytogenetic karyotyping are identified in approximately 1 in 7000 births. Common deletions may be referred to by eponyms—for example, del 5p is called *cri du chat syndrome*.

Microdeletions and Microduplications. When a deletion or duplication is smaller than 3 to 5 million base pairs, it is too small to be detected with a standard karyotype analysis. CMA permits identification of these microdeletions and microduplications (p. 325). When CMA is used, the region of DNA that is missing or duplicated is termed a *genomic copy number variant.* A microdeletion or duplication may involve a stretch of DNA that contains multiple genes. This causes a *contiguous gene syndrome*, which can encompass serious but unrelated phenotypic abnormalities (Schmickel, 1986). In some cases, a microduplication may involve the exact DNA region that causes a recognized microdeletion syndrome (Table 16-2). When a specific microdeletion syndrome is suspected clinically, it is confirmed using either CMA or FISH.

22q11.2 Microdeletion Syndrome. This syndrome is also known as DiGeorge syndrome, Shprintzen syndrome, and velocardiofacial syndrome. It is the most common microdeletion, with a prevalence of 1 case in 3000 to 6000 births. Inheritance is autosomal dominant—offspring of affected individuals have a 50-percent chance of inheriting the syndrome. However, more than 90 percent of cases arise from a de-novo mutation. The full deletion contains 3 million base pairs, encompasses 40 genes, and includes 180 different features (Shprintzen, 2008). This is emblematic of a contiguous gene syndrome and poses counseling challenges because features can vary widely, even among family members. With prenatal diagnosis of an affected fetus, genetic testing is offered to the pregnant patient and her partner.

Approximately 75 percent of affected individuals have an associated conotruncal cardiac anomaly, such as tetralogy of Fallot, truncus arteriosus, interrupted aortic arch, or ventricular septal defect (McDonald-McGinn, 2015). Immune deficiency, such as T-cell lymphopenia, also develops in 75 percent. More than 70 percent have velopharyngeal insufficiency or cleft palate. Characteristic facial features include short palpebral fissures, bulbous nasal tip, micrognathia, short philtrum, and small or posteriorly rotated ears. Learning disabilities, autism spectrum disorder, and intellectual disability also are common. Other manifestations include hypocalcemia, renal anomalies, esophageal dysmotility, hearing loss, behavioral disorders, and psychiatric illness, particularly schizophrenia.

Chromosomal Translocations

These are DNA rearrangements in which a DNA segment breaks away from one chromosome and attaches to another. The rearranged chromosomes are called derivative (der) chromosomes. The two types are reciprocal and robertsonian translocations.

Reciprocal Translocations. A double-segment or reciprocal translocation results when breaks occur in two different chromosomes and the broken fragments are exchanged. Each affected chromosome receives a fragment of the other. If no chromosomal material is gained or lost, the translocation is considered balanced. The prevalence of reciprocal translocations approximates 1 in 600 births.

The carrier of a balanced translocation will usually have a normal phenotype. However, repositioning of specific genes within chromosomal segments may cause major structural or developmental abnormalities in approximately 6 percent of apparently balanced translocation carriers. Using CMA technology, up to 20 percent of individuals who appear to have a balanced translocation are found instead to have missing or redundant DNA segments (Manning, 2010).

Balanced translocation carriers are at risk to produce unbalanced gametes, resulting in abnormal offspring. As shown in Figure 16-7, if an oocyte or sperm contains a translocated chromosome, fertilization results in an unbalanced translocation—monosomy for part of one affected chromosome and trisomy for part of the other. In general, translocation carriers identified after the birth of an abnormal child have a 5- to 30-percent risk of producing liveborn offspring with an unbalanced translocation. Carriers identified for other reasons, for example, during an infertility evaluation, have only a 5-percent risk. This risk is lower because gametes are so abnormal that conceptions are nonviable.

Robertsonian Translocations. These involve only the *acrocentric* chromosomes—13, 14, 15, 21, and 22. Acrocentric

TABLE 16-2. Selected Microdeletion Syndromes

Syndrome	Prevalence	Location	Features
Alagille	1:70,000	20p12.2	Cholestasis (paucity of intrahepatic bile ducts), cardiac disease, skeletal disease, ocular abnormalities, dysmorphic facies
Angelman	1:12,000 to 1:20,000	15q11.2–q13 (maternal genes)	Dysmorphic facies—"happy puppet" appearance, intellectual disability, ataxia, hypotonia, seizures
Cri-du-chat	1:20,000 to 1:50,000	5p15.2–15.3	Abnormal laryngeal development with "cat-like" cry, hypotonia, intellectual disability
Kallmann syndrome	1:30,000 males	Xp22.3	Hypogonadotropic hypogonadism, anosmia
Langer-Giedion	Rare	8q23.3	Trichorhinophalangeal syndrome, dysmorphic facies, skeletal abnormalities, sparse hair
Miller-Dieker	Rare	17p13.3	Neuronal migration abnormalities with lissencephaly and microcephaly (profound impairment), dysmorphic facies
Prader-Willi	1:10,000 to 1:30,000	15q11.2–q13 (paternal genes)	Obesity, hypotonia, hypogonadotropic hypogonadism, small hands and feet, intellectual disability
Retinoblastoma	1:280,000	13q14.2	Retinoblastoma, retinoma (benign neoplasm), non-retinal (second primary) tumors
Rubenstein-Taybi	1:100,000 to 1:125,000	16p13.3	Dysmorphic facies, broad thumbs and toes, intellectual disability, increased tumor risk
Smith-Magenis	1:15,000 to 1:25,000	17p11.2	Dysmorphic facies, speech delay, hearing loss, sleep disturbances, self-destructive behaviors, intellectual disability
Velocardiofacial syndrome	1:3000 to 1:6000	22q11.2	Conotruncal cardiac defects, cleft palate, velopharyngeal incompetence, thymic and parathyroid abnormalities, intellectual disability
WAGR	1:500,000	11p13	Wilms tumor, aniridia, genitourinary anomalies. intellectual disability (mental retardation)
Williams-Beuren	1:7500 to 1:10,000	7q11.23	Dysmorphic facies, dental malformation, aortic and peripheral pulmonary artery stenosis, intellectual disability
Wolf-Hirschhorn	1:20,000 to 1:50,000	4p16.3	Dysmorphic ("Greek helmet") facies, delayed growth and development, cleft lip/palate, coloboma, cardiac septal defects
X-linked ichthyosis	1:6000	Xp22.3	Steroid sulfatase deficiency, corneal opacities

Prevalence reflects live births.
Data from National Library of Medicine, 2021; Johns Hopkins University, 2021.

chromosomes have extremely short p arms, and the p arms contain redundant copies of genes coding for ribosomal RNA. In a robertsonian translocation, the q arms of two acrocentric chromosomes fuse at one centromere to form a derivative chromosome, and the other centromere and both p arms are lost. The lost DNA is present in multiple copies on other acrocentric chromosomes, and thus the translocation carrier is usually phenotypically normal. Because the number of centromeres determines the chromosome count, a robertsonian translocation carrier has only 45 chromosomes.

Balanced robertsonian carriers have reproductive difficulties. During fertilization, if the derivative chromosome pairs with a normal haploid chromosome, the resulting offspring will have trisomy. If the fused chromosomes are homologous, that is, from the same chromosome pair, the carrier can produce only unbalanced gametes. Each egg or sperm contains either both copies of the translocated chromosome, which would result in trisomy if fertilized, or no copy, which would result in monosomy. If the fused chromosomes are nonhomologous, four of the six possible gametes would be abnormal.

Robertsonian translocations are found in 1 in 1000 individuals. The risk to have an abnormal offspring approximates 15 percent if a robertsonian translocation is carried by the mother and 2 percent if carried by the father. However, robertsonian translocations are not a major cause of miscarriage and are identified in fewer than 5 percent of couples evaluated for recurrent pregnancy loss. If a fetus or child is found to have a translocation trisomy, both parents should be offered karyotype analysis. If neither parent is a carrier, the recurrence risk is extremely low. The most common robertsonian translocation

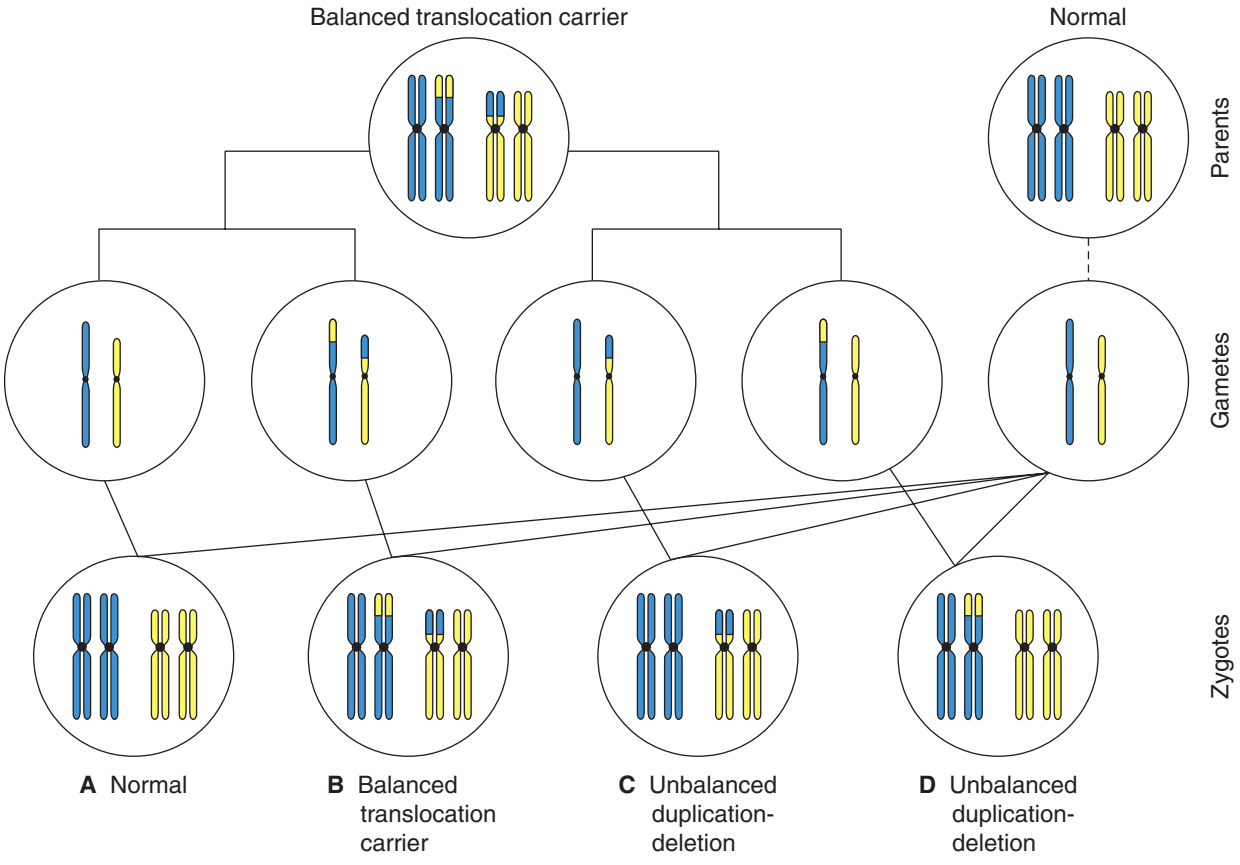

FIGURE 16-7 A carrier of a balanced translocation may produce offspring who are also carriers of the balanced rearrangement **(B)**, offspring with unbalanced translocations **(C, D)**, or offspring with normal chromosomal complements **(A)**.

is der(13;14)(q10;q10), which accounts for up to 20 percent of cases of Patau syndrome (p. 313).

Isochromosomes

When either two p arms or two q arms from the same chromosome fuse together, an isochromosome results. This may occur if the centromere breaks transversely instead of longitudinally during meiosis II or mitosis. Alternately, an isochromosome can result from a meiotic error in a chromosome with a robertsonian translocation. If the isochromosome is acrocentric, it is composed of two q arms and will behave like a homologous robertsonian translocation. Such a carrier is phenotypically normal but can produce only abnormal, unbalanced gametes. If the isochromosome is nonacrocentric, it may be composed of either two p arms or two q arms. Functionally this results in trisomy of the genes on the arms that are present and monosomy of the genes on the arms that are lost. Thus, the carrier is usually phenotypically abnormal and produces abnormal gametes. The most common isochromosome involves the long arm of the X chromosome, i(Xq), which is the etiology of 15 percent of cases of Turner syndrome.

Chromosomal Inversions

When the same chromosome breaks in two places, the intervening genetic material may invert before the breaks are repaired. Although no genetic material is lost or duplicated, an inversion may alter gene function. There are two types—pericentric and paracentric inversions.

Pericentric Inversion. This results from breaks in both the p and q arms of a chromosome, such that the inverted material spans the centromere (Fig. 16-8). A pericentric inversion causes problems in chromosomal alignment during meiosis and confers significant risk for the carrier to produce abnormal gametes and abnormal offspring. The observed risk of abnormal offspring is 5 to 10 percent if ascertainment is made after the birth of an abnormal child. The risk is only 1 to 3 percent if prompted by another indication. An important exception is inv(9)(p11q12), a pericentric inversion on chromosome 9 that is a normal variant and present in approximately 1 percent of the population.

Paracentric Inversion. If one arm of a chromosome suffers the two breaks, the inverted material does not include the centromere, and the inversion is paracentric (see Fig. 16-8). The carrier makes either normal balanced gametes or gametes that are so abnormal as to preclude fertilization. Thus, although infertility may be a problem, the risk of having an abnormal offspring is extremely low.

Ring Chromosome

If a deletion occurs at each end of the same chromosome, the ends may come together to form a ring chromosome. The telomere regions at the ends of each chromosome contain redundant nucleoprotein complexes that stabilize the chromosome. If only the telomeres are lost, all necessary genetic material is retained, and the carrier is balanced. If a deletion extends more

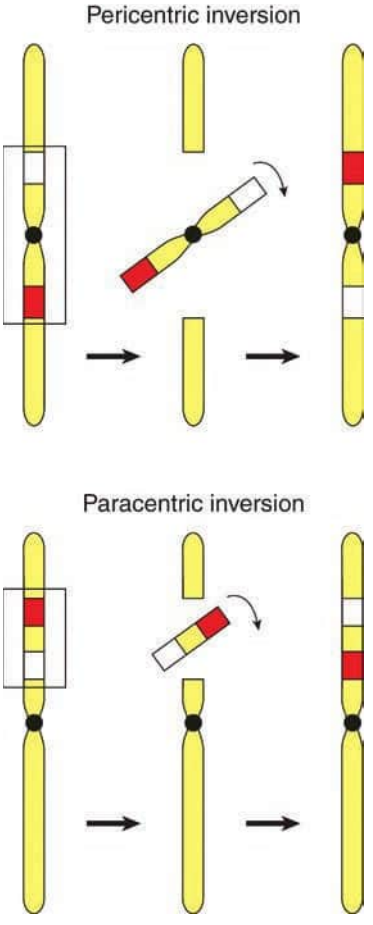

FIGURE 16-8 Pericentric inversion involves the centromere, whereas paracentric inversion does not. Individuals with pericentric inversions are at risk to have offspring with a duplication/deletion. Those with paracentric inversions are at increased risk for early pregnancy loss.

proximally than the telomere, the carrier is likely to be phenotypically abnormal. An example of this is the ring X chromosome, which may result in Turner syndrome.

■ Mosaicism

A mosaic individual has two or more cytogenetically distinct cell lines that are derived from a single zygote. Phenotypic expression of mosaicism depends on several factors, including whether the cytogenetically abnormal cells involve the fetus, part of the fetus, just the placenta, or some combination. Mosaicism is found in approximately 0.3 percent of amnionic fluid cultures (Carey, 2014). When abnormal cells are present in only a single flask of amnionic fluid, the finding is likely pseudomosaicism, caused by cell-culture artifact (Bui, 1984; Hsu, 1984). When abnormal cells involve multiple cultures, however, true mosaicism is more likely. Further testing verifies a second cell line in 60 to 70 percent of these fetuses (Hsu, 1984; Worton, 1984).

Confined Placental Mosaicism

Mosaicism involving a gene abnormality is detected in 1 to 2 percent of chorionic villus sampling specimens. Amniocentesis should be offered. In a series of more than 1000 pregnancies with mosaicism at chorionic villus sampling, subsequent amniocentesis identified true fetal mosaicism in 13 percent. Confined placental mosaicism accounted for 85 percent of cases, and uniparental disomy, discussed later (p. 322), was found in 2 percent (Malvestiti, 2015). If mosaicism is detected for a chromosome known to contain imprinted genes—such as chromosomes 6, 7, 11, 14, or 15—testing for uniparental disomy should be considered, as there may be fetal consequences (Grati, 2014a).

Although outcomes with confined placental mosaicism are generally good, risks of fetal-growth restriction and stillbirth are higher (Reddy, 2009). Fetal-growth restriction may stem from impaired functioning of the aneuploid placental cells (Baffero, 2012). In a recent series of 5500 pregnancies undergoing chorionic villus sampling, the preterm birth rate in pregnancies with confined placental mosaicism was 45 percent, and 50 percent of affected newborns were small for gestational age (Toutain, 2018). Placental mosaicism for trisomy 16 confers a particularly poor prognosis, with as few as 1 in 3 pregnancies resulting in normal outcome (Grau Madsen, 2018).

Gonadal Mosaicism

Also called germline mosaicism, this refers to having one cell line in gametes and another in somatic cells. A genetic abnormality that is confined to gamete cells will affect all cells in the offspring. Thus, gonadal mosaicism can account for apparently de-novo diseases in the offspring of normal parents. Because spermatogonia and oogonia divide throughout fetal life, and spermatogonia continue to divide throughout adulthood, a meiotic error can occur in germ cells that were previously normal. New mutations identified in an offspring whose father is older than 40 may arise through this mechanism, as discussed later (p. 319) (Wilkie, 2017). Gonadal mosaicism also explains the 6-percent recurrence risk after the birth of a child with a disease caused by a "new" mutation.

MODES OF INHERITANCE

A monogenic or *mendelian* disorder is caused by a mutation or alteration in a single locus or gene in one or both members of a gene pair. Types of mendelian inheritance include autosomal dominant, autosomal recessive, X-linked, and Y-linked (Table 16-3). Other monogenic inheritance patterns include mitochondrial inheritance, uniparental disomy, imprinting, and trinucleotide repeat expansion.

■ Relationship between Phenotype and Genotype

When considering inheritance, it is the phenotype that is dominant or recessive, not the genotype. If a disease is dominant, a normal gene directs the production of normal protein, but the phenotype will be abnormal because of protein produced by the abnormal gene. A heterozygous carrier of a recessive disease may produce detectable levels of an abnormal gene product but have no features of the condition, because the phenotype is directed by the product of the normal co-gene. For example,

TABLE 16-3. Selected Monogenic (Mendelian) Disorders

Autosomal Dominant
Achondroplasia
Acute intermittent porphyria
Adult polycystic kidney disease
Antithrombin III deficiency
BRCA1 and BRCA2 breast and/or ovarian cancer
Ehlers-Danlos syndrome
Familial adenomatous polyposis
Familial hypercholesterolemia
Hereditary hemorrhagic telangiectasia
Hereditary spherocytosis
Huntington disease
Hypertrophic obstructive cardiomyopathy
Long QT syndrome
Marfan syndrome
Myotonic dystrophy
Neurofibromatosis type 1 and 2
Tuberous sclerosis
von Willebrand disease
Autosomal Recessive
α_1-Antitrypsin deficiency
Congenital adrenal hyperplasia
Cystic fibrosis
Gaucher disease
Hemochromatosis
Homocystinuria
Phenylketonuria
Sickle-cell anemia
Tay-Sachs disease
Thalassemia syndromes
Wilson disease
X-Linked
Androgen insensitivity syndrome
Chronic granulomatous disease
Color blindness
Fabry disease
Fragile X syndrome
Glucose-6-phosphate deficiency
Hemophilia A and B
Hypophosphatemic rickets
Muscular dystrophy—Duchenne and Becker
Ocular albinism type 1 and 2

erythrocytes from carriers of sickle-cell anemia contain approximately 30 percent hemoglobin S, but because the other 70 percent is hemoglobin A, these cells do not usually sickle in vivo.

Heterogeneity

Genetic heterogeneity explains how different genetic mechanisms may result in the same phenotype. *Locus heterogeneity* indicates that a specific disease phenotype can be caused by mutations in different genetic loci. It also explains why some diseases appear to follow more than one type of inheritance. For example, retinitis pigmentosa may develop following mutations in at least 35 different genes or loci and may result in autosomal dominant, autosomal recessive, or X-linked forms. *Allelic heterogeneity* describes how different mutations of the same gene may affect presentation of a particular disease. For example, although only one gene has been associated with cystic fibrosis—the *cystic fibrosis conductance transmembrane regulator* gene—more than 2000 mutations in this gene have been described and result in variable disease severity (Chaps. 17, p. 342 and 54, p. 968). *Phenotypic heterogeneity* explains how different disease states can arise from different mutations in the same gene. As an example, mutations in the *fibroblast growth factor receptor 3 (FGFR3)* gene may result in several different skeletal disorders, including achondroplasia and thanatophoric dysplasia, both of which are discussed in Chapter 15 (p. 302).

Autosomal Dominant Inheritance

If only one copy of a gene pair determines the phenotype, that gene is considered to be dominant. Carriers have a 50-percent chance of passing on the affected gene with each conception. A gene with a dominant mutation generally specifies the phenotype in preference to the normal gene. That said, not all individuals will necessarily manifest an autosomal dominant condition the same way. Factors that affect the phenotype of an autosomal dominant condition include penetrance, expressivity, and presence of codominant genes.

Penetrance

This characteristic describes whether a dominant gene is expressed. A gene with recognizable phenotypic expression in all individuals has complete penetrance. Penetrance is incomplete if some carriers express the gene but others do not. A gene that is expressed in 80 percent of individuals is 80-percent penetrant. Incomplete penetrance explains why some autosomal dominant diseases may appear to "skip" generations.

Expressivity

Individuals with the same autosomal dominant trait may manifest the condition differently, even within the same family. Genes with variable expressivity can produce disease manifestations that range from mild to severe. Examples include neurofibromatosis, tuberous sclerosis, and adult polycystic kidney disease.

Codominant Genes

If two different alleles in a gene pair are both expressed in the phenotype, they are considered to be codominant. Blood type, for example, is determined by expression of dominant A and B red-cell antigens that can be expressed simultaneously. Another example of codominance is the group of genes responsible for hemoglobin production. If one gene directs production of hemoglobin S and the other directs production of hemoglobin C, that individual will produce both S and C hemoglobin (Chap. 59, p. 1053).

Advanced Paternal Age

Paternal age older than 40 is associated with increased risk for spontaneous genetic mutations. Spermatogonia undergo

mitotic division every 16 days, and the many replications raise the risk for single base-pair mutations. As a result, offspring of older fathers are at risk for new autosomal dominant disorders and X-linked carrier states. Several in particular have been termed *paternal age effect* disorders (Goriely 2012). These include mutations in the *fibroblast growth factor receptor 2 (FGFR2)* gene, which may cause craniosynostosis syndromes such as Apert, Crouzon, and Pfeiffer syndromes; mutations in the *FGFR3* gene, which may result in achondroplasia and thanatophoric dysplasia; and mutations in the *RET proto-oncogene,* which may cause multiple endocrine neoplasia syndromes (Toriello, 2008).

Using whole genome sequencing to study SNPs among offspring of older fathers, Kong and associates (2012) found an increase of approximately two mutations for each year of paternal age past 40. The absolute risk for any specific condition is low, because individual autosomal dominant disorders are uncommon. Thus, no screening or testing is specifically recommended.

Autosomal Recessive Inheritance

Recessive diseases develop only when both gene copies are abnormal. Unless carriers are screened for a specific disease, they usually are recognized only after the birth of an affected child or the diagnosis of an affected family member. If a couple has a child with an autosomal recessive disease, the recurrence risk is 25 percent for each subsequent pregnancy. Thus, 1/4 of offspring will be homozygous normal, 2/4 will be heterozygous carriers, and 1/4 will be homozygous abnormal. In other words, three of four children will be phenotypically normal, and 2/3 of phenotypically normal siblings are actually carriers.

A heterozygous carrier of a recessive condition is only at risk to have affected children if her or his partner is heterozygous or homozygous for the disease. Genes for rare autosomal recessive conditions have low prevalence in the general population. Thus, the likelihood that a partner will be a gene carrier is small, unless there is consanguinity or the partner is a member of an at-risk group. Carrier screening is discussed in Chapter 17 (p. 342). Preimplantation genetic testing allows a blastocyst to be genetically evaluated prior to intrauterine transfer during in vitro fertilization and is described also in Chapter 17 (p. 348).

Inborn Errors of Metabolism

Most of these autosomal recessive diseases result from absence of a crucial enzyme, leading to incomplete metabolism of proteins, lipids, or carbohydrates. The metabolic intermediates that build up are toxic to various tissues and may result in intellectual disability or other abnormalities.

Phenylketonuria. Also known as phenylalanine hydroxylase (PAH) deficiency, this autosomal recessive disease is caused by mutations in the *PAH* gene. PAH metabolizes phenylalanine to tyrosine, and homozygotes have diminished or absent enzyme activity. This leads to abnormally high levels of phenylalanine, which results in progressive intellectual impairment, autism, seizures, motor deficits, and neuropsychological abnormalities (Blau, 2010). Because phenylalanine competitively inhibits tyrosine hydroxylase, which is essential for melanin production, affected individuals also have hair, eye, and skin hypopigmentation. More than 600 *PAH* gene mutations have been characterized, and the carrier frequency varies by ethnicity. For those of Northern European origin, carrier frequency is 1 in 50, such that the disease affects up to 1 in 10,000 newborns (American College of Obstetricians and Gynecologists, 2020b). Prompt diagnosis and restriction of dietary phenylalanine beginning early in infancy are essential to prevent neurological damage. All states mandate newborn screening for phenylketonuria (PKU).

Phenylalanine restriction alone would result in inadequate protein consumption, and phenylalanine-free amino acid–based supplementation is required. Maintenance of phenylalanine concentrations in the range of 2 to 6 mg/dL (120 to 360 μmol/L) is recommended from at least 3 months prior to pregnancy and continuing throughout pregnancy (American College of Obstetricians and Gynecologists, 2020b).

Unfortunately, phenylalanine is actively transported to the fetus. Women with PKU whose phenylalanine levels remain above the recommended range during pregnancy are at risk to have otherwise normal (heterozygous) offspring who sustain significant in utero damage as a result of being exposed to toxic phenylalanine concentrations. Hyperphenylalaninemia raises the risk for miscarriage and for PKU embryopathy, which is characterized by intellectual disability, microcephaly, seizures, growth impairment, and cardiac anomalies. Among women on unrestricted diets, the risk to have a child with intellectual disability exceeds 90 percent, microcephaly develops in more than 70 percent, and as many as 1 in 6 children have cardiac defects. The Maternal Phenylketonuria Collaborative Study, which included 572 pregnancies followed more than 18 years, reported that maintenance of serum phenylalanine levels in the recommended range significantly reduced the fetal abnormality risk and resulted in normal childhood IQ scores (Koch, 2003; Platt, 2000).

Approximately 25 to 50 percent of individuals with PKU experience a significant decline in phenylalanine levels when treated with the synthetic PAH cofactor tetrahydrobiopterin (sapropterin) (Vockley, 2014). Based on registry data, sapropterin is considered a treatment option for those in whom phenylalanine levels remain elevated despite dietary therapy (Grange, 2014). Preconceptional counseling and consultation with providers from experienced PKU centers is recommended.

Consanguinity

In medical genetics, a union is consanguineous if between second cousins or closer relatives. Although uncommon in Western countries, the global estimate of consanguineous parentage approximates 10 percent of the population (Oniya, 2019). More than 1 billion people are estimated to live in countries in which 20 to 50 percent of marriages are consanguineous (Romeo, 2014). First-degree relatives share half of their genes, second-degree relatives share a fourth, and third-degree relatives—first cousins—share one eighth. Because of the potential for shared deleterious genes, consanguinity confers an increased risk to have offspring with otherwise rare autosomal recessive diseases or multifactorial disorders. In population-based

series, first cousins have *twice* the risk for offspring with congenital abnormalities (Sheridan, 2013; Stoltenberg, 1997). Consanguinity is also associated with a greater rate of stillbirth (Kapurubandara, 2016). Because CMA performed using a SNP platform may identify consanguinity, it is important that preprocedural counseling include this possibility.

Incest is defined as a sexual relationship between first-degree relatives such as parent-child or brother-sister and is universally illegal. Progeny of such unions carry the highest risk of abnormal outcomes. Older studies reported that up to 40 percent of offspring were abnormal as a result of recessive and multifactorial disorders (Baird, 1982; Freire-Maia, 1984).

X-Linked and Y-Linked Inheritance

Most X-linked diseases are recessive. Common examples include color blindness, hemophilia A and B, and Duchenne and Becker muscular dystrophy. A male with an X-linked recessive gene is usually affected by the disease it causes, because he lacks a second X chromosome to express the normal dominant gene. However, a male with an X-linked disease cannot have affected sons because they do not receive his X chromosome. When a woman carries a gene causing an X-linked recessive condition, each son has a 50-percent risk of being affected, and each daughter has a 50-percent chance of being a carrier.

Women with an X-linked recessive gene are generally unaffected by the disease it causes. In some cases, however, the random inactivation of one X chromosome in each cell—termed lyonization—is skewed, and female carriers may have features of the condition. For example, approximately 10 percent of female carriers of hemophilia A will have factor VIII levels less than 30 percent of normal, and a similar proportion of female hemophilia B carriers have factor IX levels less than 30 percent. Levels below these thresholds confer a greater risk for abnormal bleeding when affected women give birth (Plug, 2006). Indeed, even with higher levels, carriers are reported to be at increased risk for bleeding complications (Olsson, 2014). Female carriers of Duchenne or Becker muscular dystrophy carry an elevated risk for cardiomyopathy, and periodic evaluation for cardiac dysfunction and neuromuscular disorders is recommended (American Academy of Pediatrics, 2008).

X-linked dominant disorders mainly affect females, because they tend to be lethal in males. Two examples are vitamin D–resistant rickets and incontinentia pigmenti. An important exception is fragile X syndrome, discussed subsequently.

The prevalence of Y-linked disorders is low. The Y-chromosome carries genes important for sex determination and various cellular functions related to spermatogenesis and bone development. Deletion of genes on the long arm of Y results in severe spermatogenic defects, whereas genes at the tip of the short arm are critical for chromosomal pairing during meiosis and for fertility.

Mitochondrial Inheritance

Human cells contain hundreds of mitochondria, each with its own genome and associated replication system. Oocytes have approximately 100,000 mitochondria. Sperm have only about 100, and the latter are destroyed after fertilization. Each mitochondrion has multiple copies of a 16.5-kb circular DNA molecule that contains 37 genes. Mitochondrial DNA encodes peptides required for oxidative phosphorylation and encodes ribosomal and transfer RNAs.

Mitochondria are inherited exclusively from the mother. Thus, although males and females both can be affected by a mitochondrial disorder, a male cannot transmit the condition to his offspring. When a cell replicates, mitochondrial DNA sorts randomly into each of the resulting cells, a process termed replicative segregation. As a consequence of replicative segregation, any mitochondrial mutation will be propagated randomly into the newly formed cells. Because each cell holds multiple copies of mitochondrial DNA, the mitochondrion may contain only normal or only abnormal DNA, termed *homoplasmy.* Alternatively, it may contain both normal and mutated DNA, namely *heteroplasmy*. If a heteroplasmic oocyte is fertilized, the relative proportion of mutated DNA may affect whether the individual manifests a given mitochondrial disease. It is not possible to predict the potential degree of heteroplasmy among offspring, and this poses challenges for genetic counseling.

There are 33 mitochondrial diseases or conditions with known molecular bases (Johns Hopkins University, 2020). Examples include myoclonic epilepsy with ragged red fibers (MERRF), Leber optic atrophy, Kearns-Sayre syndrome, Leigh syndrome, and several forms of mitochondrial myopathy and cardiomyopathy.

DNA Triplet Repeat Expansion

Mendel's first law is that genes are passed unchanged from parent to progeny, and barring new mutations, this is often true. Certain genes, however, contain a region of DNA trinucleotide repeats that can expand during parent-to-child transmission. The expansion can occur during male meiosis, as in Huntington disease, or during female meiosis, as in fragile X syndrome. Clinically, DNA triplet repeat expansion is manifested by *anticipation*—a phenomenon in which a disease may manifest at an earlier age or become more severe with each successive generation. Examples of DNA triplet repeat diseases are shown in Table 16-4.

Fragile X Syndrome

This is the most common inherited intellectual disability. Fragile X syndrome affects approximately 1 in 3600 males and 1 in

TABLE 16-4. Some Disorders Caused by DNA Triplet Repeat Expansion

Dentatorubral-pallidoluysian atrophy
Fragile X syndrome
Friedreich ataxia
Huntington disease
Spinal and bulbar muscular atrophy
Myotonic dystrophies
Spinocerebellar ataxias

4000 to 6000 females (American College of Obstetricians and Gynecologists, 2020a). It is caused by expansion of a repeated trinucleotide DNA segment—cytosine-guanine-guanine (CGG)—at chromosome Xq27.3. When the CGG repeat number reaches a critical size—the full mutation—the *fragile X mental retardation 1 (FMR1)* gene becomes methylated and inactivated. Inactivation halts expression of the FMR1 protein, which is abundant in nerve cells and necessary for normal cognitive development.

Individuals with fragile X syndrome may have speech and language problems, attention-deficit/hyperactivity disorder, and autism or autistic-like behaviors. Intellectual disability is generally more severe in males, in whom average IQ scores are 35 to 45 (Nelson, 1995). The syndrome has characteristic phenotypic features—a narrow face with large jaw, prominent ears, connective tissue abnormalities, and macroorchidism in postpubertal males.

Both the sex of the affected individual and the number of CGG repeats determine the degree of clinical impairment. Clinically, four groups have been described (American College of Obstetricians and Gynecologists, 2020a):

- Full mutation—more than 200 repeats
- Premutation—55 to 200 repeats
- Intermediate—45 to 54 repeats
- Unaffected—fewer than 45 repeats.

Full mutations are expressed in all males and many females. Males with full mutations typically have significant cognitive and behavioral abnormalities and phenotypic features. In females, random X chromosome inactivation results in variable expression, and the disability may be much less severe. With rare exception, the parent of origin of repeat expansion that leads to a full mutation is female (Monaghan, 2013).

Counseling for a premutation is more complex. The woman with a fragile X premutation may have offspring with the full mutation, and the risk ranges from ≤5 percent with fewer than 70 CGG repeats to >95 percent with 100 to 200 CGG repeats (Nolin, 2003). Expansion is extremely unlikely in a male premutation carrier, but all of his daughters will carry the premutation. Among women with no risk factors, approximately 1 in 250 carries a fragile X premutation, and in those with a family history of intellectual disability, the risk approximates 1 in 90 (Cronister, 2008).

Fragile X premutation carriers may themselves experience significant health consequences. Males with a premutation are at risk for the fragile X tremor ataxia syndrome (FXTAS), which is characterized by memory loss, executive function deficits, anxiety, and dementia (Monaghan, 2013). Females are at decreased risk for FXTAS, but they have a 20-percent risk for fragile X-associated primary ovarian insufficiency (POI).

Carrier screening is recommended for women with a family history of fragile X syndrome, for those with unexplained intellectual disability, developmental delay, or autism, and for women with POI (American College of Obstetricians and Gynecologists, 2020a). Prenatal diagnosis can be accomplished by amniocentesis or chorionic villus sampling. Either type of specimen can be used to evaluate the CGG repeat number, but chorionic villus sampling may not accurately determine *FMR1* gene methylation status.

Imprinting

Usually, one copy of each gene is inherited from each parent, and both copies are expressed. Imprinting refers to the situation in which gene expression varies according to the parent of origin. With *maternal imprinting*, a gene inherited from the mother is transcriptionally silent and the gene inherited from the father is active. *Paternal imprinting* is the opposite. This phenomenon explains the phenotypic differences that occur in triploid pregnancies according to whether the extra chromosomal set is maternal or paternal (p. 313).

Imprinting affects gene expression by epigenetic control, that is, it modifies the phenotype without altering the underlying genetic structure or genotype. Importantly, the effect may be reversed in a subsequent generation, because a female who inherits an imprinted gene from her father will pass it in her oocytes with a maternal—rather than paternal—imprint, and vice versa.

An example of imprinting can be found in two very different diseases associated with the same region of DNA. *Prader-Willi syndrome* is characterized by pronounced hyperphagia with obesity, along with short stature, small hands and feet, and mild mental retardation. In more than 70 percent of cases, Prader-Willi is caused by microdeletion or disruption of a DNA segment on the paternal chromosome 15, 15q11.2-q13. The remaining cases are due to maternal uniparental disomy or due to maternal gene imprinting with the paternal gene inactivated.

In contrast, individuals with *Angelman syndrome* have normal stature and weight but severe intellectual disability, absent speech, seizures, ataxia, jerky arm movements, and paroxysms of inappropriate laughter. In approximately 70 percent of cases, Angelman syndrome is caused by microdeletion for the 15q11.2-q13 DNA segment on the mother's chromosome 15. This segment contains a gene that codes for *ubiquitin protein ligase E3A*, an important neural protein. Paternal gene imprinting defects—with maternal genes inactivated—account for 2 to 3 percent, and 2 percent result from paternal uniparental disomy. Table 16-5 lists selected diseases that can involve imprinting.

Uniparental Disomy

This occurs when both members of a chromosome pair are inherited from the same parent. Uniparental disomy usually

TABLE 16-5. Some Disorders That Can Involve Imprinting

Disorder	Chromosomal Region	Parental Origin
Angelman	15q11.2–q13	Maternal
Beckwith-Wiedemann	11p15.5	Paternal
Myoclonus-dystonia	7q21	Maternal
Prader-Willi	15q11.2–q13	Paternal
Pseudohypoparathyroidism	20q13.2	Variable
Russell-Silver syndrome	7p11.2	Maternal

Data from Johns Hopkins University, 2021.

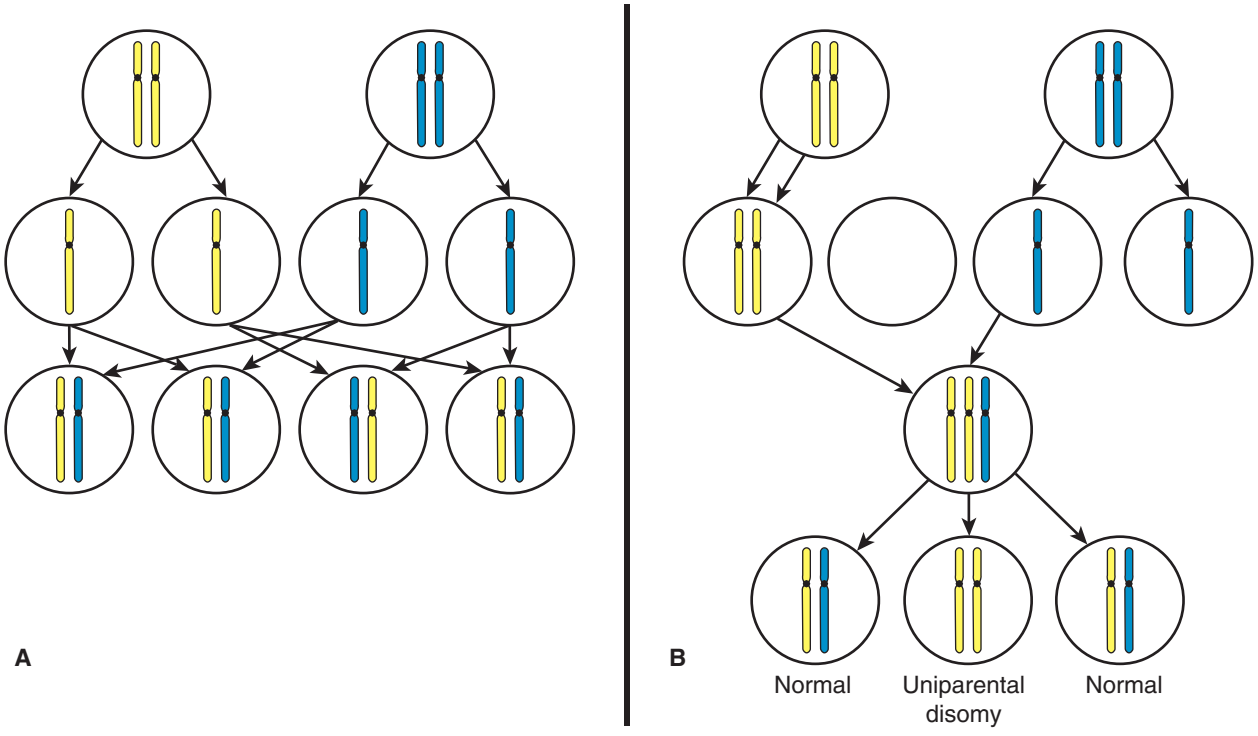

FIGURE 16-9 Mechanism of uniparental disomy arising from trisomic "rescue." **A.** In normal meiosis, one member of each pair of homologous chromosomes is inherited from each parent. **B.** If nondisjunction results in a trisomic conceptus, one homologue is sometimes lost. In a third of cases, loss of one homologue leads to uniparental disomy.

has no clinical consequences, because gene expression is not generally affected by the parent of origin and because both copies of a chromosome pair are not usually identical. However, if chromosomes 6, 7, 11, 14, or 15 are involved, offspring are at increased risk for an abnormality because of parent-of-origin differences in gene expression, that is, because of imprinting (Shaffer, 2001). Several genetic mechanisms may cause uniparental disomy, the most common of which is trisomic rescue, shown in Figure 16-9. After a nondisjunction event produces a trisomic conceptus, one of the three homologues may be lost, resulting in uniparental disomy for that chromosome in approximately one third of cases.

Uniparental *isodisomy* occurs when an individual receives two identical copies of one chromosome from the same parent. This mechanism has explained cases of cystic fibrosis in which only one parent is a carrier but the fetus inherits two copies of the same gene mutation (Spence, 1988; Spotila, 1992).

Multifactorial Inheritance

Traits or diseases that are determined by the combination of multiple genes and environmental factors are considered to have multifactorial inheritance (Table 16-6). Polygenic traits are determined by the combined effects of more than one gene. Many congenital and acquired conditions and common traits display multifactorial inheritance. Examples include malformations such as neural-tube defects, cardiac defects, and facial clefts; diseases such as diabetes and atherosclerosis; and traits such as head size or height. Multifactorial abnormalities tend to recur in families, but not according to a mendelian pattern. If a couple has had 1 child with a multifactorial birth defect, the risk that another child will be affected is empirically 3 to 5 percent. This risk declines exponentially with successively more distant family relationships.

Multifactorial traits that have a normal distribution in the population are termed continuously variable. A measurement that is more than two standard deviations above or below the population mean may be considered abnormal. Continuously variable traits tend to be less extreme in the offspring of affected individuals, because of the statistical principle of regression to the mean.

TABLE 16-6. Characteristics of Multifactorial Diseases

There is a genetic contribution
No mendelian pattern of inheritance
No evidence of single-gene disorder
Nongenetic factors are also involved in disease causation
Lack of penetrance despite predisposing genotype
Monozygotic twins may be discordant
Familial aggregation may occur
Relatives are more likely to have disease-predisposing alleles
Expression more common among close relatives
Greater concordance in monozygotic than dizygotic twins
Becomes less common in less closely related relatives—fewer predisposing alleles

Adapted from Nussbaum, 2016.

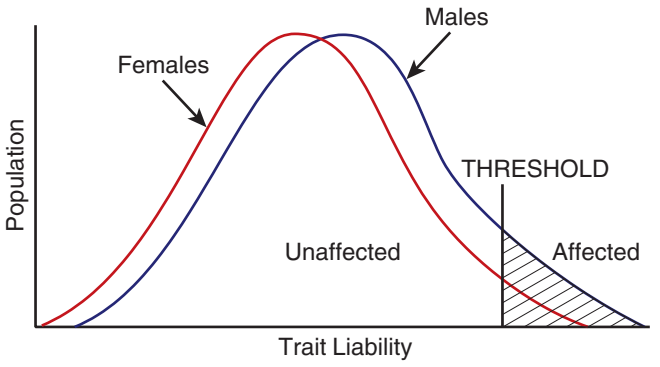

FIGURE 16-10 Schematic example of a threshold trait, such as pyloric stenosis, which has a predilection for males. Each gender is normally distributed, but at the same threshold, more males than females will develop the condition.

Threshold Traits

Some multifactorial traits do not appear until a threshold is exceeded. Genetic and environmental factors that create propensity or liability for the trait are themselves normally distributed, and only individuals at extremes of the distribution exceed the threshold and exhibit the trait or defect. The phenotypic abnormality is thus an all-or-none phenomenon.

Certain threshold traits have a clear male or female predominance. If an individual of the less affected gender has the characteristic or defect, the risk is greater in his or her offspring (Fig. 16-10). An example is pyloric stenosis, which is approximately four times more common in males (Krogh, 2012). A female with pyloric stenosis has likely inherited more predisposing genetic factors than are necessary to produce the defect in a male, and the recurrence risk for her children or siblings is thus higher than the expected 3 to 5 percent. Her brothers and sons would have the highest liability because they not only will inherit more than the usual number of predisposing genes but also are the more susceptible gender.

The recurrence risk for threshold traits is also greater if the defect is severe. For example, the recurrence risk after the birth of a child with bilateral cleft lip and palate approximates 8 percent, but it is only about 4 percent following a child with unilateral cleft lip alone.

Cardiac Defects

Structural cardiac anomalies are the most common birth defects, with a birth prevalence of 8 cases per 1000. The risk of having a child with a cardiac anomaly approximates 5 to 6 percent if the mother has the defect and 2 to 3 percent if the father is affected (Burn, 1998). Selected left-sided lesions, including hypoplastic left heart syndrome, coarctation of the aorta, and bicuspid aortic valve, may have recurrence risks four- to sixfold higher (Lin, 1988; Lupton, 2002; Nora, 1988). Observed recurrence risks for specific cardiac malformations are listed in Table 52-4 (p. 920).

Neural-tube Defects

Risk for developing a neural-tube defect (NTD) is influenced by family history, hyperthermia, hyperglycemia, teratogen exposure, obesity, ethnicity, and fetal gender. More than 50 years ago, Hibbard and Smithells (1965) postulated that abnormal folate metabolism was responsible for many NTDs. However, most NTD cases do not occur in the setting of maternal folic acid deficiency, and it has become clear that the gene-nutrient interactions underlying folate-responsive NTDs are complex. For a woman with a prior affected child, the 3- to 5-percent recurrence risk declines by at least 70 percent with 4 mg/d of periconceptional oral folic acid supplementation (Grosse, 2007; MRC Vitamin Study Research Group, 1991). Periconceptional folic acid supplementation also appears to ameliorate the fetal NTD risk in women with pregestational diabetes and in those with exposure to antiepileptic medications, fever during embryogenesis, and obesity (Kerr, 2017; Petersen, 2019). Sonographic features of NTDs are described in Chapter 15 (p. 276), their prevention with folic acid is discussed in Chapter 9 (p. 168), and fetal therapy for myelomeningocele is reviewed in Chapter 19 (p. 372).

GENETIC TESTS

All pregnant women should have the option of prenatal aneuploidy *screening* and prenatal genetic *diagnosis* (American College of Obstetricians and Gynecologists, 2018). Screening for fetal aneuploidy may be either serum analyte-based or cell-free DNA-based. Prenatal genetic carrier screening tests for cystic fibrosis and spinal muscular atrophy carrier status also are routinely offered. Additional carrier screening tests are offered to at-risk individuals. Expanded genetic carrier screening panels also are available. The American College of Obstetricians and Gynecologists considers ethnic-specific, panethnic, and expanded carrier screening acceptable strategies (American College of Obstetricians and Gynecologists, 2020a). These screening tests are discussed in Chapter 17 (p. 342).

For prenatal genetic diagnosis, the most commonly used tests are chromosomal microarray analysis (CMA), cytogenetic analysis (karyotyping), and fluorescence in situ hybridization (FISH). Testing may be performed on amnionic fluid or chorionic villi. In selected circumstances, whole genome or whole exome sequencing may be considered, but these are not recommended for routine use. To diagnose a specific disease whose genetic basis is known, DNA-based tests are often employed, typically using polymerase chain reaction (PCR) for rapid amplification of DNA sequences.

■ Cytogenetic Analysis

Also known as karyotyping, cytogenetic analysis tests for numerical chromosomal abnormalities—aneuploidy or polyploidy. It can also identify balanced or unbalanced structural rearrangements of at least 5 to 10 megabases in size. Karyotyping has diagnostic accuracy exceeding 99 percent.

Any tissue containing dividing cells or cells that can be stimulated to divide is suitable for cytogenetic analysis. The dividing cells are arrested in metaphase, and their chromosomes are stained to reveal light and dark bands. The most commonly used technique is Giemsa staining, which yields the G-bands shown in Figure 16-3. Each chromosome has a unique banding pattern that permits its identification and detection of

deleted, duplicated, or rearranged segments. The accuracy of cytogenetic analysis rises with the number of bands produced. Metaphase banding routinely yields 450 to 550 visible bands per haploid chromosome set, whereas prophase banding generally yields 850 bands.

Only dividing cells can be evaluated, so the growth of cultured cells affects the rapidity with which results are obtained. Amnionic fluid, which contains amniocytes, epithelial cells, and gastrointestinal mucosal cells, will usually yield results in 7 to 10 days (Chap. 17, p. 344). Fetal blood cells may provide results in 36 to 48 hours but are rarely needed. If fetal skin fibroblasts are evaluated postmortem, stimulation of cell growth can be more difficult. Cytogenetic analysis may take 2 to 3 weeks in such cases and has largely been replaced by CMA (Chap. 35, p. 627).

Fluorescence In Situ Hybridization

This technique is most commonly used for rapid identification of a specific chromosomal abnormality, such as trisomy 21, 18, or 13. Because of its 1- to 2-day turnaround time, FISH is typically selected for cases in which findings may alter pregnancy management. It may also be used to verify a suspected deletion syndrome, such as the 22q11.2 microdeletion (p. 315), although CMA is preferred. The American College of Obstetricians and Gynecologists (2018) recommends that decision-making based on FISH should incorporate clinical information consistent with the suspected diagnosis. Supportive data may be an abnormal aneuploidy screening test result, a sonographic finding, or a confirmatory diagnostic test such as karyotyping or CMA.

To perform FISH, cells are fixed onto a glass slide, and fluorescent-labeled probes are hybridized to the fixed chromosomes (Fig. 16-11). Each probe is a DNA sequence that is complementary to a chromosome region or gene being investigated. If the DNA sequence is present, hybridization is detected as a bright signal visible by microscopy. The number of signals indicates the number of chromosomes or genes of that type in the cell. FISH does not provide information on the entire chromosomal complement but merely the chromosomal or gene region of interest. Figure 16-12 shows an example of interphase FISH using α-satellite probes for chromosomes 18, X, and Y to confirm trisomy 18.

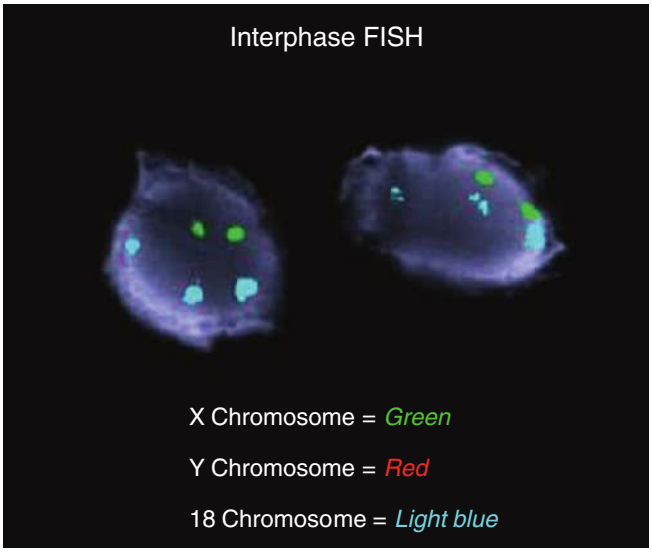

FIGURE 16-12 Interphase fluorescence in situ hybridization (FISH) using α-satellite probes for chromosomes 18, X, and Y. In this case, the three light blue signals, two green signals, and absence of red signals indicate that this is a female fetus with trisomy 18. (Reproduced with permission from Dr. Frederick Elder.)

Chromosomal Microarray Analysis

This test is 100 times more sensitive than karyotyping and detects microduplications and microdeletions as small as 50 to 100 kilobases. Direct CMA, which is performed on uncultured cells, can yield results in 3 to 7 days. If cultured cells are required, results may take 10 to 14 days (American College of Obstetricians and Gynecologists, 2018).

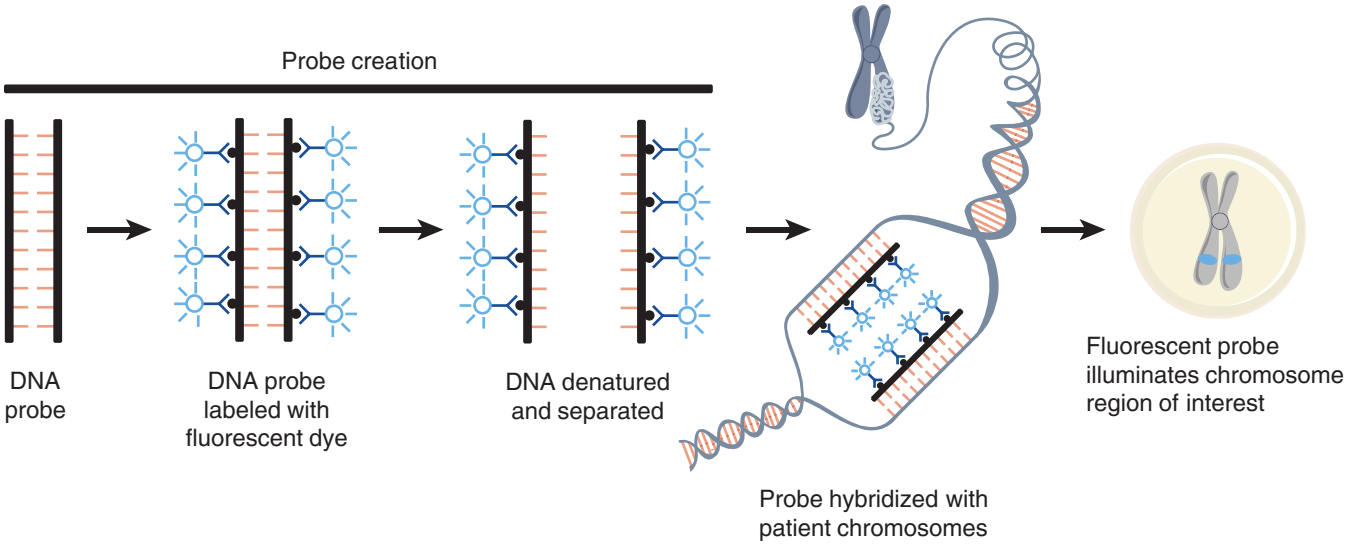

FIGURE 16-11 Steps in fluorescence in situ hybridization (FISH).

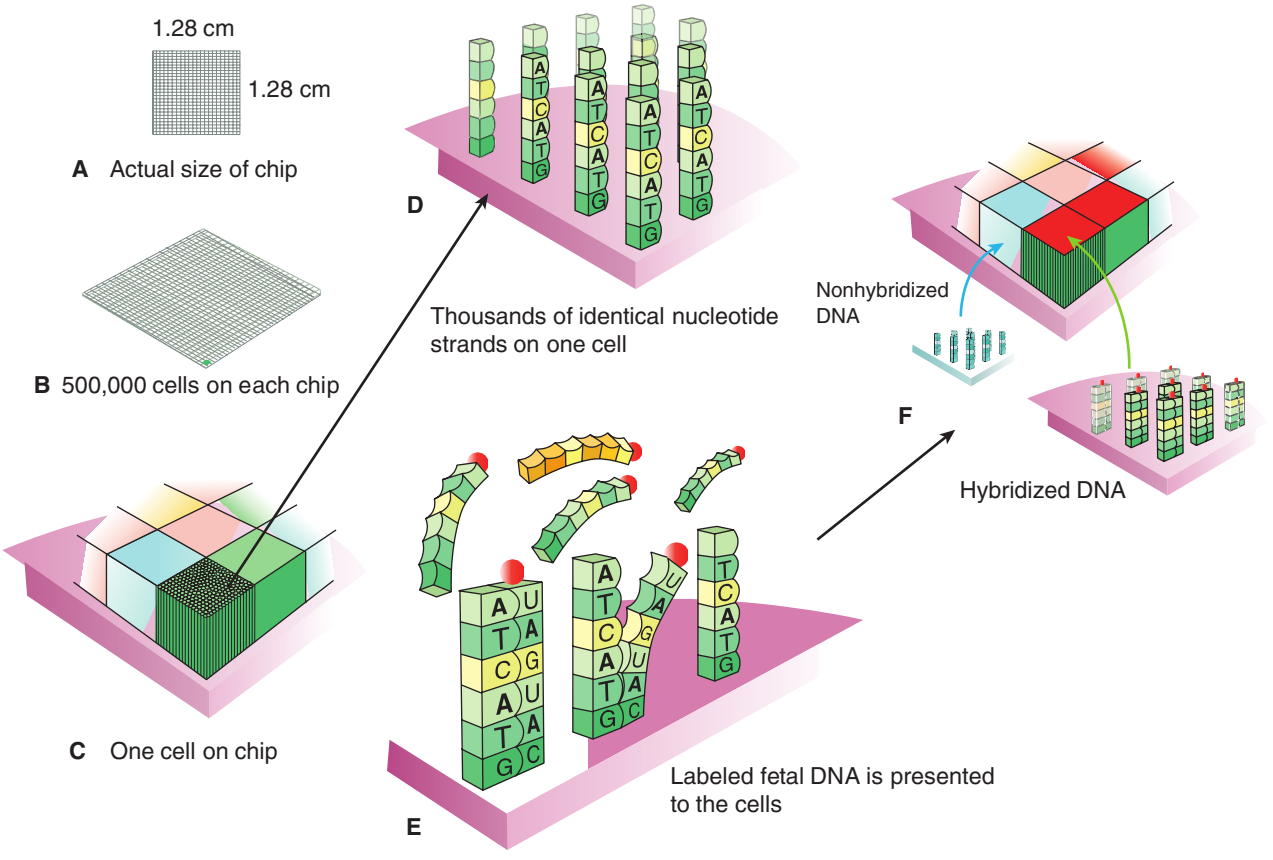

FIGURE 16-13 Chromosomal microarray analysis. **A.** Actual microarray chip size. **B.** Each chip contains thousands of cells (squares). **C** & **D.** Each cell contains thousands of identical oligonucleotides on its surface and is unique in its nucleotide content. **E.** During genetic analysis, a mixture containing tagged fetal DNA is presented to the chip. Complementary DNA sequences bind. **F.** If a laser is shined on the chip, DNA sequences that have bound will glow thus identifying a matching sequence. (Modified with permission from Doody KJ: Treatment of the infertile couple. In Hoffman BL, Schorge JO, Schaffer JI, et al (eds): Williams Gynecology, 2nd ed. New York, NY: McGraw Hill; 2012.)

Microarrays use either a comparative genomic hybridization (CGH) platform, a SNP platform, or a combination of the two. The CGH microarray platform compares specimen DNA with a normal control sample. Shown in Figure 16-13, the CGH chip contains reference DNA fragments of known sequence—oligonucleotides. Fetal DNA from the amniocentesis or chorionic villus sampling specimen is labeled with a fluorescent dye and then hybridized to the DNA on the chip. Normal control DNA is labeled with a different probe and also hybridized to the same chip. The intensity of the fluorescent signals from the two samples is compared. With a SNP array, the chip contains known DNA sequence variants, that is, single-nucleotide polymorphisms. When fetal DNA is labeled and hybridized to the chip, the fluorescent signal intensity indicates copy number variation.

Both types of platforms detect aneuploidy, unbalanced translocations, and microdeletions and microduplications. In addition, SNP arrays are able to identify triploidy and can detect *absence of heterozygosity*. The latter can occur with uniparental disomy, in which both copies of a chromosome are inherited from one parent. Absence of heterozygosity may also occur with consanguinity, and counseling prior to performance of an SNP array should include this possibility (p. 321). Importantly, neither type of array platform currently detects balanced chromosomal rearrangements. For this reason, couples with recurrent pregnancy loss should be offered karyotyping as the first-line test (Society for Maternal-Fetal Medicine, 2016).

In addition to identifying pathogenic copy number variants, CMA may detect variants that are unable to be classified as benign or pathologic and thus are considered to be of uncertain clinical significance. In recent series, these variants of uncertain significance are identified in approximately 1 percent of prenatal specimens (Brady, 2014; Chong, 2019; Wang, 2018). Not unexpectedly, variants of uncertain significance may be a source of distress to families, even with comprehensive pretest counseling.

Clinical Applications

In pregnancies at increased risk for autosomal trisomy based on aneuploidy screening results, karyotyping or FISH plus karyotyping should be offered, and CMA should be made available (American College of Obstetricians and Gynecologists, 2018). Clinicians are increasingly offering CMA in this setting. If the karyotype is normal, CMA has identified clinically relevant copy number variants in approximately 6.5 percent of pregnancies with fetal abnormalities and in 1 to 2 percent of those without obvious fetal abnormality (Callaway, 2013; Chong, 2019). The American College of Obstetricians and Gynecologists (2018) and the Society for Maternal-Fetal Medicine (2016) recommend CMA as the first-tier test when fetal structural abnormalities are identified. If a particular

anomaly that strongly suggests a specific aneuploidy is identified, such as an endocardial cushion defect (trisomy 21) or alobar holoprosencephaly (trisomy 13), then karyotyping or FISH may be offered as the initial test. Genetic counseling should include information regarding the benefits and limitations of both CMA and karyotyping. Each should be made available to women who elect prenatal diagnosis (Society for Maternal-Fetal Medicine, 2016). CMA may identify instances of autosomal dominant genetic disorders that have not yet manifested in an affected parent, and it may also identify instances of nonpaternity.

For stillbirth evaluation, CMA is significantly more likely than standard karyotyping to provide a genetic diagnosis, in part because it does not require dividing cells. The Stillbirth Collaborative Research Network found that when karyotyping was uninformative, approximately 6 percent of cases had either aneuploidy or a pathogenic copy number variant identified with CMA (Reddy, 2012). In a recent metaanalysis of more than 900 stillbirths with normal karyotype, CMA identified pathogenic copy number variants in 6 percent with structural abnormalities and 3 percent with no abnormalities evident (Martinez-Portilla, 2019). Overall, CMA yielded results 15 percent more often than karyotyping alone.

Whole Genome and Whole Exome Sequencing

Most fetuses with structural abnormalities have a normal karyotype and a normal CMA result. Whole genome sequencing (WGS) is a technique for analyzing the entire genome. Whole exome sequencing (WES) analyzes only the DNA coding regions, which account for approximately 1.5 percent of the genome. These next-generation sequencing tools are increasingly used postnatally to evaluate suspected genetic syndromes and intellectual disability.

Several prospective, multicenter series have evaluated WES for pregnancies in which fetuses have structural abnormalities, no karyotypic evidence of aneuploidy, and normal CMA. WES identified genetic abnormalities in approximately 10 percent of such cases (Lord, 2019; Petrovski, 2019). Utility was higher in cases with cardiac, skeletal, or multiorgan system anomalies.

Importantly, WGS and WES have significant limitations in their current form. These include prohibitively long turnaround times, high costs, and increased rates of false-positive and false-negative results and variants of uncertain significance (American College of Medical Genetics, 2012; Atwal, 2014). In addition, because sequencing is generally performed on the fetus and parents simultaneously, one parent may be identified or suspected to have an unrelated but medically actionable finding, which further complicates counseling (American College of Obstetricians and Gynecologists, 2020c). As a result, the clinical utility of this promising technology for prenatal cases is currently limited, and it is not recommended for routine clinical use.

Fetal DNA in the Maternal Circulation

Fetal cells are present in maternal blood at a very low concentration, only 2 to 6 cells per milliliter (Bianchi, 2006). Intact fetal cells sometimes persist in the maternal circulation for decades following delivery. Persistent fetal cells may engraft in the mother, causing microchimerism (Chap. 62, p. 1109). This has been implicated in maternal autoimmune diseases such as scleroderma, systemic lupus erythematosus, and Hashimoto thyroiditis (Kinder, 2017). From the standpoint of prenatal diagnosis, use of intact fetal cells from maternal blood is limited by low cell concentration, cell persistence into successive pregnancies, and difficulties in distinguishing fetal and maternal cells. Cell-free DNA overcomes these limitations.

Cell-free DNA

Also known as cell-free fetal DNA or noninvasive prenatal screening (NIPS), this screening test uses DNA fragments derived from maternal cells and from apoptotic placental trophoblast cells. "Fetal" is thus a misnomer. Cell-free DNA is reliably detected in maternal blood after 9 to 10 weeks' gestation (Bianchi, 2018). The proportion of total cell-free DNA that is placental is called the fetal fraction, and it accounts for approximately 10 percent of the total circulating cell-free DNA in maternal plasma. Unlike intact fetal cells, cell-free DNA is cleared within minutes from maternal blood.

Current clinical applications of cell-free DNA are aneuploidy screening and Rh D genotyping (Fig. 16-14). Commercial laboratories have also offered two other applications of cell-free DNA: (1) screening for selected microdeletion and microduplication syndromes and (2) genome-wide screening for deletions and duplications larger than 7 megabase pairs. Currently, prospective data on these promising applications are limited, and neither is recommended for routine screening (American College of Obstetricians and Gynecologists, 2020c).

Additional applications for cell-free DNA are on the horizon. In research settings, numerous single-gene disorders have been detected and include skeletal dysplasias, hemoglobinopathies, cystic fibrosis, congenital adrenal hyperplasia, hemophilia, muscular dystrophy, myotonic dystrophy, and spinal muscular atrophy (Camunas-Soler, 2018; Jenkins, 2018; Zhang, 2019).

Aneuploidy Screening. Several different assay platforms are used to screen for fetal autosomal trisomies and sex chromosomal aneuploidies. These include massively parallel sequencing, which is a WGS technique; chromosome-selective or targeted sequencing; and analysis of SNPs (American College of Obstetricians and Gynecologists, 2018, 2020c). By simultaneously sequencing millions of chromosome-specific DNA fragments, investigators can identify whether the proportion or ratio of fragments from one chromosome is higher than expected. Thus, samples from women with a Down syndrome fetus will have a larger proportion of DNA sequences from chromosome 21.

The screening performance of cell-free DNA is excellent. In a metaanalysis of 35 studies of largely high-risk pregnancies, the pooled sensitivity to detect Down syndrome was 99.7 percent, and to identify trisomies 18 and 13, 98 and 99 percent, respectively (Gil, 2017). For each, the specificity was at least 99.9 percent, such that the cumulative false-positive rate was below 1 percent. Aneuploidy screening reports commonly include information about fetal sex, which may be clinically useful if the fetus is at risk for an X-linked disorder or for congenital adrenal hyperplasia (Chap. 17, p. 335). In a metaanalysis, the

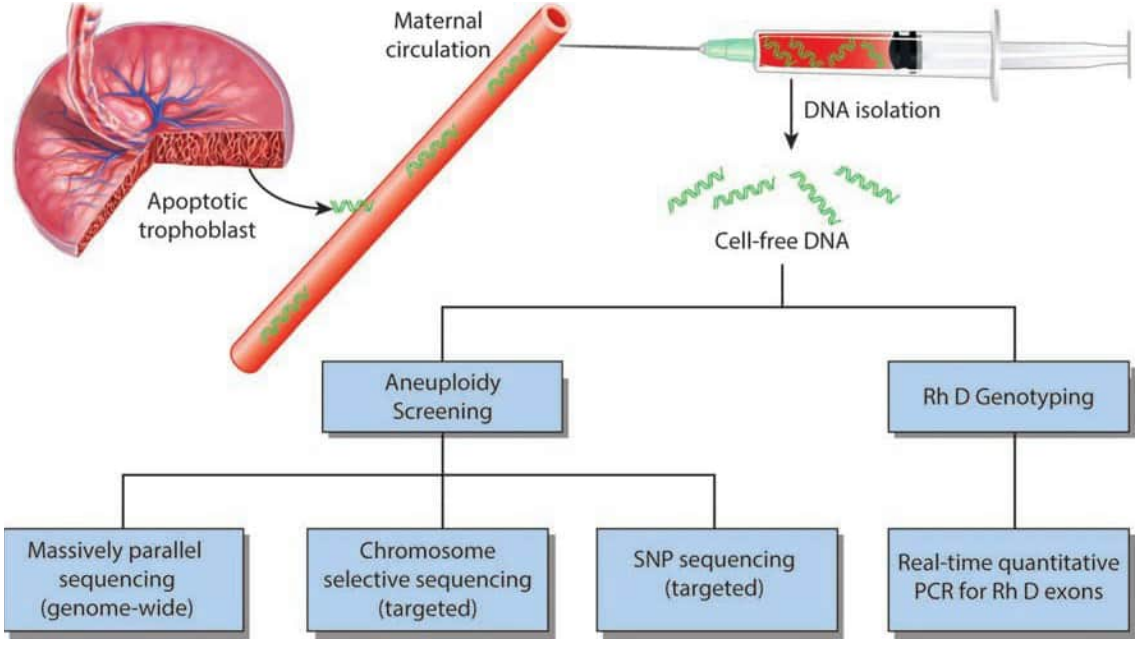

FIGURE 16-14 Cell-free DNA screening. These DNA fragments are derived from apoptotic trophoblast cells. Screening for autosomal trisomies and sex chromosomal aneuploidies may be performed using whole-genome sequencing, chromosome-selective or -targeted sequencing, and analysis of single-nucleotide polymorphisms (SNPs). Real-time quantitative polymerase chain reaction (PCR) also may be used to target specific regions or sequences, a technique used for Rh D genotyping.

sensitivity of cell-free DNA testing for fetal sex determination was reported to be 95 percent between 7 and 12 weeks' gestation and 99 percent after 20 weeks (Devaney, 2011).

Causes of false-positive and false-negative screening results are listed in Table 16-7. As with any other screening test, diagnostic confirmation should be performed before irreversible medical intervention. Cell-free DNA screens do not yield a result in 2 to 4 percent of cases. This may be due to assay failure, high assay variance, or low fetal fraction (Norton, 2012; Pergament, 2014; Quezada, 2015). Importantly, such pregnancies carry a greater risk for fetal aneuploidy. In addition, results may not reflect the fetal DNA complement but rather may indicate confined placental mosaicism, early demise of an aneuploid co-twin, maternal mosaicism, or rarely, occult maternal malignancy (Bianchi, 2015; Curnow, 2015; Grati, 2014b; Wang, 2014). Recommendations for counseling are discussed in Chapter 17 (p. 336).

TABLE 16-7. Selected Etiologies Creating Inaccurate Cell-free DNA Results

Abnormality not detected—false negative
Low fetal fraction
Fetal chromosomal abnormality
Multifetal gestation
Maternal obesity
Low-molecular-weight heparin
Confined placental mosaicism (normal placenta, aneuploid fetus)
Normal fetus but abnormal screen—false positive
Confined placental mosaicism (normal fetus, aneuploid placenta)
Multifetal gestation with loss of aneuploid fetus
Maternal aneuploidy (e.g. 47,XXX)
Maternal mosaicism (e.g. 46,XX/45,X) or fetal mosaicism
Maternal cancer (lymphoma, breast, colon, leukemia, others)
Vitamin B_{12} deficiency

Data from Bianchi, 2018.

Rh D Genotype Evaluation. Many fetuses of Rh D-negative women are also Rh D-negative. In a predominantly white population, this prevalence approaches 40 percent. Fetal Rh D genotype assessment from maternal blood can eliminate administration of anti-D immune globulin in such cases, thereby reducing costs and potential risk. When Rh D alloimmunization is suspected, early identification of an Rh D-negative fetus might avoid unnecessary middle cerebral artery Doppler assessment or amniocentesis. Evaluation using cell-free DNA is done using real-time PCR to target several exons of the *RHD* gene, typically exons 4, 5, 7, and 10.

Rh D-genotyping is performed routinely with cell-free DNA in Denmark, Finland, and the Netherlands (Clausen, 2012; de Haas, 2016; Haimila, 2017). In population-based studies of more than 35,000 Rh D-negative women screened at 24 to 27 weeks' gestation, the false-negative rate—in which Rh D-negative status was missed—was only 0.03 percent. The false-positive rate—in which Rh immune globulin would be given unnecessarily—was less than 1 percent (de Haas, 2016; Haimila, 2017). Similar results were reported from the United Kingdom, although the false-negative rate was higher in the first trimester. Investigators concluded that false-negative screening results might increase the alloimmunization risk but by less than 1 case per million births (Chitty, 2014). Rh D alloimmunization is discussed in Chapter 18 (p. 353).

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CHAPTER 17

Prenatal Diagnosis

Prenatal diagnosis is the science of identifying congenital abnormalities and genetic conditions in the fetus. It encompasses the diagnosis of structural malformations with specialized ultrasound, screening tests for aneuploidy, carrier screening for genetic diseases, and diagnostic tests performed on chorionic villi and amnionic fluid.

Based on population-based registry data including births, fetal deaths, and pregnancy terminations, 4 per 1000 pregnancies have a chromosomal abnormality (Wellesley, 2012). If chromosomal microarray analysis (CMA) is performed on chorionic villi or amnionic fluid, an additional 4 per 1000 are found to have a pathogenic copy number variant, such as a microdeletion or microduplication (Srebniak, 2017). It is important for all pregnant women to be offered both screening and diagnostic tests.

The goal of prenatal diagnosis is to provide accurate information about short- and long-term prognosis, recurrence risk, and potential therapy. Nondirective counseling and provision of unbiased knowledge are paramount. Management of an affected pregnancy that includes diagnostic testing, discussion of potential fetal therapy options and postnatal care, and decisions related to expectant management or pregnancy termination are all incorporated into counseling (Flessel, 2011). Fetal imaging of congenital anomalies is discussed in Chapter 15, fetal therapy in Chapter 19, and pregnancy termination in Chapter 11.

HISTORICAL PERSPECTIVE

Nearly 50 years ago, Brock (1972, 1973) observed that pregnancies complicated by neural-tube defects had higher levels of alpha-fetoprotein (AFP) in maternal serum and amnionic fluid. Widespread serum screening began in 1977, after a collaborative trial from the United Kingdom established the association between elevated maternal serum AFP levels (MSAFP) and fetal open neural-tube defects (Wald, 1977). Screening at 16 to 18 weeks' gestation detected 90 percent of fetuses with anencephaly and 80 percent of those with open spina bifida, similar to current screening performance (American College of Obstetricians and Gynecologists, 2019c).

The terms *level I* and *level II* ultrasound were coined in this context. In the California MSAFP Screening Program of the 1980s and early 1990s, the first step in evaluation of an abnormally elevated MSAFP was a level I ultrasound examination. This screening examination demonstrated that one third of pregnancies with MSAFP elevation had incorrect gestational age, multifetal gestation, or fetal demise as the etiology (Filly, 1993). Amniocentesis was then offered to the remaining two thirds. If the amnionic fluid AFP concentration was elevated, a level II ultrasound examination was performed to detect and characterize a fetal abnormality.

Additionally, an elevated amnionic fluid AFP level prompted a concurrent assay for amnionic fluid acetylcholinesterase.

TABLE 17-1. Estimated Risks for Fetal Trisomy 21 and Any Aneuploidy According to Maternal Age and Timing of Diagnosis

	Trisomy 21			Any Aneuploidy	
Age	Chorionic Villus Sampling	Amniocentesis	Delivery	Amniocentesis	Delivery
35	1/249	1/280	1/356	1/132	1/204
36	1/196	1/220	1/280	1/105	1/167
37	1/152	1/171	1/218	1/83	1/130
38	1/117	1/131	1/167	1/65	1/103
39	1/89	1/100	1/128	1/53	1/81
40	1/68	1/76	1/97	1/40	1/63
41	1/51	1/57	1/73	1/31	1/50
42	1/38	1/43	1/55	1/25	1/39
43	1/29	1/32	1/41	1/19	1/30
44	1/21	1/24	1/30	1/15	1/24
45	1/16	1/18	1/23	1/12	1/19

Adapted from Hook, 1983; Snidjers, 1999.

Because acetylcholinesterase leaks from the exposed neural tissue into the amnionic fluid, presence of both analytes was used to confirm the diagnosis. However, other fetal abnormalities are associated with elevated amnionic fluid AFP and positive assay results for acetylcholinesterase. These include ventral wall defects, esophageal atresia, fetal teratoma, cloacal exstrophy, and skin abnormalities such as epidermolysis bullosa.

Most neural-tube defects are now detected with a standard ultrasound examination, and the detailed ultrasound examination is the preferred diagnostic test (American College of Obstetricians and Gynecologists, 2019c; Dashe, 2006). Level II ultrasound is no longer an appropriate synonym for detailed ultrasound examination, because the study now includes a much more comprehensive evaluation of fetal anatomy (Chap. 14, p. 251).

As MSAFP screening was being adopted, the designation "advanced maternal age" (AMA) became popular. A 1979 National Institutes of Health Consensus Development Conference recommended advising pregnant women who were 35 years and older about the possibility of amniocentesis for fetal karyotyping. The threshold was based on the greater risk for selected fetal chromosomal abnormalities with increasing maternal age (Table 17-1). There was also an assumption that the loss rate attributable to amniocentesis was equivalent to the fetal Down syndrome risk at maternal age 35. *This is no longer the case.*

In 1984, Merkatz and colleagues reported that midtrimester MSAFP levels were lower in pregnancies with trisomies 21 and 18 than in unaffected pregnancies. Maternal age was incorporated into the calculation, which enabled assignment of a specific risk (DiMaio, 1987; New England Regional Genetics Group, 1989). The MSAFP screen detected approximately 25 percent of cases of fetal trisomy 21 when the threshold ratio for a positive result was set at 1:270—the approximate second-trimester risk at maternal age 35. This trisomy 21 risk threshold and the associated 5-percent false-positive rate became standards that remain in use in some laboratories.

ANEUPLOIDY SCREENING

Aneuploidy is the presence of one or more extra chromosomes, usually resulting in trisomy, or loss of a chromosome—monosomy (Chap. 16, p. 309). Of recognized pregnancies with chromosomal abnormalities, trisomy 21 accounts for approximately half of cases; trisomy 18 accounts for 15 percent; trisomy 13, for 5 percent; and the sex chromosomal abnormalities—45,X, 47,XXX, 47,XXY, and 47,XYY—for approximately 12 percent. Screening tests are available for some or all of these aneuploidies.

The risk for fetal trisomy increases with maternal age, particularly after age 35 (Fig. 16-2, p. 310). The positive predictive value of all aneuploidy screening tests is higher for women aged 35 years and older. Such women account for 18 percent of deliveries in the United States (Fig. 17-1). At Parkland Hospital, the majority of Down syndrome births occur in this age group (Hussamy, 2019). Other important aneuploidy risk factors include a numerical chromosomal abnormality or structural chromosomal rearrangement in the woman or her partner—such as a balanced translocation—or a prior pregnancy with autosomal trisomy or triploidy.

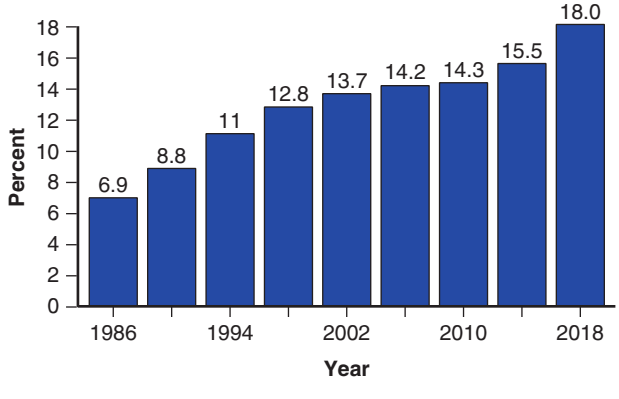


FIGURE 17-1 Trends in the percentage of births to women aged 35 to 44 years. (Data from the Centers for Disease Control and Prevention, 2015, 2019).

Broadly speaking, there are two types of aneuploidy screening tests, those that are analyte-based and those that are cell-free DNA-based. Cell-free DNA (cfDNA) screening is more sensitive and specific than analyte-based screening, and it has a much higher positive predictive value. One prospective screening study for trisomy 21 in 15,000 pregnancies found that the average positive predictive value was 80 percent for cfDNA but only 3 percent for first-trimester screening (Norton, 2015). However, analyte-based screening has the unusual benefit that an abnormal result may indicate a genetic abnormality for which screening was not specifically performed (p. 337). The position of the American College of Obstetricians and Gynecologists (2020e) is that no one screening test is superior in all circumstances. No aneuploidy screening test is diagnostic, and prenatal diagnosis is strongly recommended before acting upon a result.

There are selected circumstances in which aneuploidy screening is *not* recommended. Following diagnosis of a major fetal abnormality, prenatal diagnosis with amniocentesis or chorionic villus sampling is advised. The fetal risk cannot be normalized with a negative aneuploidy screening result. Screening results can be falsely negative, and major abnormalities confer risk for genetic syndromes not identified through screening tests. Analyte-based screening tests are not valid in the setting of an abnormality that affects the AFP component, such as a neural-tube defect or ventral-wall defect. Additionally, all aneuploidy screening methods are less accurate in twin gestations and are invalid in triplet gestations and higher-order multiples.

Aneuploidy screening should be an informed patient choice that incorporates the patient's clinical circumstances, values, interests, and goals. Counseling should be individualized, with the understanding that at least 20 percent of women prefer not to receive aneuploidy screening, even when financial barriers are removed (Kuppermann, 2014). Elements of counseling prior to aneuploidy screening are listed in Table 17-2. The screening test(s) offered and elected may depend on factors such as gestational age, provider location or practice setting, and the patient's out-of-pocket costs.

Test Characteristics

Validity characteristics convey information about how well an aneuploidy screening test differentiates affected from unaffected pregnancies. The sensitivity, also known as the detection rate, is the proportion of fetuses with a particular aneuploidy who are detected by the screening test. The converse is the false-negative rate. If a woman elects a first-trimester aneuploidy screen with a sensitivity of 80 percent for trisomy 21, the false-negative rate is 20 percent, so the test is anticipated to miss 1 in 5 affected pregnancies.

Specificity is the proportion of *unaffected* pregnancies with a negative screening result. The converse of specificity is the

TABLE 17-2. Aneuploidy Screening Counseling Elements

All pregnant women have 3 options: screening, diagnostic testing, and no screening or testing.
The purpose of a screening test is to provide information, not to dictate a course of action.
Diagnostic testing is safe and effective and provides information that screening does not.
There are differences between a screening test and a diagnostic test.
Screening evaluates whether the pregnancy is at increased risk for specific conditions and estimates the degree of risk. Screening does not provide information regarding all genetic abnormalities.
With a negative screening test result, the risk is decreased but not eliminated.
With a positive screening result, a diagnostic test is recommended if the patient wants to know whether the fetus is affected.
Irreversible management decisions should not be based on screening test results.
Cell-free DNA screening does not always provide a result, and the aneuploidy risk is increased in such cases.
Basic information is provided regarding the conditions for which screening is performed and the limitations of the screening test.
Information may include prevalence of a genetic condition, associated abnormalities, and prognosis.
Diagnosis may aid earlier identification of associated abnormalities.
In the case of trisomy 18 or 13, diagnosis may affect pregnancy management if complications arise such as growth restriction or nonreassuring fetal heart rate.
All screening tests are less effective in multifetal gestations.
Phenotypic expression of sex chromosome aneuploidies varies widely.
A-priori risk for fetal aneuploidy may affect whether a woman elects a screening test or diagnostic test.
Age-related risk information may be found in reference tables.
If a patient has had a prior fetus with autosomal trisomy, robertsonian translocation, or other chromosomal abnormality, additional evaluation and counseling are recommended.
If a major fetal abnormality has been identified with ultrasound, a diagnostic test is preferred, and aneuploidy screening is not recommended.

American College of Obstetricians and Gynecologists, 2020e; Dashe, 2016.

TABLE 17-3. Positive Predictive Value of Cell-Free DNA Screening for Autosomal Trisomies and Sex Chromosome Abnormalities, According to Maternal Age at Term

Maternal Age	Trisomy 21	Trisomy 18	Trisomy 13	45,X	47,XXX	47,XXY	47,XYY
20	48%	14%	6%	41%	27%	29%	25%
25	51%	15%	7%	41%	27%	29%	25%
30	61%	21%	10%	41%	27%	29%	25%
35	79%	39%	21%	41%	28%	30%	25%
40	93%	69%	50%	41%	45%	52%	25%
45	98%	90%	NA	41%	73%	77%	NA

NA = not available.
Positive predictive values were obtained using the Cell Free DNA Screening Predictive Value Calculator from the Perinatal Quality Foundation, 2020.
Calculations based on prevalence at 16 weeks' gestation using sensitivities and specificities from Gil, 2015.

false-positive rate, those without aneuploidy who nonetheless screen positive. Because aneuploidies are individually uncommon, the screen-positive rate, which is the overall proportion of tests with a positive result, is usually similar to the false-positive rate. Aneuploidy screening tests generally have screen-positive rates no higher than 5 percent.

Sensitivity and specificity do not convey any information regarding individual risk. The positive predictive value (PPV) is the proportion with a positive screening result who have an aneuploid fetus. PPV may be viewed as the test result. It is usually expressed as a 1:X ratio or as a percentage. Because PPV is directly affected by disease prevalence, it is higher in women aged 35 years and older than in younger women (Table 17-3). Negative predictive value is the proportion of those with a negative screening test result who have unaffected (euploid) fetuses. Because the prevalence of aneuploidy is low, the negative predictive value of all aneuploidy screening tests generally exceeds 99 percent (Gil, 2017; Norton, 2015).

■ Cell-free DNA Screening

This screening test identifies DNA fragments derived primarily from apoptotic trophoblasts, which are placental cells undergoing programmed cell death. Thus, the term cell-free *fetal* DNA is a misnomer. Differences between placental and fetal DNA may cause false-positive and false-negative results. There are three types of assays: whole-genome sequencing, chromosome selective or targeted sequencing, and single nucleotide polymorphism analysis. CfDNA screening can be performed at any time after 9 to 10 weeks' gestation. When it was first introduced, cfDNA screening was offered primarily to pregnancies with increased aneuploidy risk, but it has since become widely available (American College of Obstetricians and Gynecologists, 2020e).

CfDNA screening is most commonly used to screen for autosomal trisomies—trisomy 21, trisomy 18, and trisomy 13. It may also be used to screen for 45,X (Turner syndrome), 47,XXX, 47,XXY, and 47,XYY. A recent metaanalysis concluded that the number of reported sex aneuploidy cases is too small for accurate assessment of screening performance (Gil, 2017). The prognosis for these sex chromosomal aneuploidies differs considerably from that of the autosomal trisomies (Chap. 16, p. 313). If screening for sex chromosomal abnormalities is elected, counseling should include this information.

CfDNA has the highest sensitivity and specificity of any aneuploidy screening test. In a metaanalysis of 35 studies of largely high-risk pregnancies, the pooled sensitivity to detect trisomy 21 was 99.7 percent, and for trisomies 18 and 13, 98 percent and 99 percent, respectively (Gil, 2017). For each of these autosomal trisomies, the specificity is 99.9 percent, and the combined false-positive rate is less than 0.2 percent. If the screening platform includes other genetic conditions, each additional condition increases the overall false-positive rate for the test.

The PPV of a positive cfDNA result is provided in the report or may be estimated from an online calculator or reference table (see Table 17-3). Because the risk estimate for each aneuploidy depends on maternal age, such information may be included as part of pretest counseling. This can help to avoid the misconception that a positive screen indicates aneuploidy—*it does not*.

Because cfDNA screening has a PPV far higher than analyte screening, it may be offered as a secondary screening test for women who wish to avoid amniocentesis. Such an approach has important caveats. If cfDNA is used as a secondary screening test and yields a negative result, the residual risk for a chromosomal abnormality may be as high as 2 percent (Norton, 2014). And, if the cfDNA result is positive, the delay in definitive diagnosis may affect management options.

In addition to the aforementioned aneuploidies, cfDNA screening is available for other genetic conditions. These include aneuploidies such as trisomies 16 and 22, specific microdeletion syndromes, and large copy number changes throughout the genome. Currently, the American College of Obstetricians and Gynecologists (2020e) does *not* recommend cfDNA screening for these other conditions. Sensitivity and specificity of cfDNA screening have not been established for them, and screening accuracy has not been validated clinically.

Limitations of cfDNA Screening

In 2 to 4 percent of pregnancies screened with cfDNA, no result is obtained. These cases are termed "no-call," or indeterminate.

TABLE 17-4. Characteristics of Screening Tests for Trisomy 21 in Singletons

Screening Test	Detection Rate	False-Positive Rate	Positive Predictive Value[a]
Quadruple screen:			
AFP, hCG, estriol, inhibin	80–82%	5%	3%
First-trimester screen:			
NT, hCG, PAPP-A	80–84%	5%	3–4%
First-trimester NT alone	64–70%	5%	
Integrated screening	94–96%	5%	5%
Sequential screening:			
Stepwise	92–97%	5.1%	5%
Contingent	91–95%	4.5%	5%
Cell-free DNA screening:			
Positive result	99%	0.1%	Table 17-3
Low fetal fraction or no result	—	2–4%	3–4%

[a]The positive predictive value represents the overall population studied and cannot be applied to any individual patient.
AFP = alpha-fetoprotein; hCG = human chorionic gonadotropin; NT = nuchal translucency; PAPP-A = pregnancy-associated plasma protein A.
Data from Aldred, 2017; Baer, 2015; Dashe, 2016; Gil, 2015; Malone, 2005b; Norton, 2015; Pergament, 2014; Quezada, 2015.

With a no-call result, the fetal aneuploidy risk is as high as 4 percent (Norton, 2015). As shown in Table 17-4, this result is similar to the average risk conferred by a positive analyte screening test result.

Low fetal fraction is a common reason for no-call results. The fetal fraction is the proportion of cfDNA in the maternal circulation that is placental rather than maternal in origin. The fetal fraction approximates 10 percent in the late first trimester, increasing slightly thereafter (Ashoor, 2013; Scott, 2018). Low fetal fraction is usually defined as <4 percent of the total, and it is more prevalent before 10 weeks' gestation and in the setting of maternal obesity (Ashoor, 2013; Juul, 2020; Scott, 2018). The no-call rate may exceed 10 to 20 percent in women whose body mass index is 40 kg/m^2 or greater (Juul, 2020). Low fetal fraction is also more common in the setting of aneuploidy, particularly trisomies 18 and 13 (Norton, 2015; Pergament, 2014). The American College of Medical Genetics and Genomics recommends that the fetal fraction be included in cfDNA reports because it assists with interpretation of results (Gregg, 2016). Pretest counseling should include the possibility of a no-call result and its clinical significance (see Table 17-2).

If the cfDNA screening test is positive or yields a no-call result, additional genetic counseling is indicated, and amniocentesis should be offered. If cfDNA screening is repeated, the risk for repeat screen failure approximates 40 percent (Dar, 2014; Quezada, 2015; Rolnik, 2018). Detailed ultrasound examination may be offered, but it is not a substitute for amniocentesis, and the residual aneuploidy risk following normal detailed ultrasound examination is unknown.

It is important to remember that cfDNA results may not reflect the fetal DNA complement. Rather, a positive result may be caused by confined placental mosaicism or early demise of an aneuploid co-twin. Alternately, it may indicate maternal aneuploidy, mosaicism, or even occult maternal malignancy (Bianchi, 2015; Curnow, 2015; Grati, 2014; Wang, 2014). If ultrasound identifies an empty second gestational sac, cfDNA screening is not recommended. The patient should be informed of such limitations prior to screening.

■ Analyte-based Aneuploidy Screening

The three categories of multiple marker-serum analyte screening are first-trimester screens, second-trimester screens, and combined first- and second-trimester screens. The serum concentration of each analyte is converted to a multiple of the median (MoM) of the unaffected population by adjusting for maternal age, maternal weight, and gestational age. The serum AFP concentration is further adjusted for maternal race and for presence of diabetes, which affect calculation of neural-tube defect risk (Greene, 1988; Huttly, 2004).

The analyte-based screening result is based on a composite likelihood ratio, and the maternal age-related risk is multiplied by this ratio. Adjustment normalizes the distribution of analyte levels and permits comparison of results from different laboratories and populations. Each woman is provided with a specific risk for trisomy 21 and for trisomy 18—or in the first trimester, for trisomy 18 or 13 in some cases. Each screening test has a predetermined value at or above which it is deemed "positive" or abnormal. For second-trimester tests, this threshold has traditionally been set at the risk for fetal Down syndrome at a maternal age of 35 years—approximately 1 in 270 in the second trimester. The trisomy 21 risk may be further modified based on selected ultrasound markers (p. 340).

A benefit of analyte screening is that pregnancies with abnormal results may have genetic abnormalities other than those for which screening was performed. For example, in a review of more than 2500 pregnancies with genetic abnormalities from the California Prenatal Screening Program, combined first- and second-trimester screening results were abnormal in 93 percent with trisomies 21 and 18 (Norton, 2016). However, results were also abnormal in 80 percent with trisomy 13, in 80 percent with 45,X, in nearly 60 percent with other sex chromosomal abnormalities, and in more than 50 percent with other genetic abnormalities. Alamillo and associates (2013) similarly identified an abnormal karyotype other than trisomies 21, 18, or 13 in 2 percent of pregnancies with abnormal first-trimester screening results, accounting for 30 percent of abnormal karyotypes in the series.

Women younger than 35 are at lower risk for the specific autosomal trisomies for which cfDNA screening is typically performed. Thus, if the goal is to select a screening test that will identify the highest proportion of fetuses with *any* chromosomal abnormality, the yield may be comparable or even slightly higher with integrated or sequential screening than with current cfDNA screening (Baer, 2015; Norton, 2014).

First-trimester Aneuploidy Screening

This test includes human chorionic gonadotropin (hCG), pregnancy-associated plasma protein A (PAPP-A), and ultrasound measurement of the nuchal translucency (NT). It is performed between 11 and 14 weeks' gestation. Pregnancies with fetal trisomy 21 are characterized by higher levels of hCG and lower PAPP-A. With trisomy 18 and trisomy 13, levels of both analytes are lower (Cuckle, 2000; Malone, 2005b).

Nuchal Translucency. This is the maximum thickness of the subcutaneous translucent area between the skin and soft tissue overlying the fetal spine at the back of the neck (Fig. 17-2). It is measured in the sagittal plane and is valid when the crown-rump length (CRL) measurement is between 38 to 45 mm and 84 mm, with the lower limit varying according to the laboratory. Measurement criteria are listed in Table 14–4 (p. 250). The NT should be imaged and measured with a high degree of precision for aneuploidy detection to be accurate. This has led to standardized training, certification, and ongoing quality review programs.

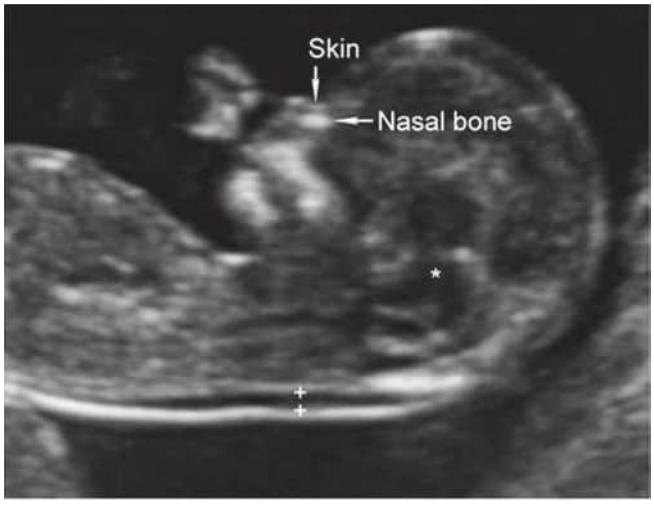


FIGURE 17-2 Sagittal image of a normal, 12-week fetus shows correct caliper placement (+) for nuchal translucency measurement. The fetal nasal bone and overlying skin are indicated. The nasal tip and the 3rd and 4th ventricles (*asterisk*), which are other landmarks that should be visible in the nasal bone image, also are shown. (Reproduced with permission from Dr. Michael Zaretsky.)

An increased NT is not a fetal abnormality but rather a marker that confers increased risk. It is helpful to differentiate from cystic hygroma, which appears sonographically as a septated hypoechoic space behind the neck that extends down the back (Fig. 15-30, p. 286). The fetal aneuploidy risk is five times greater with first-trimester cystic hygroma than with increased NT (Malone, 2005a). An increased NT measurement is associated with other genetic syndromes and various birth defects, especially fetal cardiac abnormalities (Clur 2008; Simpson, 2007). If the NT measurement is at least 3 mm or reaches the 99th percentile for CRL, a detailed ultrasound examination should be offered. Similarly, fetal echocardiography may be considered if the NT measurement is at least 3 mm and is recommended if the NT measurement is 3.5 mm or greater (American College of Obstetricians and Gynecologists, 2020e; American Institute of Ultrasound in Medicine, 2019).

As an isolated marker, NT detects only 70 percent of trisomy 21 fetuses, and for this reason it is not used to screen singleton pregnancies (Alldred, 2017; Malone, 2005b). If cfDNA screening has already been performed, the NT measurement does not improve fetal aneuploidy detection and is not recommended for this purpose (American College of Obstetricians and Gynecologists, 2020e; Reiff, 2016). NT evaluation may be helpful in multifetal gestations because serum screening is less accurate, may not be available, and cannot provide information specific to each fetus. The NT distribution is similar in twins and singletons (Cleary-Goldman, 2005).

Efficacy of First-trimester Screening. Before first-trimester screening became widely adopted, four large prospective trials were conducted, together including more than 100,000 pregnancies (Reddy, 2006). When the screen-positive rate was set at 5 percent, trisomy 21 detection was 84 percent. A recent metaanalysis also reported detection of 87 percent of trisomy 21 fetuses (Alldred, 2017). First-trimester screening similarly detects approximately 80 percent of fetuses with trisomy 18 and 50 percent with trisomy 13 (Norton, 2015).

Maternal age affects the performance of first-trimester aneuploidy screening. In women younger than age 35 at delivery, fetal trisomy 21 detection ranges from 67 to 75 percent (Malone, 2005b; Wapner, 2003). Among women older than 35 at delivery, detection is as high as 90 to 95 percent, albeit at a higher false-positive rate of 15 to 22 percent.

In twin pregnancies, serum free β-hCG and PAPP-A levels are approximately double the singleton values (Vink, 2012). Even with specific curves, a normal dichorionic co-twin will tend to normalize screening results. Thus the aneuploidy detection rate is at least 15-percent lower (Bush, 2005).

Analyte abnormalities are termed *unexplained* if prenatal diagnostic testing results are normal. There is a significant

association between serum PAPP-A levels below the 5th percentile and preterm birth, growth restriction, preeclampsia, and fetal demise (Cignini, 2016; Dugoff, 2004; Jelliffe-Pawlowski, 2015). Similarly, low levels of free β-hCG have been associated with fetal demise (Goetzl, 2004). The sensitivity and PPVs of these markers are too low to make them clinically useful as screening tests (American College of Obstetricians and Gynecologists, 2020c).

Second-trimester Aneuploidy Screening

The quadruple marker or "quad" screening test is performed from 15 through 20 or 21 weeks' gestation depending on the laboratory. Pregnancies with fetal trisomy 21 are characterized by lower MSAFP, higher hCG, lower unconjugated estriol, and higher dimeric inhibin levels. In large prospective trials, trisomy 21 detection was 81 to 83 percent at a 5-percent screen-positive rate (Malone, 2005b; Wald, 1996, 2003). In cases of trisomy 18, levels of MSAFP, hCG, and unconjugated estriol are all decreased, and inhibin is not part of the calculation. Trisomy 18 detection is similar to that for trisomy 21, but the false-positive rate is just 0.5 percent (Benn, 1999). As with first-trimester screening, aneuploidy detection rates are lower in younger women and higher in women older than 35 years at delivery. If second-trimester serum screening is used in twin pregnancies, aneuploidy detection rates are significantly lower (Vink, 2012).

Quadruple-marker screening offers no benefit over first-trimester screening from the standpoint of trisomy 21 or trisomy 18 detection. As a stand-alone test, it is generally used if women do not begin care until the second trimester or if first-trimester screening and cfDNA screening are not available. In 2019, women who initiated prenatal care beyond the first trimester made up more than 20 percent of pregnancies in the United States (Martin, 2020). As subsequently discussed, combining first- and second-trimester screening yields greater aneuploidy detection.

Maternal Serum AFP Elevation: Neural-tube Defect Screening. AFP is the major protein in fetal serum, analogous to albumin in a child or adult. Defects in fetal integument, such as neural-tube and ventral-wall defects, permit AFP to leak into the amnionic fluid and result in dramatically increased maternal serum levels. Accurate gestational age assessment is imperative because the AFP value rises by approximately 15 percent per week during the screening window (Knight, 1992).

Using an MSAFP level of 2.5 MoM as the upper limit of normal, the neural-tube defect detection rate approximates 95 percent for anencephaly and 80 percent for spina bifida, with a screen-positive rate of 1 to 3 percent (American College of Obstetricians and Gynecologists, 2019c; Palomaki, 2019). The overall PPV approximates just 2 percent. Higher screening threshold values are used in twin pregnancies, which have twice the AFP level of singletons (Cuckle, 1990). Importantly, because nearly all cases of anencephaly and most with spina bifida are detected during the standard second-trimester ultrasound examination, MSAFP screening is considered optional (American College of Obstetricians and Gynecologists, 2019c; Dashe, 2006; Norem, 2005).

TABLE 17-5. Conditions Associated with MSAFP Level Elevation

Underestimated gestational age
Multifetal gestation
Fetal death
Neural-tube defect
Gastroschisis
Omphalocele
Cystic hygroma
Esophageal or intestinal obstruction
Liver necrosis
Renal anomalies—polycystic kidneys, renal agenesis, congenital nephrosis, urinary tract obstruction
Cloacal exstrophy
Osteogenesis imperfecta
Sacrococcygeal teratoma
Congenital skin abnormality
Pilonidal cyst
Chorioangioma of placenta
Placenta intervillous thrombosis
Placental abruption
Oligohydramnios
Preeclampsia
Fetal-growth restriction
Maternal hepatoma or teratoma

MSAFP = maternal serum alpha-fetoprotein.

If the serum AFP is elevated, a detailed ultrasound examination is recommended, and characteristic sonographic findings are diagnostic (Chap. 15, p. 276). Other abnormalities and conditions also may result in MSAFP elevation (Table 17-5). Amniocentesis for measurement of amnionic fluid AFP and acetylcholinesterase levels can help to diagnose whether a myelomeningocele is open or closed, which is relevant when considering fetal surgical repair (Chap. 19, p. 372).

Most pregnancies with MSAFP elevation have no fetal abnormality. The patient should receive counseling about the benefits and limitations of detailed ultrasound examination for the diagnosis of neural-tube defects and other potential etiologies. These include other fetal abnormalities, placental abnormalities, and selected adverse pregnancy outcomes (Table 17-5). The likelihood of any abnormality or adverse outcome increases in proportion to the AFP level.

There are similarly significant associations between second-trimester elevation of either hCG or dimeric inhibin alpha levels and adverse pregnancy outcomes. The likelihood of adverse outcome is greater if multiple analytes are elevated (Dugoff, 2005). The sensitivity and positive predictive values of these markers are considered too low to be useful for screening or management. No specific program of maternal or fetal surveillance has been found to favorably affect pregnancy outcomes (Dugoff, 2010).

Low Maternal Serum Estriol Level. A maternal serum estriol level less than 0.25 MoM has been associated with two uncommon but important conditions. *Smith-Lemli-Opitz syndrome* is

an autosomal recessive condition resulting from mutations in the 7-dehydrocholesterol reductase gene. It is characterized by abnormalities of the central nervous system, heart, kidney, and extremities; with ambiguous genitalia; and with fetal-growth restriction. Detailed sonography should be offered if an unconjugated estriol level is <0.25 MoM (American Institute of Ultrasound in Medicine, 2019; Dugoff, 2010). An elevated amnionic fluid 7-dehydrocholesterol level can confirm the diagnosis.

The second condition is *steroid sulfatase deficiency*, also known as *X-linked ichthyosis*. It is typically an isolated condition, but it may also occur in the setting of a contiguous gene deletion syndrome (Chap. 16, p. 315). In such cases, it may be associated with Kallmann syndrome, chondrodysplasia punctata, and/or mental retardation (Langlois, 2009). If the estriol level is <0.25 MoM and the fetus appears to be male, chromosomal microarray analysis or fluorescence in situ hybridization to assess the steroid sulfatase locus on the X-chromosome may be considered.

Integrated and Sequential Screening

If first-trimester screening is combined with second-trimester screening, aneuploidy detection is significantly improved. Combined screening test options require that specimens are obtained at the correct gestational age and sent to the same laboratory. The first- and second-trimester components cannot be performed independently, because the false-positive rate would be higher and providing accurate risk assessment would be problematic.

Three types of screening strategies are available:

1. *Integrated screening* combines results of first- and second-trimester tests. This includes a combined measurement of fetal NT and serum analyte levels at 11 to 14 weeks' gestation plus quadruple markers at approximately 15 to 21 weeks. Trisomy 21 detection is 94 to 96 percent (see Table 17-4).
2. *Sequential screening* involves informing the patient of the results after first-trimester screening, with plan to offer prenatal diagnostic testing if the calculated risk value lies above a specified threshold. There are two testing strategies in this category:
   - With *stepwise sequential screening*, women whose first-trimester risk is at or below the threshold receive second-trimester screening. Using data from the First- and Second-Trimester Evaluation of Risk trial, when the first-trimester threshold is set at approximately 1:30, and the overall threshold is set at 1:270, stepwise sequential screening resulted in a 92-percent trisomy 21 detection rate (Cuckle, 2008). The false-positive rate remained 5 percent (see Table 17-4).
   - With *contingent sequential screening*, women are divided into high-, moderate-, and low-risk groups. Those at highest risk for trisomy 21—for example, risk >1:30, are counseled and offered diagnostic testing. Women at moderate risk, between 1:30 and 1:1500, undergo second-trimester screening, whereas those at lowest risk of <1:1500 receive negative screening test results and have no further testing (Cuckle, 2008). Using this strategy, more than 75 percent of those screened are provided with reassuring results almost immediately. Assuming that women accept diagnostic testing when informed that the risk is elevated, detection approaches 91 percent.

Ultrasound Screening

Ultrasound can improve aneuploidy screening by providing accurate gestational age assessment, by detecting multifetal gestations, and by identifying major structural abnormalities and minor aneuploidy markers. With rare exception, the aneuploidy risk associated with any major abnormality is high enough to recommend prenatal diagnosis with chromosomal microarray analysis. We do not recommend aneuploidy *screening* after

TABLE 17-6. Aneuploidy Risk Associated with Selected Major Fetal Anomalies

Abnormality	Birth Prevalence	Aneuploidy Risk (%)	Common Aneuploidies[a]
Cystic hygroma	1/5000	50–70	45,X; 21; 18; 13; triploidy
Nonimmune hydrops	1/1500–4000	10–20	21; 18; 13; 45,X, triploidy
Ventriculomegaly	1/1000–2000	5–25	13; 18; 21; triploidy
Holoprosencephaly	1/10,000–15,000	30–40	13; 18; 22; triploidy
Dandy-Walker malformation	1/12,000	40	18; 13; 21; triploidy
Cleft lip/palate	1/1000	5–15	18; 13
Cardiac defects	5–8/1000	10–30	21; 18; 13; 45,X; 22q11.2 microdeletion
Diaphragmatic hernia	1/3000–5000	5–15	18; 13; 21
Esophageal atresia	1/4000	10	18; 21
Duodenal atresia	1/10,000	30	21
Gastroschisis	1/2000	No increase	
Omphalocele	1/3000–5000	30–50	18; 13; 21; triploidy
Clubfoot	1/1000	5–30	18; 13

[a]Numbers indicate autosomal trisomies except where indicated. For example, 45,X indicates Turner syndrome.

Data from Best, 2012; Canfield, 2006; Colvin, 2005; Cragan, 2009; Dolk, 2010; Ecker, 2000; Gallot, 2007; Long, 2006; Orioli, 2010; Pavone, 2018; Pedersen, 2012; Sharma, 2011; Solomon, 2010; Walker, 2001.

detection of a major abnormality, because of the many genetic conditions are not detectable with screening tests. Counseling should include the association of the abnormality with aneuploidy (Table 17-6). A caveat is that fetal abnormalities are frequently not isolated, and associated-but-undetectable abnormalities may greatly affect prognosis.

Importantly, fetuses with trisomy 21 and other genetic syndromes may not have obvious ultrasound abnormalities. Just one third of trisomy 21 fetuses have a major abnormality identified with second-trimester ultrasound evaluations (Bromley, 2002; Hussamy, 2019; Vintileos, 1995). If major anomalies and minor aneuploidy markers are considered, 50 to 75 percent of pregnancies affected by Down syndrome are found to have a sonographic abnormality. This is not unexpected, because nearly 40 percent of infants with trisomy 21 do not have major organ system abnormalities identified in the newborn period (Hussamy, 2019). In contrast, the vast majority of fetuses with trisomies 18 and 13 and with triploidy do have ultrasound abnormalities detectable in the second trimester.

Aneuploidy Markers

For more than three decades, investigators have recognized that ultrasound detection of aneuploidy, particularly trisomy 21, may be improved by minor markers that are collectively referred to as "soft signs." Minor markers are normal variants rather than fetal abnormalities, and in the absence of aneuploidy or an associated abnormality, they do not significantly affect prognosis. One or more markers are present in at least 10 percent of pregnancies (Bromley, 2002; Nyberg, 2003). Examples are listed in Table 17-7 and depicted in Figure 17-3.

TABLE 17-7. First- and Second-Trimester Ultrasound Markers Associated with Fetal Trisomy 21

First trimester
Ductus venosus with A-wave absence or flow reversal
Nasal bone absence or hypoplasia
Nuchal translucency enlargement
Tricuspid valve regurgitation
Second trimester
Brachycephaly or shortened frontal lobes
Clinodactyly (hypoplastic middle phalanx of fifth digit)
Echogenic bowel
Flat-appearing facies
Echogenic intracardiac focus
Nasal bone absence or hypoplasia
Nuchal fold thickening
Renal pelvis dilatation
"Sandal gap" between first and second toes
Short ear length
Single transverse palmar crease
Single umbilical artery
Short femur
Short humerus
Subclavian artery aberrant (right side)
Widened iliac angle

Markers listed alphabetically.

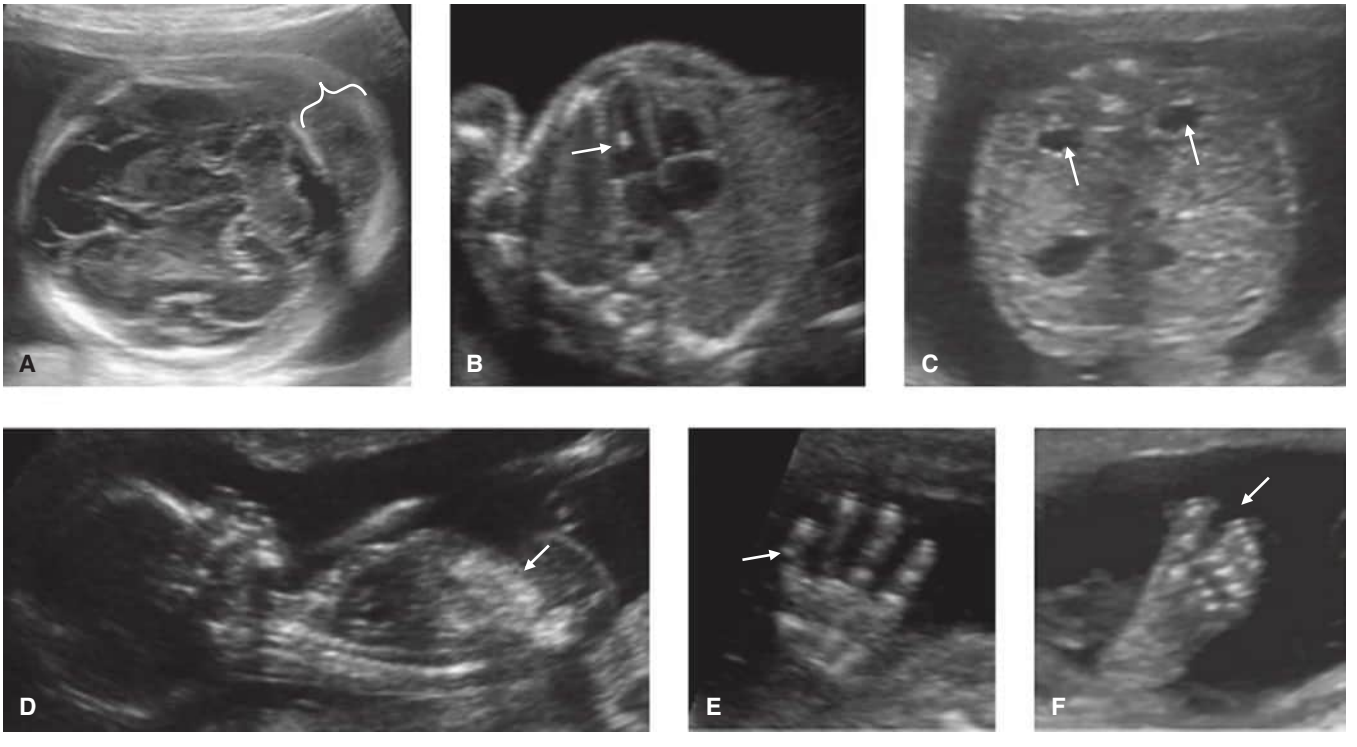


FIGURE 17-3 Minor sonographic markers that are associated with increased risk for fetal Down syndrome. **A.** Nuchal skinfold thickening (*bracket*). **B.** Echogenic intracardiac focus (*arrow*). **C.** Mild renal pelvis dilatation (pyelectasis) (*arrows*). **D.** Echogenic bowel (*arrow*). **E.** Clinodactyly—hypoplasia of the 5th finger middle phalanx creates an inward curvature (*arrow*). **F.** "Sandal-gap" (*arrow*).

A minor marker is an indication for a detailed survey of fetal anatomy to determine if it is isolated (American Institute of Ultrasound in Medicine, 2019).

If an isolated marker is identified and aneuploidy screening has not yet been performed, it should be offered. A benefit of cfDNA screening is that isolated aneuploidy markers no longer factor into the aneuploidy risk, because the negative predictive value of a normal cfDNA test is so high. Conversely, if a cfDNA result is abnormal, the absence of minor markers is not considered reassuring.

First-trimester Markers. Detection of first-trimester findings associated with aneuploidy requires specialized imaging. NT evaluation is discussed earlier (p. 337). Other first-trimester markers are not routinely used in the United States but may be available at specialized centers. The Perinatal Quality Foundation's Nuchal Translucency Quality Review Program offers an education program in first-trimester nasal bone assessment. The Fetal Medicine Foundation also provides online instruction and certification in first-trimester assessment of nasal bone, ductus venosus flow, and tricuspid flow.

There are additional benefits of first-trimester ultrasound evaluation in women who elect aneuploidy screening, including accurate assessment of gestational age and early detection of multifetal gestation or fetal demise. As discussed in Chapter 14 (p. 249), standard first-trimester sonography may identify selected major anomalies associated with aneuploidy, such as cystic hygroma.

Second-trimester Markers. If analyte-based aneuploidy screening has been performed, minor markers may be used to modify the risk using likelihood ratios (Table 17-8). The risk increases with the number of markers identified. Risk modification should follow a protocol that specifies criteria for each marker (Reddy, 2014).

TABLE 17-8. Likelihood Ratios and False-Positive Rates for Isolated Second-Trimester Markers Used in Trisomy 21 Screening Protocols

Sonographic Marker	Likelihood Ratio	Prevalence in Unaffected Fetuses (%)
Nuchal skinfold thickening	11–17	0.5
Renal pelvis dilation	1.5–1.9	2.0–2.2
Echogenic intracardiac focus	1.4–2.8	3.8–3.9[a]
Echogenic bowel	6.1–6.7	0.5–0.7
Short femur	1.2–2.7	3.7–3.9
Short humerus	5.1–7.5	0.4
Any one marker	*1.9–2.0*	*10.0–11.3*
Two markers	*6.2–9.7*	*1.6–2.0*
Three or more	*80–115*	*0.1–0.3*

[a]Higher in Asian individuals.
Data from Bromley, 2002; Nyberg, 2001; Smith-Bindman, 2001.

The *nuchal skinfold* is imaged in the transcerebellar view of the head and is measured from the outer edge of the skull to the outer border of the skin (see Fig. 17-3A). The skinfold is considered thickened if it measures ≥6 mm at 15 to 20 weeks (Benacerraf, 1985). This finding is seen in approximately 1 per 200 pregnancies and confers more than tenfold risk for trisomy 21 (Bromley, 2002; Nyberg, 2001; Smith-Bindman, 2001).

An *echogenic intracardiac focus* is a focal papillary muscle calcification that is neither a structural nor functional cardiac abnormality (see Fig. 17-3B). It is present in 4 to 7 percent of normal fetuses. The fetal trisomy 21 risk is approximately doubled. The finding is more commonly identified in Asian individuals (Shipp, 2000). Fetuses with trisomy 13 may have bilateral echogenic foci (Nyberg, 2001).

Mild *renal pelvis dilatation* is usually transient or physiologic (Chap. 15, p. 298). The renal pelves are measured anterior-to-posterior in a transverse image of the kidneys, with calipers placed at the inner borders of the fluid collection (see Fig. 17-3C). A measurement ≥4 mm is found in about 2 percent of fetuses and approximately doubles the risk for trisomy 21. The degree of pelvic dilatation beyond 4 mm correlates with the likelihood of an underlying renal abnormality, and third-trimester sonography is recommended at approximately 32 weeks.

Echogenic fetal bowel is defined as bowel that is sonographically as bright as fetal bone (see Fig. 17-3D). It is identified in approximately 0.5 percent of pregnancies and often represents a small amount of swallowed blood, not infrequently in the setting of MSAFP elevation. The fetal trisomy 21 risk is increased approximately sixfold. Echogenic bowel is also associated with fetal cytomegalovirus infection and cystic fibrosis—representing inspissated meconium in the latter. Follow-up ultrasound evaluation is suggested at 32 weeks' gestation to evaluate fetal growth (American College of Obstetricians and Gynecologists, 2020e).

For the purpose of Down syndrome screening, the fetal *femur* and *humerus* are considered short if below the 2.5th percentile for gestational age (American College of Obstetricians and Gynecologists, 2020e). Third-trimester ultrasound evaluation is suggested to assess fetal growth. Fetuses with trisomy 21 and short femur are not more likely to be growth restricted, however (Herrera, 2019).

The fetal *nasal bone* is absent in 30 percent of second-trimester fetuses with trisomy 21 and hypoplastic in more than 50 percent (Moreno-Cid, 2014). Absent nasal bone occurs in approximately 1 in 200 euploid fetuses (American College of Obstetricians and Gynecologists, 2020e; Viora, 2005). The finding represents delayed ossification rather than true absence. The nasal bone is measured between 15 and 22 weeks' gestation. Hypoplasia may be defined as shorter than 2.5 mm, as >2 standard deviations below the mean, or based on a ratio to the biparietal diameter (Cicero, 2003). The fetal profile and nasal bone are components of the detailed fetal anatomic survey, but they are not assessed as part of the standard examination and thus not used for routine screening (American Institute of Ultrasound in Medicine, 2019).

One or more *choroid plexus cysts* are seen in 1 to 2 percent of euploid pregnancies (Fig. 16-5, p. 312). The cyst is a benign,

normal variant of no clinical consequence. If associated with structural abnormalities however, the trisomy 18 risk is increased (Reddy, 2014).

CARRIER SCREENING FOR GENETIC DISORDERS

The goal of genetic carrier screening is to provide individuals with meaningful information to guide pregnancy planning according to their personal values (American College of Obstetricians and Gynecologists, 2020b). There are three approaches, each of which is an acceptable strategy: ethnicity-based carrier screening, panethnic screening (performed regardless of ethnicity), and expanded carrier screening—which is a type of panethnic screening performed for a large number of conditions. All carrier screening is optional and should be an informed choice.

Carrier screening is ideally performed prior to conception so that both partners can have the opportunity to consider the results and pursue options such as preimplantation genetic testing (p. 348) or donor gametes. If the screen detects a genetic condition, partner screening should be offered. No screening test will identify all carriers of a condition. Genetic counseling should include the residual risk for the condition if the partner's screen is negative, as well as prenatal diagnosis options (American College of Obstetricians and Gynecologists, 2020b). Prenatal diagnosis is increasingly available if disease-causing mutation or mutations are known. The Genetic Testing Registry of the National Institutes of Health contains detailed information regarding more than 18,000 genetic conditions and 78,000 genetic tests (www.ncbi.nlm.nih.gov/gtr/). In the setting of consanguinity, additional genetic counseling is indicated.

Ethnicity-based carrier screening is offered for selected autosomal recessive conditions that are found in greater frequency in specific racial or ethnic groups. The *founder effect* occurs when an otherwise rare gene is found with greater frequency in a certain population and can be traced back to a single family member or small group of ancestors. It may develop when generations of individuals procreate only within their own groups because of religious or ethnic prohibitions or geographical isolation. Because assignment of a single ethnicity is often difficult, *panethnic* screening is increasingly preferred.

Expanded carrier screening has the advantage of screening for many conditions simultaneously, ranging from a few dozen to more than 1000 (Chokshvilli, 2018). An unfortunate result is that much of the population—more than 50 percent of those screened–may be identified to be carriers for at least 1 condition. Some conditions are so rare that information about detection and residual risk are limited. Counseling regarding phenotypic expression of different mutations and determination of whether variants have clinical significance has become increasingly complex. Thus, expanded carrier screening can cause anxiety for families and may pose challenges to already-strained genetic counseling resources. The American College of Obstetricians and Gynecologists (2020b) has the following guidelines for conditions included in expanded panels:

1. The carrier frequency should be at least 1:100, which corresponds to a population prevalence of 1:40,000.
2. The condition should have a well-defined phenotype, lead to a detrimental effect on quality of life, cause cognitive or physical impairment, or require surgical or medical intervention.
3. Conditions with adult onset are not recommended for inclusion.

There is a long-held principle that genetic carrier screening for a particular condition not be repeated in a subsequent pregnancy. The number of mutations for which testing is available has greatly increased in recent years, but the additional yield of rescreening is usually low. Consultation with a provider with genetic expertise should be considered before screening is repeated (American College of Obstetricians and Gynecologists, 2020a).

Cystic Fibrosis

This disorder is caused by a mutation in the *cystic fibrosis conductance transmembrane regulator (CFTR)* gene, which is located on the long arm of chromosome 7 and encodes a chloride-channel protein. Although the most common *CFTR* mutation associated with classic cystic fibrosis (CF) is the Δ*F508* mutation, more than 2100 mutations have been identified (Cystic Fibrosis Mutation Database, 2020). CF may develop from either *homozygosity* or *compound heterozygosity* for mutations in the *CFTR* gene. One mutation must be present in each copy of the gene, but they need not be the same mutation. There is a wide range of clinical disease severity. Median survival length is 42 years, but approximately 15 percent have milder disease and can survive for decades longer. Care of the pregnant woman with CF is discussed in Chapter 54 (p. 968).

For more than two decades, the American College of Obstetricians and Gynecologists (2020a) has recommended that all women who are pregnant or considering pregnancy be offered CF carrier screening. Such screening should include, at minimum, a panel of 23 panethnic gene mutations, selected because they are present in at least 0.1 percent of patients with classic CF. The CF-mutation carrier frequency approximates 1:25 in Ashkenazi Jews and those of non-Hispanic white ethnicity, 1:60 in African Americans and those of Hispanic white ethnicity, and 1:95 Asian Americans. Using the 23-mutation panel, the residual carrier risk after a negative test result was roughly 1:380 for Ashkenazi Jews and 1:170 to 1:200 for other ethnicities (American College of Obstetricians and Gynecologists, 2020a).

More recently however, expanded panels that use gene sequencing have been reported to improve detection of at-risk couples by 30 percent compared with the 23-mutation panel (Beauchamp, 2019). The American College of Medical Genetics now recommends either a targeted approach to carrier screening, in which the standard mutation panel may be used, or a more comprehensive approach in which specific variant classifications may be reported (Deignan, 2020).

CF is included in all newborn screening panels but is not a substitute for carrier screening because it only identifies affected individuals. If the patient carries a mutation, her partner should be offered screening. If both parents are carriers, genetic counseling is indicated, and prenatal diagnostic testing should be offered.

Spinal Muscular Atrophy

This autosomal recessive disorder results in spinal cord motor neuron degeneration that leads to skeletal muscle atrophy and generalized weakness. There is currently no effective treatment. The prevalence of spinal muscular atrophy (SMA) is 1 in 6000 to 10,000 live births. Types I, II, III, and IV are caused by mutations in the *survival motor neuron (SMN1)* gene, which is located on the long arm of chromosome 5 (5q13.2) and encodes the SMN protein. Types I and II account for 80 percent of cases and are both lethal (American College of Obstetricians and Gynecologists, 2020a). SMA type I, known as Werdnig-Hoffmann disease, is the most severe. Disease onset is within the first 6 months, and affected children die of respiratory failure by age 2 years. Type II generally has onset before age 2 years, and the age at death can range from 2 years to the third decade of life. Type III also presents before age 2 years, with disease severity that is milder and more variable. Type IV does not present until adulthood.

The American College of Obstetricians and Gynecologists (2020a) recommends that carrier screening for SMA be offered to all women who are considering pregnancy or are currently pregnant. Prior to screening, the potential spectrum of severity, carrier frequency, and detection rate should be provided. Posttest counseling should include the residual risk after a negative result, which differs according to ethnicity and also according to the number of *SMN1* copies detected. The SMA carrier frequency approximates 1:35 in those of non-Hispanic white ethnicity, 1:41 in Ashkenazi Jews, 1:53 in Asians, 1:66 in African Americans, and 1:117 in those of Hispanic white ethnicity (Hendrickson, 2009). Carrier detection rates range from 90 to 95 percent for each ethnicity except African Americans, in whom it approximates 70 percent (MacDonald, 2014).

Although there is usually one copy of the *SMN1* gene on each chromosome, approximately 3 to 4 percent of carriers have no copies of this gene on one chromosome and two copies on the other. Because such individuals have two copies in total, they are not detected if a quantitative polymerase chain reaction test is used. Carrier screening is less sensitive in African American individuals, because they are more likely to have this genetic variation. Additionally, some individuals have three copies of the gene and are at even lower risk. If the patient or her partner has a family history of SMA, or if carrier screening is positive, genetic counseling is indicated.

Hemoglobinopathies

These include the sickle hemoglobinopathies—sickle cell anemia and sickle cell hemoglobin C disease, thalassemias, and sickle cell–β-thalassemia. Their pathophysiology and management are discussed in Chapter 59 (p. 1053). The risk is increased in women who are of African or African-American, Mediterranean, Middle Eastern, or Southeast Asian ethnicity. In such individuals, hemoglobin electrophoresis should be offered prenatally or prior to conception (American College of Obstetricians and Gynecologists, 2019a).

Sickle Hemoglobinopathies

Approximately 1 in 12 African Americans has sickle-cell trait, 1 in 40 carries hemoglobin C, and 1 in 40 carries the trait for β-thalassemia. Hemoglobin S is also more common among individuals of Mediterranean, Middle Eastern, and Asian Indian descent (Davies, 2000). If a couple is at risk to have a child with a sickle hemoglobinopathy, genetic counseling should be offered. Prenatal diagnosis can be performed with either chorionic villus sampling or amniocentesis.

Thalassemias

These are the most common single-gene disorders worldwide. Thalassemias are characterized as alpha (α) or beta (β) depending on whether α- or β-hemoglobin chains are affected. In general, α-thalassemia is more likely to be caused by *deletions* of α-globin chains, whereas β-thalassemia more often stems from *mutations* in β-globin chains.

In α-thalassemia, the number of α-globin genes that are deleted may range from one to all four. If two α-globin genes are deleted, both may be deleted from the same chromosome—*cis* configuration (αα/––), or one may be deleted from each chromosome—*trans* configuration (α–/α–). The *cis* configuration is more prevalent among Southeast Asians, whereas those of African descent are more likely to inherit the trans configuration. Alpha-thalassemia trait results in mild anemia. However, if the patient and her partner both carry cis deletions, offspring are at risk for an absence of α-hemoglobin, called Hb Barts disease. This can lead to hydrops and fetal loss (Chap. 18, p. 360). Hemoglobin electrophoresis cannot detect α-thalassemia or α-thalassemia trait. Molecular genetic testing should be considered if there is microcytic anemia in the absence of iron deficiency and if the hemoglobin electrophoresis is normal, particularly among individuals of Southeast Asian descent (American College of Obstetricians and Gynecologists, 2019a).

In β-thalassemia, β-globin genes may cause reduced or absent production of β-globin chains. If the mutation affects one gene, it results in β-thalassemia minor. If both copies are affected, the result is either β-thalassemia major—termed Cooley anemia—or β-thalassemia intermedia. Hemoglobin electrophoresis demonstrates elevated levels of hemoglobins that do not contain β-chains, which are hemoglobins F and A_2. β-Thalassemia minor should be considered if an individual of one or more of the aforementioned ethnicities is found to have microcytic anemia in the absence of iron deficiency. A hemoglobin A_2 level exceeding 3.5 percent confirms the diagnosis.

Recessive Diseases in Ashkenazi Jewish Individuals

Among Jewish individuals of Eastern and Central European (Ashkenazi) descent, there are three severe diseases for which the carrier frequency and detection rate are high enough that screening should be offered: Tay-Sachs disease, Canavan disease, and familial dysautonomia (American College of Obstetricians and Gynecologists 2020a). The carrier rate approximates 1 in 30 for Tay-Sachs disease, 1 in 40 for Canavan disease, and 1 in 32 for familial dysautonomia. For each, the detection rate is at least 98 percent. As for other genetic conditions, screening is ideally performed prior to conception or during early pregnancy.

There are several other autosomal recessive conditions for which the College also recommends that screening be

considered. These include Bloom syndrome, familial hyperinsulinism, Fanconi anemia, Gaucher disease, glycogen storage disease type I (von Gierke disease), Joubert syndrome, maple syrup urine disease, mucolipidosis type IV, Niemann-Pick disease, and Usher syndrome. Gaucher disease differs from the other conditions listed because it has a wide range in phenotype and because treatment is available in the form of enzyme repletion and substrate reduction therapy.

Tay-Sachs Disease

This lysosomal-storage disease causes progressive neurodegeneration and death in early childhood. It is characterized by deficiency of the enzyme hexosaminidase A, which results in accumulation of GM2 gangliosides in the central nervous system. Affected individuals have almost complete absence of the enzyme, whereas carriers are asymptomatic but have less than 55-percent hexosaminidase A activity. An international Tay-Sachs carrier screening campaign was initiated in the 1970s and met with unprecedented success in the Ashkenazi Jewish population. The incidence of Tay-Sachs disease subsequently declined more than 90 percent (Kaback, 1993). Other groups at increased risk for Tay-Sachs disease include those of French-Canadian and Cajun descent.

Carrier screening for Tay-Sachs disease is performed with DNA-based mutation analysis or hexosaminidase activity testing. DNA-based mutation analysis is the preferred test in Ashkenazi Jewish individuals and other high-risk groups but has a lower detection rate in the general population. Therefore, hexosaminidase activity testing is recommended for screening in individuals from lower-risk ethnicities. If a woman is pregnant or taking oral contraceptives, a hexosaminidase activity test should be performed on leukocytes to avoid a high false-positive rate (American College of Obstetricians and Gynecologists, 2020a). If both partners are found to be carriers, prenatal diagnostic testing should be offered. Hexosaminidase activity may be measured from chorionic villi or amnionic fluid.

PRENATAL AND PREIMPLANTATION DIAGNOSTIC TESTS

Diagnostic procedures used in prenatal diagnosis include amniocentesis and chorionic villus sampling (CVS). Fetal blood sampling is rarely performed solely for genetic diagnosis but may be used in conjunction with intrauterine transfusion. Preimplantation genetic tests for aneuploidies, structural chromosomal rearrangements, and monogenic disorders are available for couples undergoing in vitro fertilization (IVF).

In the setting of a fetal structural abnormality, chromosomal microarray analysis (CMA) is recommended. CMA is preferred to cytogenetic analysis (karyotyping) because it can detect clinically significant chromosomal abnormalities in approximately 6.5 percent of fetuses with normal karyotype (Callaway, 2013; de Wit, 2014, Wapner, 2012). And, in the absence of a fetal structural abnormality, CMA has detected additional chromosomal abnormalities (pathogenic copy number variants) in up to 1 percent of those with normal karyotype. CMA is therefore made available whenever a prenatal diagnostic procedure is performed (American College of Obstetricians and Gynecologists, 2018; Callaway, 2013). Types of CMA platforms and their benefits and limitations are reviewed in Chapter 16 (p. 326).

Karyotyping identifies aneuploidy and polyploidy. Additionally, it can identify *balanced* chromosomal rearrangements that are currently undetectable with CMA. For example, karyotyping performed when a couple has experienced recurrent pregnancy loss may reveal that one parent carries a balanced robertsonian translocation (Chap. 16, p. 315). An additional indication is the fetus with a structural abnormality that strongly suggests a particular aneuploidy—such as endocardial cushion defect in trisomy 21 or holoprosencephaly in trisomy 13.

If rapid identification of a specific chromosomal abnormality, such as trisomy 21, 18, or 13, is needed, fluorescence in situ hybridization (FISH) may be used in conjunction with CMA or karyotyping. Decision-making based on FISH should incorporate clinical information consistent with the suspected diagnosis, such as a screening result or ultrasound finding (American College of Obstetricians and Gynecologists, 2018).

Because of improvements in aneuploidy screening tests, there has been a dramatic drop in the number of prenatal diagnostic procedures. Larion and coworkers (2014) reported a 70-percent decline in CVS and a nearly 50-percent drop in amniocentesis procedures since the introduction of cfDNA screening in 2012. This further amplified the decrease in amniocentesis procedures that occurred with the advent of first-trimester screening (Warsof, 2015). Unfortunately, fewer than 40 percent of women with a positive screening result elect prenatal diagnosis (Dar, 2014). If prenatal diagnosis is elected, however, the percent with an abnormal result has increased significantly (Awomolo, 2018).

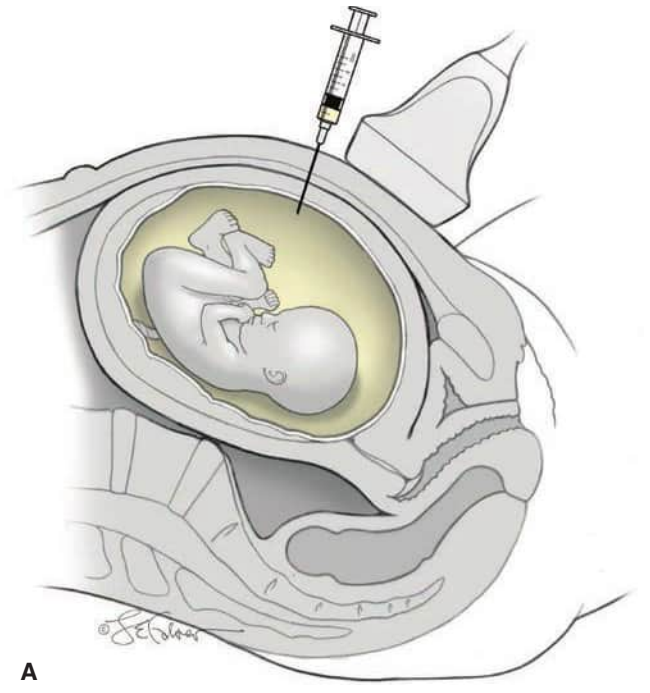
■ Amniocentesis

Because of its established safety and efficacy, amniocentesis is offered to all pregnant women (American College of Obstetricians and Gynecologists, 2020e). Amnionic fluid is withdrawn transabdominally under direct ultrasound guidance. Although typically performed between 15 and 20 weeks' gestation, amniocentesis may be done at any point later in gestation. Tests include those for genetic conditions, congenital infections, and alloimmunization. Fetal lung maturity is no longer routinely assessed, based on recommendations against using it to assist with delivery timing (American College of Obstetricians and Gynecologists, 2019b).

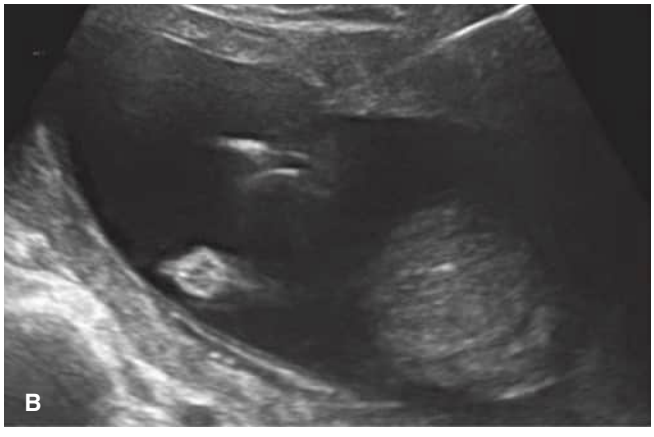
Technique

Amniocentesis is performed with a 20- or 22-gauge needle using aseptic technique (Fig. 17-4). A standard spinal needle is 9 cm long. A longer needle may be required for obese patients. To aid in needle selection, we find it helpful to measure the distance from skin to amnionic fluid with ultrasound prior to the procedure. After the patient empties her bladder, the skin is prepared with an antiseptic such as povidone-iodine. Shellfish allergy is not a contraindication to the povidone-iodine antiseptic (Westermann-Clark, 2015).

All aspects of the procedure are performed under direct ultrasound guidance. A pocket of amnionic fluid close to the midline is selected, avoiding fetal parts and being cognizant



A



B

FIGURE 17-4 A. Amniocentesis. **B.** The amniocentesis needle is seen in the upper right portion of this sonogram. (Figures 17-4, 17-5, and 17-7 are reproduced with permission from Mastrobattista JM, Espinoza J: Invasive prenatal diagnostic procedures. In Yeomans ER, Hoffman BL, Gilstrap LC III, et al (eds): Cunningham and Gilstrap's Operative Obstetrics, 3rd ed. New York, NY: McGraw Hill; 2017.)

of uterine size and shape. The needle is inserted perpendicular to the skin, gently puncturing the chorioamnion rather than pushing or "tenting" it away from the uterine wall. The amnion usually fuses with the underlying chorion by 16 weeks' gestation, and the procedure is generally deferred until after chorioamnion fusion. Discomfort from the procedure is considered minor and is related more to focal myometrial contraction than needle discomfort at the skin. Local anesthetic has not been found to be beneficial (Mujezinovic, 2011).

The amniotic fluid should be clear and colorless or pale yellow. Blood-tinged fluid is more frequent with transplacental passage of the needle and generally clears with continued aspiration. Needle passage through the placenta occurs in approximately 60 percent of cases with anterior placentation and is not associated with pregnancy loss (Bombard, 1995, Marthin, 1997). Dark brown or greenish fluid may represent a past episode of intraamnionic bleeding.

TABLE 17-9. Selected Tests Performed on Amniotic Fluid and Volume of Fluid Required

Test	Volume (mL)[a]
Chromosomal microarray analysis	20
Fetal karyotype	20
FISH[b]	10
Genotype studies (alloimmunization)	20
PCR tests for cytomegalovirus, toxoplasmosis, or parvovirus	1–2 each test
Cytomegalovirus culture	2–3
Tests no longer commonly used:	
Fetal lung maturity tests	10
Delta OD 450 (bilirubin analysis)	2–3
Alpha-fetoprotein	2

[a]The volume of fluid needed for each test may vary according to individual laboratory specifications.
[b]Fluorescence in situ hybridization (FISH) is typically performed for chromosomes 21, 18, 13, X, and Y.
PCR = polymerase chain reaction.

The volume of fluid generally needed for commonly performed analyses is shown in Table 17-9. Because the initial 1 to 2 mL of fluid aspirate may be contaminated with maternal cells, it is often discarded. Approximately 20 to 30 mL of fluid is then collected for either fetal CMA or karyotyping before the needle is withdrawn. The uterine puncture site is observed for bleeding, and fetal cardiac motion is documented following the procedure. If the patient is Rh D-negative and unsensitized, anti-D immune globulin is administered after the procedure (Chap. 18, p. 356).

Multifetal Pregnancy. When performing the procedure in a dichorionic or monochorionic diamnionic twin gestation, careful attention is paid to the location of each sac and the dividing membrane. Until recently, a small quantity of dilute indigo carmine dye was often injected before removing the needle from the first sac, with return of clear amnionic fluid anticipated following needle placement into the second sac. Because of widespread shortages of indigo carmine dye, experienced providers typically offer amniocentesis without dye injection. Methylene blue dye is contraindicated because it has been associated with jejunal atresia and neonatal methemoglobinemia (van der Pol, 1992).

Complications

Midtrimester losses attributable to amniocentesis have decreased with improvements in imaging technology. When performed by an experienced provider, the procedure-related loss rate is estimated to be 0.1 to 0.3 percent, or about 1 per 500 procedures (American College of Obstetricians and Gynecologists, 2018; Odibo, 2008, Salomon, 2019). The loss rate may be doubled in women whose body mass index exceeds 40 kg/m^2 (Harper, 2012). In twin pregnancies, Cahill and coworkers (2009) reported a loss rate of 1.8 percent attributable to amniocentesis.

When counseling regarding fetal loss following a procedure, it can be helpful to explain the difference between overall losses and procedure-related losses. In a recent metaanalysis that included more than 60,000 amniocentesis procedures and 300,000 control pregnancies, the loss rate in the absence of a procedure was 0.6 percent, approximately twice the rate of losses attributable to procedures (Salomon, 2019). The indication for the procedure is also relevant, because severe fetal abnormalities and hydrops can significantly increase the loss rate, regardless of a procedure.

Other complications of amniocentesis include amnionic fluid leakage or transient vaginal spotting in 1 to 2 percent. Leakage of amnionic fluid generally occurs within 48 hours of the procedure. Leakage of fluid typically resolves after a few days, and fetal survival exceeds 90 percent (Borgida, 2000). Management recommendations include pelvic rest and avoidance of strenuous activity. Needle injuries to the fetus are rare. If karyotyping is performed, amnionic fluid culture is successful in more than 99 percent of cases, although cells are less likely to grow if the fetus is abnormal (Persutte, 1995).

Early Amniocentesis

Amniocentesis was formerly offered between 11 and 14 weeks' gestation. The technique is the same as for traditional amniocentesis, but the procedure may be more challenging because of lack of membrane fusion to the uterine wall. Approximately 1 mL is withdrawn for each week of gestation. Early amniocentesis is associated with significantly higher rates of fetal loss and other procedure-related complications than other procedures. Complications include development of talipes equinovarus (clubfoot) and amnionic fluid leakage (Canadian Early and Mid-Trimester Amniocentesis Trial, 1998; Philip, 2004). For these reasons, early amniocentesis is not recommended (American College of Obstetricians and Gynecologists, 2018).

Chorionic Villus Sampling

Biopsy of chorionic villi is typically performed between 10 and 13 weeks' gestation. As with amniocentesis, the specimen is usually sent for CMA or karyotype analysis. The primary advantage of CVS is that results are available earlier in pregnancy, permitting more time for decision-making and safer pregnancy termination, if desired.

Technique

CVS is performed transcervically or transabdominally. Both approaches are equally safe and effective (American College of Obstetricians and Gynecologists, 2018). The transcervical approach uses a flexible polyethylene catheter that contains a blunt-tipped, malleable stylet. Transabdominal sampling is performed with an 18- or 20-gauge spinal needle. Both use aseptic technique and are performed under direct transabdominal ultrasound guidance. The catheter or needle is inserted into the early placenta—*chorion frondosum*, and villi are aspirated into a syringe that contains tissue culture media (Fig. 17-5).

Relative contraindications include vaginal bleeding or spotting, active genital tract infection, extreme uterine ante- or retroflexion, or body habitus precluding adequate visualization. If the patient is Rh D-negative and unsensitized, anti-D immune globulin is administered after the procedure.

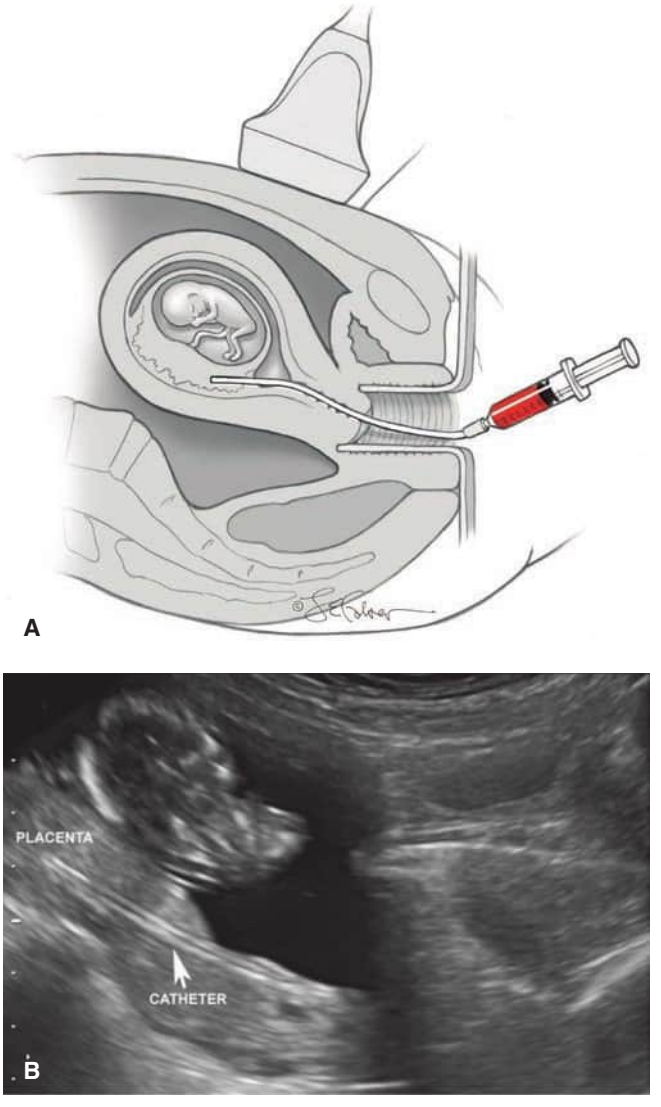


FIGURE 17-5 A. Transcervical chorionic villus sampling. **B.** Catheter entering the placenta is marked and labeled.

Complications

The *overall* fetal loss rate following CVS is higher than that with midtrimester amniocentesis. This is because of losses that would have occurred between the first and second trimester in the absence of a procedure. The procedure-related loss rate is comparable to that with amniocentesis, approximately 0.1 to 0.3 percent (American College of Obstetricians and Gynecologists, 2018). In fact, a recent metaanalysis identified no significant losses from CVS when controls with similar risk profiles were selected (Salomon, 2019). As with amniocentesis, CVS indication will affect the loss rate. For example, fetuses with increased NT thickness have a greater likelihood of demise. There is also a learning curve associated with safe performance of CVS (Silver, 1990; Wijnberger, 2003).

An early problem with CVS was its association with *limb-reduction defects* and *oromandibular limb hypogenesis,* shown in Figure 17-6 (Firth, 1991, 1994; Hsieh, 1995). These were

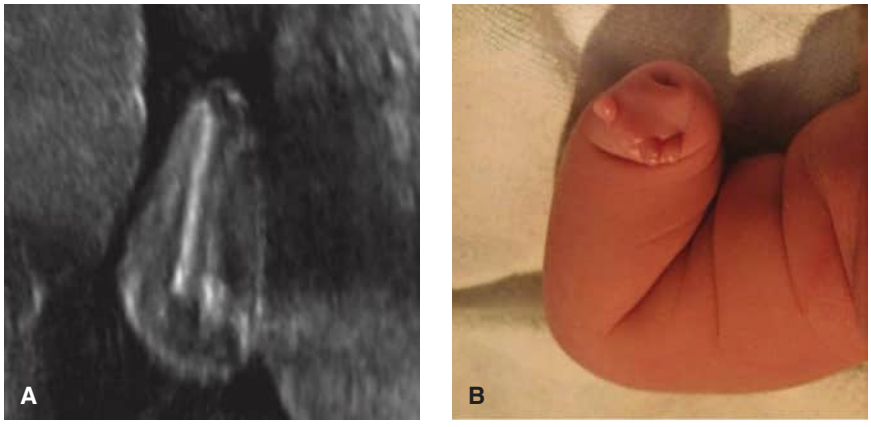


FIGURE 17-6 Oromandibular limb hypogenesis is characterized by transverse limb deficiency and absence or hypoplasia of the tongue or mandible. This is hypothesized to result from vascular disruption with subsequent loss of tissue. **A.** Sonogram obtained at 25 weeks' gestation demonstrates a fetal limb reduction defect involving the right hand. **B.** Photograph of the right extremity of the same newborn. Chorionic villus sampling was not performed in this pregnancy. (Reproduced with permission from Dr. Jamie Morgan.)

subsequently found to be associated with procedures performed at 7 weeks' gestation (Holmes, 1993). When performed at or after 10 weeks' gestation, the incidence of limb defects does not exceed the background population rate of approximately 1 case per 1000 (Evans, 2005; Kuliev, 1996).

Vaginal spotting is not uncommon following transcervical sampling, but it is self-limited and not associated with pregnancy loss. The incidence of infection or leakage of amnionic fluid is less than 0.5 percent (American College of Obstetricians and Gynecologists, 2018).

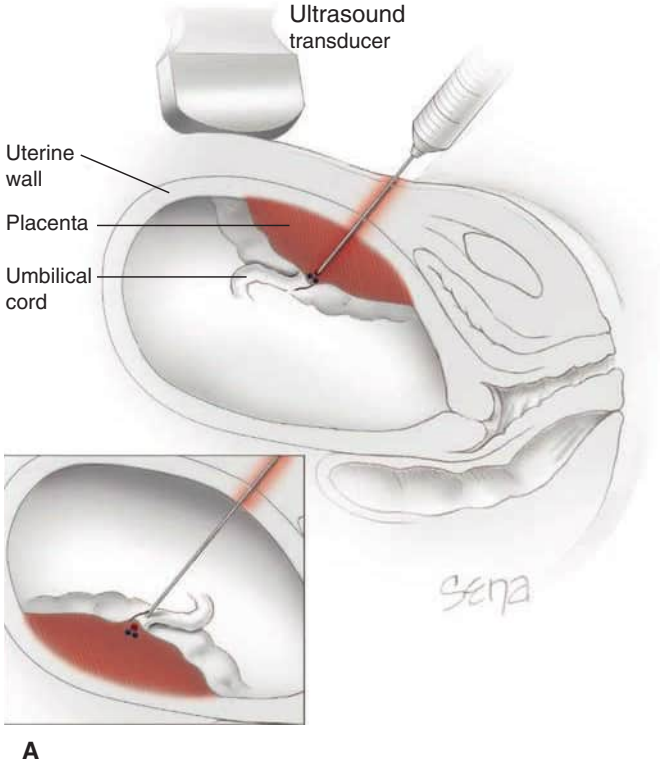
A limitation of CVS is that chromosomal mosaicism is identified in up to 2 percent of specimens (Malvestiti, 2015). In most cases, the mosaicism reflects confined placental mosaicism rather than a true second cell line within the fetus. This is discussed in Chapter 16 (p. 318). Amniocentesis should be offered, and if the result is normal, the mosaicism is usually presumed to be confined to the placenta. Confined placental mosaicism is associated with fetal-growth restriction (Baffero, 2012; Toutain, 2018).

Fetal Blood Sampling

This procedure is also called cordocentesis or percutaneous umbilical blood sampling (Fig. 17-7). It was initially described for fetal transfusion of red blood cells in the setting of anemia from alloimmunization, and fetal anemia assessment remains the most common indication (Chap. 18, p. 356). Other indications include assessment and treatment of platelet alloimmunization and for fetal karyotype determination, particularly in cases of mosaicism identified following amniocentesis or CVS. Improvements in testing using an amniocentesis specimen have eliminated the need for fetal blood sampling in most cases (Society for Maternal-Fetal Medicine, 2013).

Technique

Using aseptic technique, a 22- or 23-gauge spinal needle is introduced into the umbilical vein under direct ultrasound guidance, and blood is slowly withdrawn into a heparinized syringe. Precise visualization of the needle is essential. As with



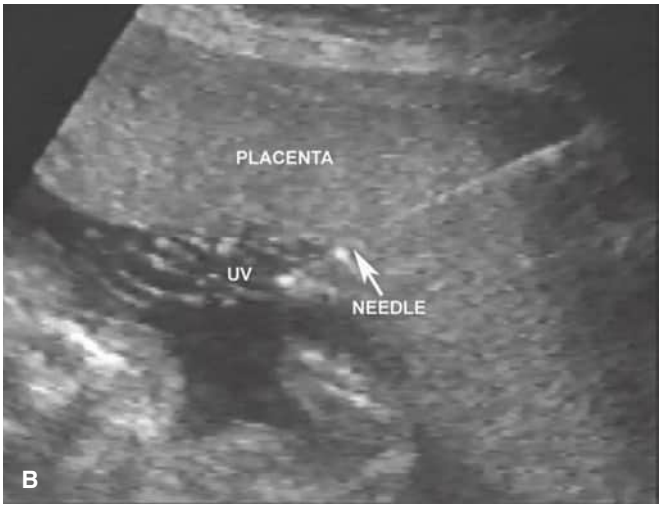


FIGURE 17-7 Fetal blood sampling. **A.** Access to the umbilical vein varies depending on placental location and cord position. With an anterior placenta, the needle may traverse the placenta. Inset: With posterior placentation, the needle passes through amnionic fluid before penetrating the umbilical vein. Alternatively, a free loop of cord may be accessed. **B.** Sonogram shows an anterior placenta with transplacental needle passage into the umbilical vein (UV).

amniocentesis, a longer needle may be required for obese patients. Fetal blood sampling is often performed near the placental cord insertion site, where it may be easier to enter the cord if the placenta lies anteriorly. Alternatively, a free loop of cord may be punctured. Because fetal blood sampling requires more time than other fetal procedures, a local anesthetic may be administered. Prophylactic antibiotics are used at some centers, although no trials support this policy. Arterial puncture is avoided, because it may result in vasospasm and fetal bradycardia. After the needle is removed, fetal cardiac motion is documented, and the site is observed for bleeding.

Complications

The procedure-related fetal loss rate following fetal blood sampling approximates 1 percent (Tongsong, 2001, Tanvisut, 2020). The actual loss rate varies according to the procedure indication and the fetal status. Other complications may include cord vessel bleeding in 20 to 30 percent of cases, fetal-maternal bleeding in approximately 40 percent of cases in which the placenta is traversed, and fetal bradycardia in 5 to 10 percent (Boupaijit, 2012; Society for Maternal-Fetal Medicine, 2013; Tanvisut, 2020). Most complications are transitory, with complete recovery, but some result in fetal loss.

In one series of more than 2000 procedures comparing fetal blood sampling near the placental cord insertion site with puncture of a free loop, rates of procedure success, pregnancy loss, visible bleeding from the cord, and fetal bradycardia did not differ. Time to complete the procedure was significantly shorter if the cord was sampled at the placental insertion site rather than in a free loop—5 versus 7 minutes. However, sampling at the insertion site had a higher rate of maternal blood contamination (Tangshewinsirikul, 2011).

■ Preimplantation Genetic Tests

For couples undergoing IVF, several types of genetic tests may be performed on oocytes (polar bodies) or embryos prior to uterine transfer. These include preimplantation genetic testing for aneuploidy, abbreviated PGT-A, prenatal genetic testing for structural rearrangements (PGT-SR), and prenatal genetic testing for monogenic disorders (PGT-M). Testing is typically performed via trophectoderm biopsy at the blastocyst stage but may be performed on polar bodies of oocytes or via blastomere biopsy of a cleavage-stage embryo (Fig. 17-8). False-positive and false-negative results are possible with each type of PGT. Therefore, prenatal diagnosis with CVS or amniocentesis should be offered (American College of Obstetricians and Gynecologists, 2020d). Comprehensive genetic counseling is required before consideration of each of these procedures (ESHRE PGT Consortium Steering Committee, 2020).

PGT-A is a type of aneuploidy screening test that evaluates the number of each chromosome. Although clearly an appealing prospect, available data are limited, and an optimal testing platform is not yet established. Importantly, if PGT-A is performed with next-generation sequencing following trophectoderm biopsy, mosaicism is frequently identified (Vera-Rodriguez, 2017). Despite an increased risk for poor outcome, many such cases have resulted in healthy, normal children (Victor, 2019).

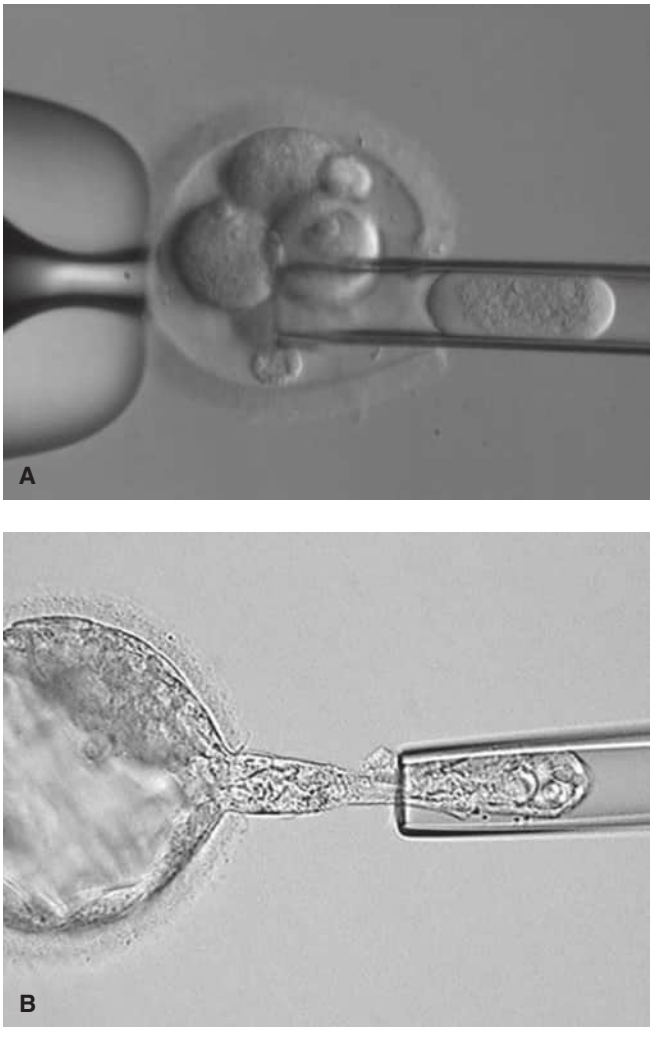


FIGURE 17-8 A. Blastomere biopsy. After a blastomere is selected, it is then drawn into the pipette. **B.** Trophectoderm biopsy. (Reproduced with permission from Doody KJ: Treatment of the infertile couple. Hoffman BL, Schorge JO, Halvorson LM, et al (eds): Williams Gynecology, 4th ed. New York, NY: McGraw Hill; 2020.)

The American Society for Reproductive Medicine (2018) has concluded that the utility of routine performance of PGT-A for all IVF pregnancies has yet to be determined.

PGT-M may be performed when there is increased risk for a particular single-gene disorder or a hereditary cancer syndrome (American College of Obstetricians and Gynecologists, 2020d). It is a test for a specific condition rather than a panel. In selected cases, this technique may also be used identify a suitable future donor of umbilical cord blood for an affected family member.

PGT-SR is offered if one of the parents is a carrier of such a rearrangement, such as a duplication, deletion, translocation, insertion, or inversion. The test will identify an unbalanced chromosomal rearrangement but will not detect a balanced carrier. Counseling should therefore include this limitation.

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CHAPTER 18

Fetal Disorders

Fetal disorders may be acquired—such as alloimmunization; may be genetic—congenital adrenal hyperplasia; or may be sporadic—like many structural malformations. This chapter reviews fetal anemia and thrombocytopenia and immune and nonimmune fetal hydrops. Hydrops is perhaps the quintessential fetal disorder, as it can be a manifestation of severe illness from a wide variety of etiologies. Fetal structural malformations are reviewed in Chapter 15, genetic abnormalities in Chapters 16 and 17, and conditions amenable to medical or surgical fetal therapy in Chapter 19. Because congenital infections arise as a result of maternal infection or colonization, they are discussed in Chapters 67 and 68.

FETAL ANEMIA

Anemia may result from alloimmunization, infection, genetic disorders, or fetomaternal hemorrhage. Red cell alloimmunization results from transplacental passage of maternal antibodies that destroy fetal red cells. Alloimmunization leads to overproduction of immature fetal and neonatal red cells—*erythroblastosis fetalis*—a condition now referred to as *hemolytic disease of the fetus and newborn (HDFN)*. Congenital infections are also associated with fetal anemia, particularly parvovirus B19, discussed in Chapter 67 (p. 1191). In Southeast Asian populations, α^0-thalassemia is a common cause of severe anemia and nonimmune hydrops. Rare genetic causes of anemia include red cell production disorders—such as Diamond-Blackfan anemia and Fanconi anemia; red cell enzymopathies—glucose-6-phosphate dehydrogenase deficiency and pyruvate kinase deficiency; red cell structural abnormalities—hereditary spherocytosis and elliptocytosis; lysosomal storage diseases—Gaucher disease, Niemann-Pick, and mucopolysaccharidosis VII; and myeloproliferative disorders—leukemias. Fetomaternal hemorrhage is discussed on page 357. Fetal anemia is typically identified through Doppler evaluation of the fetal middle cerebral artery (MCA) peak systolic velocity (p. 355).

Progressive fetal anemia from any cause leads to heart failure, hydrops fetalis, and ultimately death. Treatment with intrauterine transfusions can be lifesaving. Severely anemic fetuses transfused in utero have survival rates exceeding 90 percent, and even in cases of hydrops fetalis, survival rates approach 80 percent (Lindenberg, 2013; Mizuuchi, 2021; Zwiers, 2017).

Red Cell Alloimmunization

Currently, 36 different blood group systems and 360 erythrocyte antigens are recognized by the International Society of Blood Transfusion (Storry, 2019). Blood banks routinely screen for erythrocyte antigens. Some are immunologically and genetically important, but many are rare and of little clinical significance. An individual who lacks a specific erythrocyte antigen may produce antibodies against it when exposed to that antigen. Such antibodies can prove harmful if an individual receives an incompatible blood transfusion. During pregnancy, these antibodies may cross the placenta and lyse fetal red cells that contain the associated antigens, resulting in anemia.

The fetus typically inherits at least one erythrocyte antigen from the father that is lacking in the mother. The pregnant woman may become sensitized if enough fetal red cells reach her circulation to elicit an immune response. Importantly, alloimmunization is uncommon for the following reasons: (1) low prevalence of incompatible erythrocyte antigens; (2) insufficient transplacental passage of fetal antigens and maternal antibodies; (3) maternal-fetal ABO incompatibility, which leads to rapid clearance of fetal erythrocytes before they elicit an immune response; (4) variable antigenicity; and (5) variable maternal immune response to the antigen.

The prevalence of red cell alloimmunization in pregnancy approximates 1 percent (Bollason, 2017; Koelewijn, 2008). Most cases of severe fetal anemia requiring antenatal transfusion are attributable to anti-D, anti-Kell, anti-c, or anti-E alloimmunization (de Haas, 2015).

Maternal blood type and antibody screen are routinely assessed at the first prenatal visit. Unbound antibodies in maternal serum are detected with an *indirect Coombs test* (Chap. 10, p. 178). If the result is positive, the specific antibodies are identified; their immunoglobulin subtype is determined as either immunoglobulin G (IgG) or M (IgM); and the titer is quantified. Only IgG antibodies are concerning, because IgM antibodies do not cross the placenta. Selected antibodies and their potential to cause fetal hemolytic anemia are listed in Table 18-1. The *critical titer* is the level at which significant fetal anemia may develop. It may vary according to antibody and laboratory but is usually between 1:8 and 1:32. If the laboratory's critical titer threshold for anti-D antibodies is 1:16, a titer ≥1:16 indicates the possibility of severe hemolytic disease. An important exception is Kell sensitization, which is discussed on page 354.

CDE (Rh) Blood Group Incompatibility

The CDE system includes five erythrocyte antigens: C, c, D, E, and e. There is no "d" antigen, and D-negativity is defined as the absence of the D antigen. Although most people are D positive or negative, more than 200 D antigen variants exist (Daniels, 2013). The CDE group was formerly termed Rh or rhesus, due to a misconception that red cells from rhesus monkeys expressed these human antigens. In transfusion medicine, "rhesus" is no longer used (Sandler, 2017).

CDE antigens are clinically important. D-negative individuals may become sensitized after a single exposure to as little as 0.1 mL of fetal erythrocytes (Bowman, 1988). The two responsible genes—*RHD* and *RHCE*—are located on the short arm of chromosome 1 and are inherited together, independent of other blood group genes. Antigen positivity varies according to race and ethnicity. Nearly 85 percent of non-Hispanic white Americans are D-positive, as are approximately 90 percent of Native Americans, 93 percent of African Americans and Hispanic Americans, and 99 percent of Asian Americans (Garratty, 2004).

TABLE 18-1. Selected Red Cell Antigens and Their Relationship to Fetal Hemolytic Disease

Blood Group System	Antigens	Fetal Hemolysis Potential
CDE (Rh)	D, c	Severe disease risk
	E, Be^a, Ce, Cw, Cx, ce, Dw, Evans, e, G, Goa7, Hr, Hro, JAL, HOFM, LOCR, Riv, Rh29, Rh32, Rh42, Rh46, STEM, Tar	Severe disease infrequent, mild disease risk
Kell	K	Severe disease risk
	k, Kp^a, Kp^b, K11, K22	Severe disease infrequent, mild disease risk
	Ku, Js^a, Js^b, Ula	
Duffy	Fy^a	Severe disease infrequent, mild disease risk
	Fy^b	Not associated with fetal hemolytic disease
Kidd	Jk^a	Severe disease infrequent, mild disease risk
	Jk^b, Jk^3	Mild disease possible
MNS	M, N, S, s, U, Mt^a, Ena, Far, Hil, Hut, Mi^a, Mit, Mut, Mur, Mv, sD, Vw	Severe disease infrequent, mild disease risk
Colton	Co^a, Co^3	Severe disease infrequent, mild disease risk
Diego	Di^a, Di^b, Wr^a, Wr^b	Severe disease infrequent, mild disease risk
Dombrock	Do^a, Gy^a, Hy, Jo^a	Mild disease possible
Gerbich	Ge^2, Ge^3, Ge^4, Ls^a	Mild disease possible
Scianna	Sc2	Mild disease possible
I	I, i	Not associated with fetal hemolytic disease
Lewis	Le^a, Le^b	Not associated with fetal hemolytic disease

Data from de Haas, 2015; Moise, 2008; Weinstein, 1982.

The prevalence of D alloimmunization complicating pregnancy ranges from 0.5 to 0.9 percent (Koelewijn, 2008; Martin, 2005). Without anti-D immune globulin prophylaxis, a D-negative woman delivered of a D-positive, *ABO-compatible* newborn has a 16-percent likelihood of developing alloimmunization. Two percent will become sensitized by the time of delivery, 7 percent by 6 months postpartum, and the remaining 7 percent will be "sensibilized"—producing detectable antibodies only in a subsequent pregnancy (Bowman, 1985). If there is *ABO incompatibility*, the D alloimmunization risk decreases to 2 percent because erythrocyte destruction of incompatible cells limits sensitization (Bowman, 2006). D sensitization may also occur following first-trimester pregnancy complications, prenatal diagnostic procedures, and maternal trauma (Table 18-2).

The C, c, E, and e antigens have lower immunogenicity than the D antigen but can cause hemolytic disease. Sensitization to E, c, and C antigens complicates approximately 0.3 percent of pregnancies in screening studies and accounts for about 30 percent of red cell alloimmunization cases (Howard, 1998; Koelewijn, 2008). Anti-E alloimmunization is the most common, but the need for fetal or neonatal transfusions is greater with anti-c alloimmunization than with anti-E or anti-C (de Haas, 2015; Hackney, 2004; Koelewijn, 2008).

The Grandmother Effect. In virtually all pregnancies, small amounts of maternal blood enter the fetal circulation. Polymerase chain reaction (PCR) has identified maternal D-positive DNA in peripheral blood from preterm and full-term D-negative newborns (Lazar, 2006). Thus, a D-negative female fetus exposed to maternal D-positive red cells might develop sensitization, and later might produce anti-D antibodies before or during pregnancy. This mechanism is called the *grandmother effect* because the fetus in the current pregnancy is jeopardized by maternal antibodies that were initially provoked by his or her *grandmother's* erythrocytes.

TABLE 18-2. Causes of Fetomaternal Hemorrhage Associated with Red Cell Antigen Alloimmunization[a]

Pregnancy Loss
Abortion, spontaneous or elective
Ectopic pregnancy
Fetal death (any trimester)
Procedures
Amniocentesis
Chorionic villus sampling
Fetal blood sampling
Molar pregnancy evacuation
Other
Antepartum bleeding, including threatened abortion
Delivery, vaginal or cesarean
External cephalic version
Placental abruption
Trauma to the abdomen during pregnancy

[a]For each of the above, anti-D immune globulin is recommended.
Expanded from American Academy of Pediatrics, 2017; American College of Obstetricians and Gynecologists, 2019b.

Alloimmunization to Minor Antigens

Because routine administration of anti-D immune globulin prevents anti-D alloimmunization, proportionately more cases of hemolytic disease are caused by red cell antigens other than D (American College of Obstetricians and Gynecologists, 2019a; Koelewijn, 2008). These are also known as minor antigens. Kell antigens are among the most frequent. Other antigens with potential to cause severe alloimmunization include Duffy group A—Fy^a, MNS, and Kidd—Jk^a (de Hass, 2015; Moise, 2008). In most cases, sensitization to a minor antigen results from an incompatible blood transfusion. However, if an IgG red cell antibody is detected and there is any doubt as to its significance, the pregnancy should be evaluated for hemolytic disease.

Only a few blood group antigens pose *no* fetal risk. Lewis antibodies—Le^a and Le^b—are cold agglutinins, as are I antibodies. They are predominantly IgM and are not expressed on fetal red cells (American College of Obstetricians and Gynecologists, 2019a). Another antibody that does not cause fetal hemolysis is Duffy group B—Fy^b.

Kell Alloimmunization. Approximately 90 percent of non-Hispanic white Americans and up to 98 percent of African Americans are Kell antigen negative. Kell type is not routinely determined. Transfusion history is important, as nearly 90 percent of Kell sensitization cases result from transfusion with Kell-positive blood.

Kell sensitization may develop more rapidly and may be more severe than with sensitization to D and other blood group antigens. This is because Kell antibodies attach to erythrocyte precursors in the fetal bone marrow and thereby impair the normal hemopoietic response to anemia. With fewer erythrocytes produced, there is less hemolysis, and thus severe anemia may not be predicted by the maternal Kell antibody titer.

Slootweg and colleagues (2018) reviewed 93 pregnancies with Kell alloimmunization in which the fetus was confirmed to be Kell-positive. They found that a titer of 1:4 had 100 percent sensitivity, 27 percent specificity, and 60 percent positive predictive value for transfusion requirement in the fetal or neonatal period. More than 50 percent of Kell antigen–positive fetuses ultimately needed transfusions. Given the potential for severe anemia, the American College of Obstetricians and Gynecologists (2019a) has recommended that antibody titers not be used to monitor Kell-sensitized pregnancies.

ABO Blood Group Incompatibility

Incompatibility for the major blood group antigens A and B is the most common cause of hemolytic disease in newborns, but it does not cause appreciable hemolysis in the fetus. This is because most anti-A and anti-B antibodies are IgM types and do not cross the placenta. Also, fetal red cells have fewer A and B antigenic sites than adult cells and are thus less immunogenic. Approximately 20 percent of newborns have ABO blood

group incompatibility, although only 5 percent are affected clinically. In such cases, the resulting anemia is typically mild.

The condition differs from CDE incompatibility in several respects. First, ABO incompatibility is often seen in firstborn neonates, unlike sensitization to other blood group antigens. This is because most group O women have developed anti-A and anti-B isoagglutinins before pregnancy from exposure to bacteria displaying similar antigens. Additionally, ABO alloimmunization rarely becomes more severe in successive pregnancies. Fetal surveillance and early delivery are not indicated in pregnancies with prior ABO incompatibility. Postnatally however, neonates are evaluated for hyperbilirubinemia, which may require treatment with phototherapy or occasionally transfusion (Chap. 33, p. 606).

Management of the Alloimmunized Pregnancy

Of fetuses from D-alloimmunized pregnancies, 25 to 30 percent will have mild to moderate hemolytic anemia, and up to 25 percent have anemia severe enough to cause hydrops (Tannirandorn, 1990). If alloimmunization is detected and the titer is below the critical value, the titer is generally repeated every 4 weeks for the duration of the pregnancy (American College of Obstetricians and Gynecologists, 2019a). In any pregnancy in which the antibody titer has reached a critical value, there is no benefit to repeating the titer. The pregnancy is at risk even if the titer drops, and further evaluation is required. Similarly, if a prior pregnancy was complicated by alloimmunization, the pregnancy is considered at risk regardless of titer.

Fetal Risk Assessment

The presence of anti-D antibodies reflects maternal sensitization but does not indicate whether the fetus is D-positive or D-negative. Up to 40 percent of D-negative pregnant women carry a D-negative fetus. If a woman is sensitized from a prior pregnancy, her antibody titer may rise during the current pregnancy even if the current fetus is D-negative because of an *amnestic response.* In a non-Hispanic white couple in which the woman is D-negative, there is an 85-percent chance that the man is D-positive. However, there is a 60-percent likelihood that he is heterozygous at the D-locus, and only half of his children will be at risk for hemolytic disease.

Initial evaluation of alloimmunization begins with determining the paternal erythrocyte antigen status. *Provided that paternity is certain*, if the father is negative for the red cell antigen to which the mother is sensitized, the pregnancy is not at risk. A prior blood transfusion may be the cause of alloimmunization to a red cell antigen other than D. In a D-alloimmunized pregnancy in which the father is D-positive, it is helpful to determine paternal zygosity for the D antigen using DNA-based analysis. If the father is heterozygous—or if paternity is not known—the woman should be offered assessment of fetal genotype. Traditionally, this was done with amniocentesis and PCR testing of uncultured amniocytes, which has a positive predictive value of 100 percent and negative predictive value of approximately 97 percent (Van den Veyver, 1996). Fetal testing for other antigens—such as E/e, C/c, Duffy, Kell, Kidd, and M/N—also is available with this method. Chorionic villus sampling is not recommended because of greater risk for fetomaternal hemorrhage and subsequent worsening of alloimmunization (American College of Obstetricians and Gynecologists, 2019a).

Noninvasive fetal D genotyping has been performed using cell-free DNA (cfDNA) from maternal plasma (Chap. 17, p. 335). The reported sensitivity exceeds 99 percent, the specificity exceeds 95 percent, and positive or negative predictive values are similarly very high (Johnson, 2017; Moise, 2016; Pazourkova, 2021). Fetal D genotyping with cfDNA is routinely used in parts of Europe but is not yet a widely used clinical tool in the United States (American College of Obstetricians and Gynecologists, 2019a). Two potential indications for cfDNA use in D-negative pregnant women are: (1) in the setting of D alloimmunization, testing can identify fetuses who are also D-negative and do not require anemia surveillance, and (2) in women *without* D alloimmunization, anti-D immune globulin might be withheld if the fetus is D negative. In the case of the latter, the American College of Obstetricians and Gynecologists (2019b) does not recommend routine cfDNA screening in D-negative pregnancies until it has been demonstrated to be cost-effective.

Management of the alloimmunized pregnancy typically consists of maternal antibody titer surveillance followed by ultrasound monitoring of the fetal MCA peak systolic velocity if a critical antibody titer is reached. As noted earlier (p. 354), pregnancies with Kell alloimmunization often receive ultrasound surveillance regardless of titer. Fetal blood sampling is generally performed if the MCA peak systolic velocity exceeds the threshold for severe anemia, with plan for concurrent intrauterine transfusion as needed. Spectrophotometric analysis of amniotic fluid bilirubin, also known as the ΔOD_{450} test, is no longer recommended (Society for Maternal-Fetal Medicine, 2015a).

Recent efforts have focused on use of maternal intravenous immunoglobulin (IVIG) therapy to postpone the initial intrauterine transfusion to beyond 20 weeks in severely affected pregnancies (Maisonneuve, 2021). Its mechanism of action is unclear, but IVIG therapy has been reported to delay need for transfusion by an average of 3 weeks and to lower the risk for hydrops (Zwiers, 2018).

Middle Cerebral Artery Doppler Velocimetry. Serial measurement of the peak systolic velocity of the fetal MCA is the recommended test to detect fetal anemia (Society for Maternal–Fetal Medicine, 2015a). The anemic fetus shunts blood preferentially to the brain to maintain adequate oxygenation. The velocity rises because of increased cardiac output and decreased blood viscosity. Measurement technique is discussed in Chapter 14 (p. 262).

In a landmark study, Mari and coworkers (2000) measured the MCA peak systolic velocity serially in 111 fetuses at risk for anemia and in 265 normal control fetuses. The threshold value of 1.5 multiples of the median (MoM) for gestational age correctly identified all fetuses with moderate or severe anemia. This provided a sensitivity of 100 percent, with a false-positive rate of 12 percent.

MCA peak systolic velocity is followed serially, and values are plotted on a curve like the one shown in Figure 18-1.

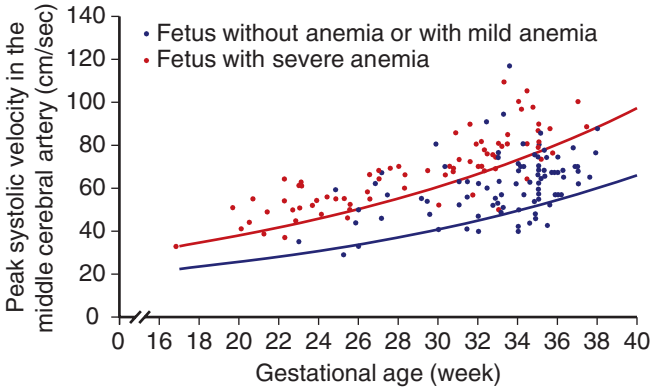

FIGURE 18-1 Doppler measurements of the peak systolic velocity in the middle cerebral artery (MCA) in 165 fetuses at risk for severe anemia. The blue line indicates the median peak systolic velocity in normal pregnancies, and the red line shows 1.5 multiples of the median. (Reproduced with permission from Oepkes D, Seaward PG, Vandenbussche et al: Doppler ultrasonography versus amniocentesis to predict fetal anemia, N Engl J Med. 2006 Jul 13;355(2):156–164.)

If the velocity is between 1.0 and 1.5 MoM and the slope is rising—such that the value is approaching 1.5 MoM—MCA Doppler surveillance is generally performed at least weekly. The false-positive rate of MCA peak systolic velocity increases significantly beyond 34 weeks' gestation and stems from the normal rise in cardiac output that develops at this gestational age (Moise, 2008; Zimmerman, 2002). At Parkland Hospital, MCA peak systolic velocity is not measured beyond 35 weeks, but ultrasound evaluation for hydrops is performed as needed.

Fetal Blood Transfusion

If the MCA peak systolic velocity exceeds 1.5 MoM or if hydrops develops and anemia is the leading etiology, fetal blood sampling and intrauterine transfusion should be considered. Fetal transfusion is typically performed prior to 34 to 35 weeks' gestation (Society for Maternal-Fetal Medicine, 2015a). Later in gestation, the benefits of transfusion may be outweighed by the risks of delaying delivery. Transfusion is most commonly intravascular. However, the umbilical vein may be too narrow in the early second trimester to readily permit needle entry, and severe hemolysis may necessitate intraperitoneal fetal transfusion. In the setting of hydrops, peritoneal absorption may be impaired, and some prefer to transfuse into both the fetal peritoneal cavity and umbilical vein.

Transfusion is generally recommended only if the fetal hematocrit is <30 percent (Society for Maternal-Fetal Medicine, 2015a). If hydrops has developed, the hematocrit is usually 15 percent or lower. The red cells transfused are type O, D-negative, cytomegalovirus-negative, packed to a hematocrit of approximately 80 percent to prevent volume overload, irradiated to prevent fetal graft-versus-host reaction, and leukocyte-poor. The fetal–placental volume allows rapid infusion of a relatively large quantity of blood. Before transfusion, a paralytic agent such as vecuronium may be given to the fetus to minimize movement. In a nonhydropic fetus, the target hematocrit is 40 to 50 percent. The volume transfused may be estimated by multiplying the estimated fetal weight in grams by 0.02 for each 10-percent rise in hematocrit needed (Giannina, 1998). In the severely anemic fetus at 18 to 24 weeks' gestation, a smaller volume is transfused initially, and another transfusion may be planned for approximately 2 days later. Subsequent transfusions take place every 2 to 4 weeks, depending on the hematocrit.

The MCA peak systolic velocity threshold for severe anemia is higher following an initial transfusion—1.70 MoM rather than 1.50 MoM (Society for Maternal-Fetal Medicine, 2015a). It is hypothesized that the change in threshold compensates for the contribution of donor cells in the initial transfusion, because the donor cells are from adults and have a smaller mean corpuscular volume. Following transfusion, the fetal hematocrit drops by approximately 1 percent per day. The initial decline may be more rapid if hydrops has developed.

Outcomes. The overall survival rate approximates 95 percent (Zwiers, 2017; Mizuuchi, 2021). Complications include fetal death in 2 percent, need for emergent cesarean delivery in 1 percent, and infection and preterm rupture of membranes in 0.3 percent each, respectively. The stillbirth rate exceeds 15 percent if transfusion is required before 20 weeks (Lindenberg, 2013; Zwiers, 2017). For hydropic fetuses, the neonatal survival rate is about 80 percent (Emiroglu, 2020; Van Kamp, 2001). In one series, 95 percent of neonates survived if hydrops resolved following intrauterine transfusion compared with fewer than 40 percent if hydrops persisted (Van Kamp, 2001).

Lindenberg (2012) reviewed long-term outcomes following intrauterine transfusion in a cohort of more than 450 alloimmunized pregnancies. Alloimmunization was secondary to anti-D in 80 percent, anti-Kell in 12 percent, and anti-c in 5 percent. Approximately a fourth of affected fetuses had hydrops, and more than half also required exchange transfusion in the neonatal period. Among nearly 300 children aged 2 to 17 years who participated in neurodevelopmental testing, fewer than 5 percent had severe impairments.

■ Prevention of Anti-D Alloimmunization

Anti-D immune globulin has been used for more than five decades to prevent D alloimmunization. Unfortunately, 50 percent of women around the world who would benefit from anti-D immune globulin do not receive it (Pegoraro, 2020). In countries without access, up to 10 percent of D-negative pregnancies are complicated by hemolytic disease of the fetus and newborn (Zipursky, 2015). With immunoprophylaxis, however, the alloimmunization risk may be reduced to <0.2 percent. Despite long-standing and widespread use, its mechanism of action is not completely understood.

Fetomaternal hemorrhage at delivery accounts for as many as 90 percent of alloimmunization cases. Routine postpartum administration of anti-D immune globulin to at-risk pregnancies within 72 hours of delivery lowers the alloimmunization rate by 90 percent (Bowman, 1985). Additionally, provision of anti-D immune globulin at 28 weeks' gestation reduces the third-trimester alloimmunization rate from approximately 2 percent to 0.1 percent (Bowman, 1988). *Whenever there is doubt whether to give anti-D immune globulin, it should be given.* If not needed, it will not cause harm, but failure to provide it when needed may have severe consequences.

Anti-D immune globulin is derived from human plasma donated by individuals with high-titer anti-D immunoglobulin D antibodies. Formulations prepared by cold ethanol fractionation and ultrafiltration must be administered intramuscularly because they contain plasma proteins that could result in anaphylaxis if given intravenously. Formulations prepared using ion exchange chromatography may be administered either intramuscularly or intravenously, which is relevant when treating significant fetomaternal hemorrhage. Both preparation methods effectively remove viral particles, including hepatitis and human immunodeficiency viruses. Depending on the preparation, the half-life of anti-D immune globulin ranges from 16 to 24 days, which is why it is given both in the third trimester and following delivery. The standard intramuscular dose of anti-D immune globulin—300 μg or 1500 IU—will protect the average-sized mother from a fetal hemorrhage of up to 30 mL of fetal whole blood or 15 mL of fetal red cells.

In the United States, anti-D immune globulin is given prophylactically to all D-negative, unsensitized women at approximately 28 weeks' gestation, and a second dose is given after delivery if the newborn is D-positive (American College of Obstetricians and Gynecologists, 2019b). Before the 28-week dose of anti-D immune globulin, repeat antibody screening is recommended to identify individuals who have become alloimmunized (American Academy of Pediatrics, 2017). Following delivery, anti-D immune globulin should be given within 72 hours. Recognizing that 40 percent of neonates born to D-negative women are also D negative, administration of immune globulin is recommended only after the newborn is confirmed to be D positive (American College of Obstetricians and Gynecologists, 2019b). If immune globulin is inadvertently not administered following delivery, it should be given as soon as the omission is recognized, because there may be some protection up to 28 days postpartum (Bowman, 2006). Anti-D immune globulin is also administered after pregnancy-related events that could result in sensitization (see Table 18-2). In the first trimester, smaller doses of 50 or 120 μg may be suitable, as discussed in Chapters 11 and 12 (p. 203 and 221).

Anti-D immune globulin may produce a weakly positive—1:1 to 1:4—indirect Coombs titer in the mother. This is harmless and should not be confused with development of alloimmunization. Additionally, as the body mass index increases above 27 to 40 kg/m^2, serum antibody levels decrease by 30 to 60 percent and may be less protective (MacKenzie, 2006; Woelfer, 2004). D-negative women who receive other types of blood products—including platelet transfusions and plasmapheresis—also are at risk of becoming sensitized, and this can be prevented with anti-D immune globulin. Rarely, a small amount of antibody crosses the placenta and results in a weakly positive direct Coombs test in cord and infant blood. Despite this, passive immunization does not cause significant fetal or neonatal hemolysis.

In 2 to 3 per 1000 pregnancies, the volume of fetomaternal hemorrhage may exceed 30 mL of whole blood (American College of Obstetricians and Gynecologists, 2019b). A single dose of anti-D immune globulin would be insufficient in such situations. If additional anti-D immune globulin is considered only for women with risk factors such as those shown in Table 18-2, *half* of those who require additional immune globulin may be missed. For this reason, all D-negative women should be screened at delivery, typically with a rosette test, followed by quantitative testing if indicated (American College of Obstetricians and Gynecologists, 2019b).

The rosette test is a qualitative test that identifies whether fetal D-positive cells are present in the circulation of a D-negative woman. A sample of maternal blood is mixed with anti-D antibodies that coat any D-positive fetal cells present in the sample. Indicator red cells bearing the D-antigen are then added, and rosettes form around the fetal cells as the indicator cells attach to them by the antibodies. Thus, if rosettes are visualized, there are fetal D-positive cells in that sample. In the setting of D incompatibility, or any time a large fetomaternal hemorrhage is suspected—regardless of antigen status, a Kleihauer-Betke test or flow cytometry test are used. These are discussed on page 358.

The dosage of anti-D immune globulin is calculated from the estimated volume of the fetal-to-maternal hemorrhage, as described on page 358. One 300-μg dose is given for each 15 mL of fetal red cells or 30 mL of fetal whole blood to be neutralized. If using an intramuscular preparation of anti-D immune globulin, no more than five doses may be given in a 24-hour period. If using an intravenous preparation, two ampules—totaling 600 μg—may be given every 8 hours. A positive indirect Coombs test or the presence of circulating fetal cells on a rosette test demonstrate that the dose was sufficient.

Serological Weak D Phenotypes

Formerly called *D*^{u}, these are the most common antigenic D variants in the United States and Europe (American College of Obstetricians and Gynecologists, 2019a). Serological weak D phenotypes have been further refined into two general categories using molecular analysis to complete RHD genotyping. *Molecular weak D phenotypes* carry reduced numbers of intact D antigens on the red cell surface. *Partial D types* have protein deletions associated with abnormal D antigens that lack epitopes (Sandler, 2017).

Many individuals who test positive for weak D have weak D phenotypes 1, 2, or 3. These phenotypes may be managed as if D-positive. The pregnancy is not considered at risk for alloimmunization, and thus anti-D immune globulin is not needed (Sandler 2015, 2017). In contrast, individuals with partial D antigens may be at risk for D-sensitization and do require immune globulin. Molecular RHD genotyping has been suggested for pregnant women with weak D phenotype, but cost-benefit analysis of this strategy is presently lacking (American College of Obstetricians and Gynecologists, 2019b). *If molecular genetic testing has not been performed in those with serologic weak D phenotype, D immunoprophylaxis should be administered.*

FETOMATERNAL HEMORRHAGE

A small amount of fetomaternal bleeding likely occurs in all pregnancies and may be sufficient to provoke an antigen-antibody reaction in two thirds. As shown in Figure 18-2, the incidence increases with advancing gestation and with the volume of fetal blood in the maternal circulation (Choavaratana, 1997).

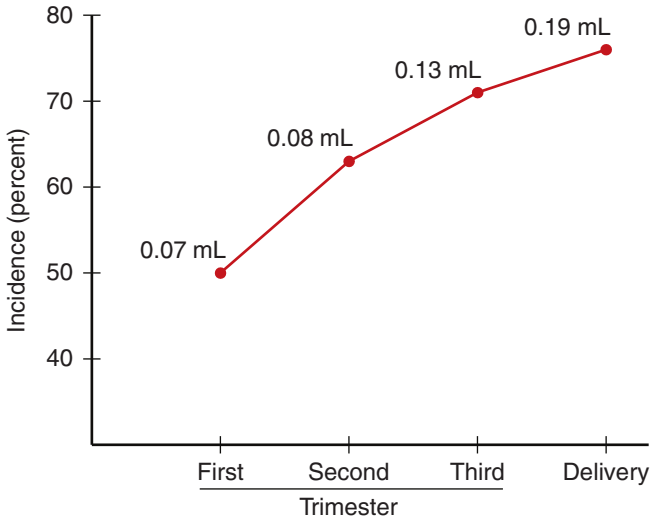

FIGURE 18-2 Incidence of fetomaternal hemorrhage during pregnancy. The numbers at each data point represent total volume of fetal blood estimated to have been transferred into the maternal circulation.

The prevalence of fetomaternal bleeding of at least 30 mL is estimated to be 3 events per 1000 pregnancies (Wylie, 2010). Fortunately, frank hemorrhage is rare. In one series of more than 30,000 pregnancies, fetomaternal hemorrhage ≥150 mL complicated 1 in 2800 births (de Almeida, 1994).

Selected causes of fetomaternal hemorrhage are shown in Table 18-2. With significant hemorrhage, the most common presenting complaint is decreased fetal movement (Bellussi, 2017; Wylie, 2010). A sinusoidal fetal heart rate pattern is infrequently seen but warrants immediate evaluation (Chap. 24, p. 451). Sonography may demonstrate elevated MCA peak systolic velocity, and indeed this is reported to be the most accurate predictor (Bellusi, 2017; Wylie, 2010). Hydrops is an ominous finding. If the MCA peak systolic velocity is elevated or hydrops is identified, urgent fetal transfusion or delivery should be considered. In more than 80 percent of cases, no etiology of the fetomaternal hemorrhage is identified.

One limitation of quantitative tests for fetal cells in the maternal circulation is that they do not provide information regarding the timing or chronicity of hemorrhage (Wylie, 2010). Anemia that develops gradually, as with alloimmunization, is generally better tolerated by the fetus than acute anemia. Chronic anemia may not produce fetal heart rate abnormalities until the fetus is moribund. In contrast, significant acute hemorrhage may result in profound fetal neurological impairment from cerebral hypoperfusion, ischemia, and infarction. In some cases, fetomaternal hemorrhage is identified during stillbirth evaluation (Chap. 35, p. 325).

■ Hemorrhage Quantification

Estimating the volume of fetomaternal hemorrhage is needed to calculate the appropriate dose of anti-D immune globulin if the woman is D-negative, and it may also influence obstetrical management. The most commonly used quantitative test for fetal red cells in the maternal circulation is the acid elution or

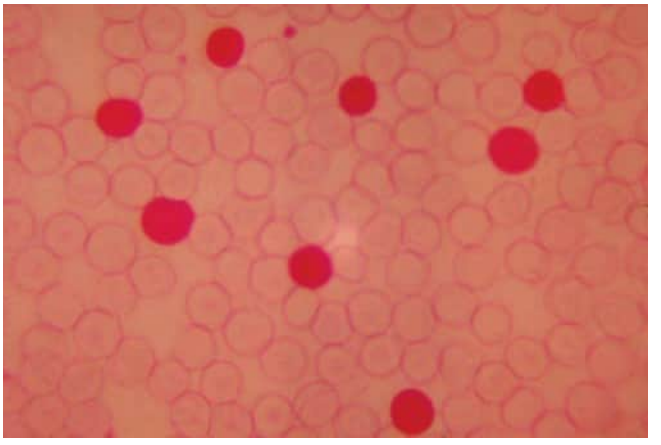

FIGURE 18-3 Kleihauer-Betke test demonstrating massive fetomaternal hemorrhage. After acid-elution treatment, fetal red cells rich in hemoglobin F stain darkly, whereas maternal red cells with only very small amounts of hemoglobin F stain lightly.

Kleihauer-Betke (KB) test (Kleihauer, 1957). Fetal erythrocytes contain hemoglobin F, which is more resistant to acid elution than hemoglobin A. Following exposure to acid, only fetal hemoglobin remains. Therefore, after staining, the fetal erythrocytes appear red and adult erythrocytes appear as "ghosts" (Fig. 18-3). The fetal cells are then counted and expressed as a percentage of adult cells. The fetal blood volume involved in the fetomaternal hemorrhage may be calculated using the following formula:

$$\text{Fetal blood volume} = \frac{\text{MBV} \times \text{maternal Hct} \times \%\ \text{fetal cells in KB test}}{\text{newborn Hct}}$$

For a pregnant woman of normal size who is normotensive and has reached full-term, the maternal blood volume (MBV) may be estimated as 5000 mL. Thus, in a woman with a hematocrit of 35 percent and whose fetus has a hematocrit of 50 percent, the calculation for a KB test demonstrating staining of 1.7 percent of sample cells is:

$$\text{Fetal blood volume} = \frac{5000 \times 0.35 \times 0.017}{0.5} = 60\ \text{mL}$$

The fetal-placental blood volume at term approximates 125 mL/kg. For a 3000-g fetus, that would equate to 375 mL. Thus, this fetus lost approximately 15 percent (60 ÷ 375 mL) of the fetal-placental volume. Assuming the hematocrit is 50 percent in a term fetus, this 60 mL of whole blood represents 30 mL of red cells lost into the maternal circulation. A loss of this magnitude should be well tolerated hemodynamically but would require two 300-μg doses of anti-D immune globulin to prevent alloimmunization. A more precise method to estimate the maternal blood volume includes a calculation based on the maternal height, weight, and anticipated physiological maternal blood volume accrual (Table 42-1, p. 732).

The KB test is labor intensive. There are also two scenarios in which the KB may be inaccurate: (1) maternal hemoglobinopathies in which the fetal hemoglobin level is elevated, such

as β-thalassemia, and (2) at or near term, because the fetus may already be producing hemoglobin A.

Another method of quantifying fetomaternal hemorrhage is with flow cytometry, which uses monoclonal antibodies to hemoglobin F or to the D antigen and then measures the degree of fluorescence (Chambers, 2012; Welsh, 2016). Flow cytometry is an automated test that can analyze a greater number of cells than the KB test. It is also unaffected by maternal levels of fetal hemoglobin and by fetal levels of hemoglobin A. Flow cytometry has been reported to be more sensitive and accurate than the KB test, however, it uses specialized technology not routinely available in many hospitals (Chambers, 2012; Corcoran, 2014; Fernandes, 2007).

FETAL THROMBOCYTOPENIA

Alloimmune Thrombocytopenia

This is also referred to as *fetal and neonatal alloimmune thrombocytopenia (FNAIT)*. Alloimmune thrombocytopenia (AIT) is the most common cause of severe thrombocytopenia among term newborns, with a frequency of 1 to 2 cases per 1000 births (Kamphuis, 2010; Pacheco, 2013; Risson, 2012). FNAIT is caused by maternal alloimmunization to paternally inherited fetal platelet antigens. Maternal antiplatelet antibodies cross the placenta in a manner similar to red cell alloimmunization (p. 352). Unlike *immune thrombocytopenia*, the maternal platelet count is normal with FNAIT. And, unlike anti-D alloimmunization, severe sequelae may affect the *initial* at-risk pregnancy.

Maternal platelet alloimmunization against human platelet antigen-1a (HPA-1a) accounts for 80 to 90 percent of cases and is associated with the greatest severity (Bussel, 1997; Knight, 2011; Tiller, 2013). This is followed in order of frequency by alloimmunization against HPA-5b, HPA-1b, and HPA-3a. Alloimmunization to other antigens accounts for only 1 percent of reported cases.

Approximately 85 percent of non-Hispanic white individuals are HPA-1a positive. Two percent are homozygous for HPA-1b and at risk for alloimmunization. However, only 10 percent of these women produce antiplatelet antibodies when carrying an HPA-1a fetus. Approximately a third of affected fetuses or neonates will develop severe thrombocytopenia, and 10 to 20 percent with severe thrombocytopenia sustain an intracranial hemorrhage (ICH) (Kamphuis, 2010). As a result, population-based screening studies have identified one case of FNAIT-associated ICH per 25,000 to 60,000 pregnancies (Kamphuis, 2010; Knight, 2011).

FNAIT has a spectrum of presentation. Neonatal thrombocytopenia may be an incidental finding, the newborn may manifest petechiae, or the fetus or neonate may develop devastating ICH. Of 600 pregnancies with FNAIT identified through a large international registry, fetal or neonatal ICH complicated just 7 percent of cases (Tiller, 2013). Hemorrhage affected the first-born child in 60 percent and occurred before 28 weeks' gestation in half. A third of affected children died soon after birth, and 50 percent of survivors had severe neurological disabilities.

Bussel and coworkers (1997) evaluated fetal platelet counts before therapy in 107 fetuses with FNAIT. Thrombocytopenia severity was predicted by a prior sibling with perinatal ICH. Fifty percent had an initial platelet count <20,000/μL. And, among those in whom the initial platelet count was >80,000/μL, it dropped by at least 10,000/μL per week in the absence of therapy.

Diagnosis and Management

AIT is typically diagnosed following delivery of a neonate with severe and unexplained thrombocytopenia to a woman whose platelet count is normal. Rarely, the diagnosis is ascertained after identifying fetal ICH. The condition recurs in 70 to 90 percent of subsequent pregnancies, is often severe, and usually develops earlier with each successive pregnancy. Traditionally, fetal blood sampling was performed to detect fetal thrombocytopenia and to tailor therapy. Platelets were transfused if the fetal platelet count was <50,000/μL. The reported rate of procedure-related complications exceeds 10 percent (Winkelhorst, 2017). For this reason, most favor empirical treatment with IVIG instead (Berkowitz, 2006; Pacheco, 2011).

Therapy may be stratified according to whether a prior affected pregnancy was complicated by perinatal ICH, and if so, at what gestational age (Table 18-3) (Pacheco, 2011). Pioneering work by Bussel (1996) and Berkowitz (2006) and their colleagues demonstrated the efficacy of such treatment. In one series of 50 pregnancies with fetal thrombocytopenia secondary to FNAIT, IVIG raised the platelet count by approximately 50,000/μL, and no fetus developed ICH (Bussel, 1996). Among pregnancies at particularly high risk, which was based on a platelet count <20,000/μL or a sibling with FNAIT-associated ICH, the addition of corticosteroids to IVIG therapy was associated with a rise in platelet count in 80 percent of cases (Berkowitz, 2006). However, a systematic review identified no consistent benefit of corticosteroid treatment compared with IVIG therapy alone (Winkelhorst, 2017). Thus, corticosteroid therapy is somewhat controversial. Cesarean delivery is generally recommended at or near term.

Immune Thrombocytopenia

Also known as immune or idiopathic thrombocytopenic purpura (ITP), this autoimmune disorder is characterized by antiplatelet IgG antibodies that attack platelet glycoproteins. The antibodies may cross the placenta and cause fetal thrombocytopenia. Maternal ITP is discussed in Chapter 59 (p. 1059).

Fetal thrombocytopenia from maternal ITP is usually mild. However, neonatal platelet levels may fall rapidly after birth and nadir at 48 to 72 hours of life. Neither the maternal platelet count, identification of antiplatelet antibodies, nor treatment with corticosteroids effectively predicts fetal or neonatal platelet counts (Hachisuga, 2014). Importantly, fetal platelet counts are usually adequate to allow vaginal delivery without an increased risk of ICH. In a review of more than 400 pregnancies with ITP, there was no case of fetal or neonatal ICH and no infant with any central nervous system abnormality (Wyszynski, 2016). Fetal blood sampling is not recommended

TABLE 18-3. Fetal-Neonatal Alloimmune Thrombocytopenia (FNAIT) Treatment Recommendations

Risk Group	Criteria	Suggested Management
1	Prior fetus or newborn with ICH, but no maternal anti-HPA antibody identified	Maternal anti-HPA antibody screening and cross-matching with paternal platelets at 12, 24, and 32 weeks' gestation; no treatment for negative test results
2	Prior fetus or newborn with thrombocytopenia and maternal anti-HPA antibody, but no ICH	Beginning at 20 wks: IVIG 1g/kg/wk and prednisone 0.5 mg/kg/d ***or*** IVIG 2 g/kg/wk Beginning at 32 wks: IVIG 2 g/kg/wk and prednisone 0.5 mg/kg/d Continue until delivery
3	Prior fetus with 3rd-trimester ICH or prior newborn with ICH, and maternal anti-HPA antibody	Beginning at 12 wks: IVIG 1 g/kg/wk Beginning at 20 wks: either increase IVIG to 2 g/kg/wk ***or*** add prednisone 0.5 mg/kg/d Beginning at 28 wks: IVIG 2 g/kg/wk ***and*** prednisone 0.5 mg/kg/d Continue until delivery
4	Prior fetus with ICH before the 3rd trimester and maternal anti-HPA antibody	Beginning at 12 wks: IVIG 2 g/kg/wk Beginning at 20 wks: add prednisone 1 mg/kg/d Continue both until delivery

HPA = human platelet antigen; ICH = intracerebral hemorrhage; IVIG = intravenous immunoglobulin G.

(Neunert, 2011). Mode of delivery is based on standard obstetrical indications.

HYDROPS FETALIS

This phrase has its origins in Middle English, Latin, and Greek. The condition was described by Ballantyne in 1892 as general dropsy, that is, edema, of the fetus (Kaiser, 1971). Hydrops can be a manifestation of severe illness from a wide variety of etiologies (Table 18-4) (Bellini, 2015).

Hydrops is diagnosed by identifying two or more fetal effusions—pleural, pericardial, or ascites—or one effusion plus anasarca (Fig. 18-4). Sonographically measured skin thickness of >5 mm constitutes edema or anasarca. Placentomegaly is defined as placental thickness ≥4 cm in the second trimester or ≥6 cm in the third trimester (Bellini, 2009; Society for Maternal–Fetal Medicine, 2015b). As hydrops progresses in severity, anasarca is an invariable feature and is usually accompanied by placentomegaly and hydramnios.

If found in association with red cell alloimmunization, hydrops is termed *immune*, otherwise, it is *nonimmune*. Immune and nonimmune hydrops are postulated to share several physiological abnormalities. The precise pathogenesis remains unknown but is likely multifactorial. As shown in Figure 18-5, these include decreased colloid oncotic pressure, increased hydrostatic or central venous pressure, and enhanced vascular permeability.

Immune Hydrops

This condition results from transplacental passage of maternal antibodies that destroy fetal red cells. The resultant anemia stimulates marrow erythroid hyperplasia and extramedullary hematopoiesis in the spleen and liver (see Fig. 18-5). The latter likely causes portal hypertension and impaired hepatic protein synthesis, which lowers plasma oncotic pressure (Nicolaides, 1985). Fetal anemia may also raise central venous pressure (Weiner, 1989). Tissue hypoxia from anemia may increase capillary permeability, such that fluid collects in the fetal thorax, abdominal cavity, and/or subcutaneous tissue.

The incidence of immune hydrops has decreased dramatically with the advent of anti-D immune globulin and with use of MCA Doppler to aid anemia detection. Only severe anemia results in immune hydrops. Mari and colleagues (2000) reviewed 70 pregnancies with fetal anemia from red cell alloimmunization and found that all with immune hydrops had hemoglobin values *<5 g/dL*. As discussed on page 356, immediate fetal blood transfusion may be lifesaving.

Nonimmune Hydrops

At least 90 percent of cases of hydrops are nonimmune (Bellini, 2012). The prevalence approximates 1 case per 1500 second-trimester pregnancies (Heinonen, 2000). The number of specific disorders that can lead to nonimmune hydrops is extensive. Etiologies and the proportion of births within each hydrops category from a review of more than 6700 affected pregnancies are summarized in Table 18-4 (Bellini, 2015).

A cause is identified in approximately 60 percent prenatally and in up to 80 percent postnatally (Bellini, 2009, 2015; Santo, 2011). Of prenatally diagnosed cases, aneuploidy accounts for approximately 20 percent, cardiovascular abnormalities for 15 percent, and infections for 14 percent—the most common of which is parvovirus B19 (Santo, 2011; Sileo, 2020; Sparks, 2019). In multifetal gestations, twin-twin transfusion syndrome is the most frequent cause (Yeom, 2015). Fetal deaths and stillbirths are common with nonimmune hydrops. Overall, only 40 percent of affected pregnancies result in a liveborn

TABLE 18-4. Categories and Etiologies of Nonimmune Hydrops Fetalis

Category	Percent[a]
Cardiovascular Structural defects: Ebstein anomaly, tetralogy of Fallot with absent pulmonary valve, hypoplastic left or right heart, premature closure of ductus arteriosus, arteriovenous malformation (vein of Galen aneurysm) Cardiomyopathies Tachyarrhythmias Bradycardia, as may occur in heterotaxy syndrome with endocardial cushion defect or with anti-Ro/La antibodies	21
Chromosomal Turner syndrome (45,X), triploidy, trisomies 21, 18, and 13	13
Hematological Hemoglobinopathies, such as α4-thalassemia Erythrocyte enzyme and membrane disorders Erythrocyte aplasia/dyserythropoiesis Decreased erythrocyte production (myeloproliferative disorders) Fetomaternal hemorrhage	10
Lymphatic Abnormalities Cystic hygroma, systemic lymphangiectasis, pulmonary lymphangiectasis	8
Infections Parvovirus B19, syphilis, cytomegalovirus, toxoplasmosis, rubella, enterovirus, varicella, herpes simplex, coxsackievirus, listeriosis, leptospirosis, Chagas disease, Lyme disease	7
Syndromic Arthrogryposis multiplex congenita, lethal multiple pterygium, congenital lymphedema, myotonic dystrophy type I, Neu-Laxova, Noonan, and Pena-Shokeir syndromes	5
Thoracic Abnormalities Cystic adenomatoid malformation Pulmonary sequestration Diaphragmatic hernia Hydro/chylothorax Congenital high airway obstruction sequence (CHAOS) Mediastinal tumors Skeletal dysplasia with very small thorax	5
Gastrointestinal Meconium peritonitis, gastrointestinal tract obstruction	1
Kidney and Urinary Tract Kidney malformations Bladder outlet obstructions Congenital (Finnish) nephrosis, Bartter syndrome, mesoblastic nephroma	2
Placental, Twin, and Cord Abnormalities Placental chorioangioma, twin-twin transfusion syndrome, twin reversed arterial perfusion sequence, twin anemia polycythemia sequence, cord vessel thrombosis	5
Other Rare Disorders Inborn errors of metabolism: Gaucher disease, galactosialidosis, GM_1 gangliosidosis, sialidosis, mucopolysaccharidoses, mucolipidoses Tumors: sacrococcygeal teratoma, hemangioendothelioma with Kasabach-Merritt syndrome	5
Idiopathic	18

[a]Percentages reflect the proportion within each category from a systematic review of 6775 pregnancies with nonimmune hydrops.

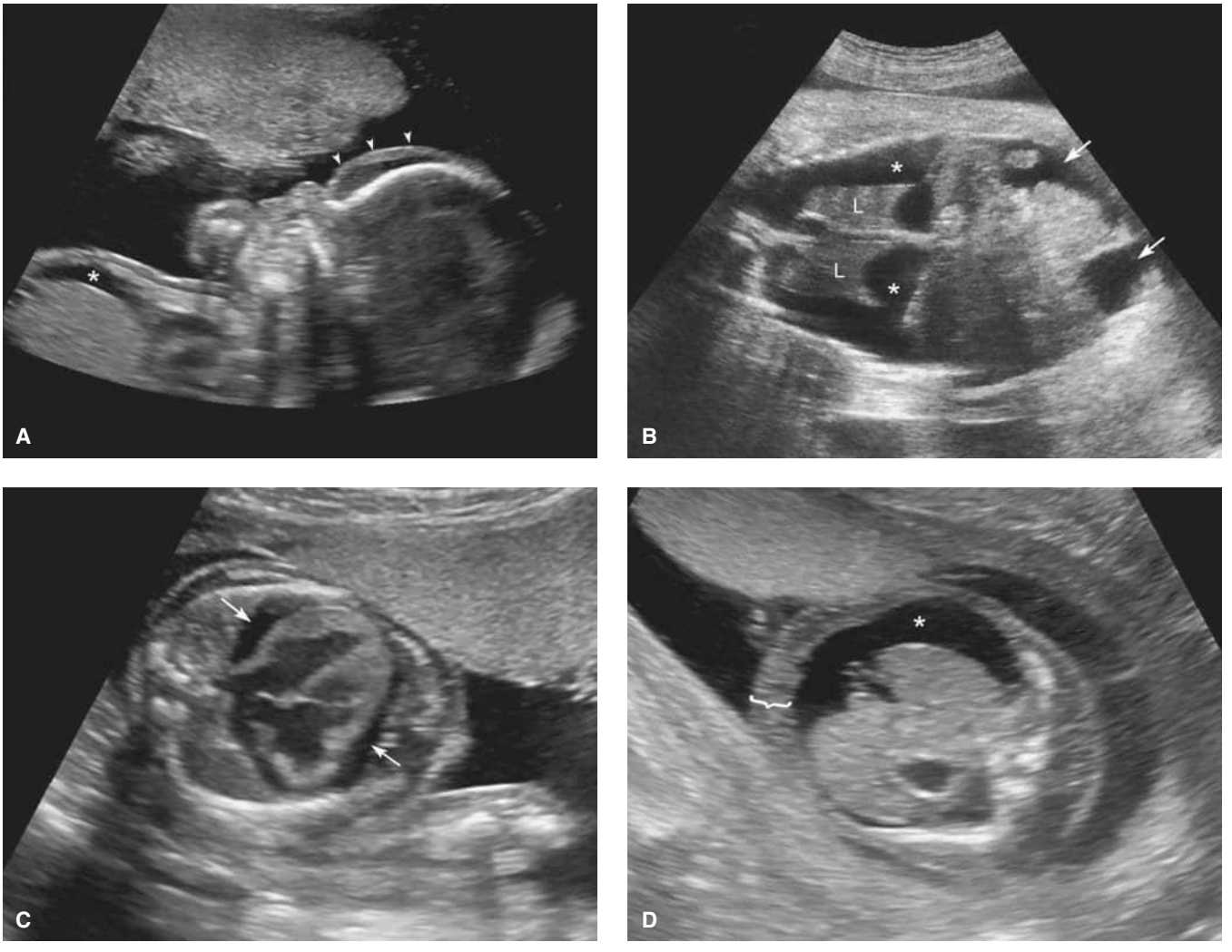

FIGURE 18-4 Sonographic findings that define hydrops. **A.** This profile of a 23-week fetus with nonimmune hydrops secondary to B19 parvovirus infection depicts scalp edema (*arrowheads*) and ascites (*). **B.** This 34-week fetus had hydrops secondary to an arteriovenous malformation in the brain, known as a vein of Galen aneurysm. In this coronal image, prominent pleural effusions (*) outline the lungs (L). Fetal ascites is also present (*arrows*), as is anasarca. **C.** This axial (transverse) image depicts a pericardial effusion (*arrows*) in a 23-week fetus with hydrops from B19 parvovirus infection. The degree of cardiomegaly is impressive, and the ventricular hypertrophy raises concern for myocarditis, which can accompany parvovirus infection. **D.** This axial (transverse) image depicts fetal ascites (*) in a 15-week fetus with hydrops secondary to large cystic hygromas. Anasarca is also seen (*bracket*).

neonate, and of these, the neonatal survival rate is just 50 percent (Nassr, 2018; Yeom, 2015).

Importantly, the etiology of nonimmune hydrops varies according to the gestational age at diagnosis. In a review of 63 pregnancies undergoing genetic testing for hydrops in the first trimester, aneuploidy was the cause in 70 percent (Sileo, 2020). Of cases diagnosed from 14 through 24 weeks, aneuploidy and congenital infection each accounted for 20 percent. When nonimmune hydrops presents before 24 weeks' gestation, the most frequent aneuploidy is 45,X—*Turner syndrome*, and in such cases, the survival rate is <5 percent (Sohan, 2001).

Recent advances in genetic testing have improved the understanding of hydrops cases that were previously considered idiopathic. In a review from the University of California Fetal-Maternal Consortium, whole exome sequencing was studied in 127 cases of unexplained nonimmune hydrops in which traditional genetic testing was uninformative (Sparks, 2020). Nearly 30 percent had a pathogenic genetic variant. The most common etiology was *RASopathies*, and many such cases resulted in Noonan syndrome. It is anticipated that as experience with whole exome sequencing accrues, the diagnostic yield will continue to increase.

Although the prognosis of nonimmune hydrops is guarded, it depends heavily on etiology. In a large series from Thailand and Southern China, α^0-thalassemia is the main cause of nonimmune hydrops. It accounts for 30 to 50 percent of cases and confers an extremely poor prognosis (Liao, 2007; Ratanasiri, 2009; Suwanrath-Kengpol, 2005). In contrast, treatable etiologies such as parvovirus infection, chylothorax, and tachyarrhythmias, which each constituting approximately 10 percent of cases, can result in survival in two thirds of cases with fetal therapy (Sohan, 2001).

Diagnostic Evaluation

Hydrops is readily detected with prenatal sonography (see Fig. 18-5). Imaging and laboratory evaluation may identify

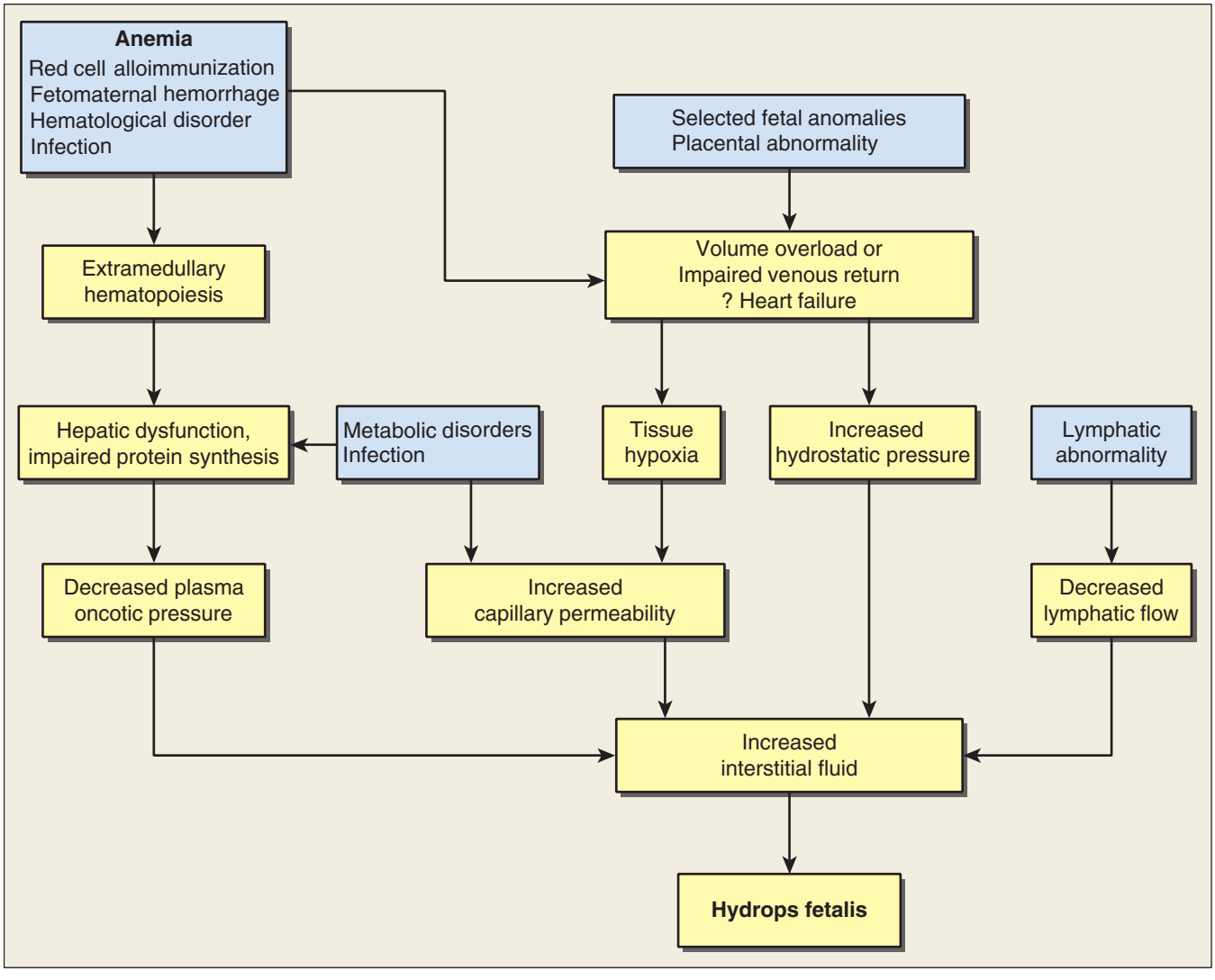

FIGURE 18-5 Proposed pathogenesis of immune and nonimmune hydrops fetalis. (Data from Bellini, 2009; Lockwood, 2009.)

fetal structural abnormalities, arrhythmias, anemia, aneuploidy, placental abnormalities, and complications of monochorionic twinning. Depending on the circumstances, initial evaluation includes the following:

1. Indirect Coombs test to identify alloimmunization
2. Detailed ultrasound examination of the fetus and placenta that includes:
   - A detailed anatomical survey to assess for the structural abnormalities listed in Table 18-4
   - Fetal echocardiography to further evaluate cardiac structure and function
   - MCA Doppler peak systolic velocity to assess for fetal anemia
3. Amniocentesis to obtain samples for chromosomal microarray analysis or karyotyping and for parvovirus B19, cytomegalovirus, and toxoplasmosis testing, as discussed in Chapter 67
4. Kleihauer-Betke test to detect fetomaternal hemorrhage if anemia is suspected, depending on findings and test results
5. Consideration of testing for alpha-thalassemia and/or inborn errors of metabolism.

Whole exome sequencing has significant potential to identify a genetic etiology if the aforementioned evaluation is not informative (Sparks, 2020). Counseling should include anticipated turnaround times, costs, and variants of uncertain significance. It is not recommended for routine use (American College of Obstetricians and Gynecologists, 2020). In addition, because sequencing is generally performed on the fetus and parents, a parent may be identified or suspected to have an unrelated but medically actionable finding, such as a cancer predisposition.

Isolated Effusion or Edema. The initial presentation of hydrops may be as a single effusion or anasarca. Although neither is diagnostic of hydrops, the above evaluation should be considered, and frequent surveillance may be prudent. A pericardial effusion may precede development of hydrops in fetal parvovirus B19 infection (Chap. 67, p. 1191). Similarly, isolated ascites may be the initial finding in fetal parvovirus B19 infection or may result from a gastrointestinal abnormality such as meconium peritonitis. An isolated pleural effusion may represent a chylothorax, which is amenable to prenatal diagnosis, and for which fetal therapy may be lifesaving if hydrops develops (Chap. 19, p. 376). Last, isolated edema, particularly involving

the upper torso or the dorsum of the hands and feet, may be found in Turner or Noonan syndrome or may represent congenital lymphedema syndrome (Chap. 16, p. 314).

Mirror Syndrome

The association between fetal hydrops and the development of maternal edema, in which the mother *mirrors* the fetus, is attributed to Ballantyne. He called the condition *triple edema* because the fetus, mother, and placenta all became edematous. Mirror syndrome has been reported to complicate at least 20 percent of hydrops cases (Chen, 2021). The etiology of the hydrops is not related to development of mirror syndrome. It has been associated with hydrops from D alloimmunization, twin-twin transfusion syndrome, placental chorioangioma, fetal cystic hygroma, Ebstein anomaly, sacrococcygeal teratoma, chylothorax, bladder outlet obstruction, supraventricular tachycardia, vein of Galen aneurysm, and various congenital infections (Braun, 2010).

In a review of more than 50 cases of mirror syndrome, Braun (2010) found that approximately 90 percent of women had edema, 60 percent had hypertension, 40 percent had proteinuria, 20 percent had liver enzyme elevation, and nearly 15 percent had headache and visual disturbances. Based on these findings, it is reasonable to consider mirror syndrome a form of severe preeclampsia (Espinoza, 2006; Midgley, 2000). Others, however, have suggested that it is a separate disease process with hemodilution rather than hemoconcentration (Carbillon, 1997; Livingston, 2007).

Some reports describe the same imbalance of angiogenic and antiangiogenic factors that is observed with preeclampsia, and this suggests a common pathophysiology (Goa, 2013; Hobson, 2020; Llurba, 2012). These findings, which include elevated concentrations of soluble fms-like tyrosine kinase 1 (sFlt-1), decreased placental growth factor (PlGF) levels, and elevation of soluble vascular endothelial growth factor receptor 1 (sVEGFR-1) concentrations, are discussed further in Chapter 40 (p. 694).

In most cases with mirror syndrome, prompt delivery is indicated and followed by resolution of maternal edema and other findings (Braun, 2010). However, in isolated cases of fetal anemia, supraventricular tachycardia, hydrothorax, or bladder outlet obstruction, successful fetal treatment has resulted in resolution of both fetal hydrops and maternal mirror syndrome (Goa, 2013; Livingston, 2007; Llurba, 2012; Midgley, 2000). Normalization of the angiogenic imbalance has also been described following fetal transfusion for parvovirus B19 infection. Fetal therapy for these conditions is reviewed in Chapter 19. Given the parallels to severe preeclampsia, delaying delivery to effect fetal therapy should be considered only with caution. If the maternal condition deteriorates, delivery is recommended.

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CHAPTER 19

Fetal Therapy

Innovative treatments developed during the past three decades have dramatically altered the course of selected fetal anomalies and conditions. Over time, fetal interventions have become less invasive, and the number of fetal centers has expanded. The North American Fetal Therapy Network now includes 36 medical centers in the United States and Canada. Some of the fetal abnormalities and conditions amenable to either medical or surgical treatment are presented here. The management of fetal anemia and thrombocytopenia is reviewed in Chapter 18, and treatment of some fetal infections is discussed in Chapters 67 and 68.

MEDICAL THERAPY

Selected medications administered to the pregnant woman are transported across the placenta in concentrations high enough to treat fetal conditions. Pregnancy physiology affects drug concentration, and transfer depends on maternal and placental metabolism (Chap. 8, p. 145).

Arrhythmias

Abnormal fetal cardiac rhythms are grouped into three categories: *tachyarrhythmias*, heart rates >180 beats per minute (bpm); *bradyarrhythmias*, heart rates <110 bpm; and ectopy, typically premature atrial contractions. If a fetal arrhythmia is suspected, M-mode ultrasound, described in Chapter 15 (p. 294), is used to measure the atrial and ventricular rates and to clarify the relationship between atrial and ventricular beats, thereby diagnosing the type of rhythm disturbance.

Premature Atrial Contractions

If the fetal heart rate is normal but the rhythm is irregular, the most common etiology is premature atrial contractions (PACs). These atrial ectopic beats are found in 1 to 2 percent of uncomplicated pregnancies (Hahurij, 2011; Strasburger, 2010). PACs represent immaturity of the cardiac conduction system. They typically resolve later in gestation or in the neonatal period. PACs are usually an isolated finding but may be associated with redundancy of the foramen ovale flap—formerly termed a foramen ovale aneurysm.

When a PAC is conducted, an extra beat is heard with handheld Doppler. However, the premature contraction more commonly arrives at the atrioventricular node during the refractory period. This results in a compensatory pause, which sounds like a dropped beat. M-mode evaluation confirms the diagnosis (Fig. 15-46, p. 295).

PACs may occur as frequently as every other beat, which means that the auscultated fetal heart rate may be as low as 60 to 80 bpm. Known as *blocked atrial bigeminy*, this condition is benign and does not require treatment (Strasburger, 2010). However, monitoring the fetus in labor may be challenging and necessitate cesarean delivery. M-mode ultrasound will differentiate atrial bigeminy from other causes of bradycardia, such as third-degree atrioventricular block.

Up to 2 percent of fetuses with PACs are later found to have *supraventricular tachycardia* (Copel, 2000; Srinivasan, 2008).

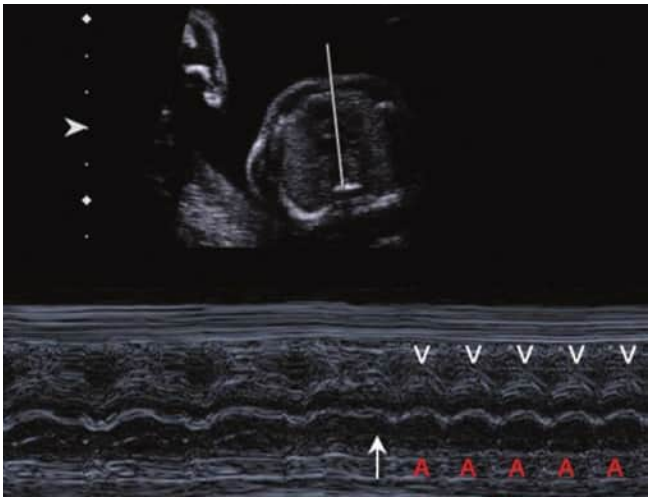

FIGURE 19-1 Supraventricular tachycardia (SVT). This M-mode image at 20 weeks' gestation demonstrates an initially normal fetal heartrate of 150 bpm. Midway through the image (*arrow*), the fetal heart rate suddenly increases to 240 bpm. With SVT, there is one atrial beat (*A*) for each ventricular beat (*V*).

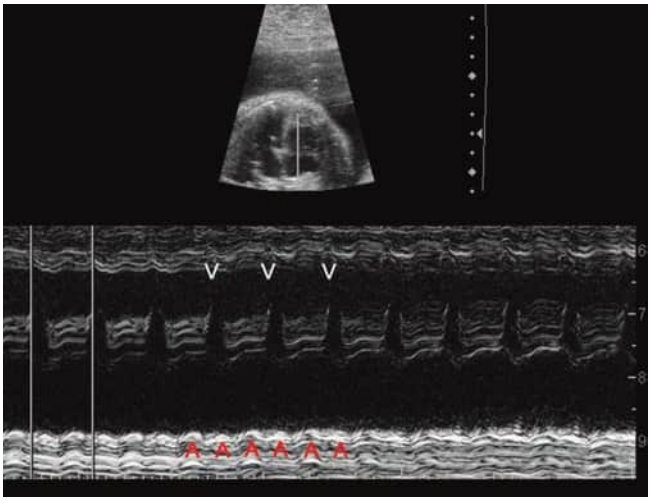

FIGURE 19-2 Atrial flutter. In this M-mode image at 32 weeks' gestation, calipers mark the ventricular rate, which is approximately 220 bpm. There are two atrial beats (*A*) for each ventricular beat (*V*), such that the atrial rate is approximately 440 bpm with 2:1 atrioventricular block.

Given the importance of prompt identification and treatment of supraventricular tachyarrhythmias, pregnancies with PACs are often monitored with fetal heart rate assessment every 1 to 2 weeks until the ectopy resolves. At Parkland Hospital, we find that auscultation with handheld Doppler is sufficient for surveillance.

Tachyarrhythmias

The two most common tachyarrhythmias are supraventricular tachycardia (SVT) and atrial flutter. SVT is characterized by an abrupt increase in the fetal heart rate to 180 to 300 bpm with 1:1 atrioventricular concordance (Fig. 19-1). The typical range is 200 to 240 bpm. SVT may develop secondary to an ectopic focus or to an accessory atrioventricular pathway leading to a reentrant tachycardia. Atrial flutter is characterized by a much higher atrial rate, generally 300 to 500 bpm, with varying degrees of atrioventricular block. As a result, the ventricular rate in a fetus with atrial flutter may range from below normal to approximately 250 bpm (Fig. 19-2). In contrast, fetal *sinus tachycardia* typically presents with a gradual heart rate rise to a rate that is only slightly above normal. With this, readily discernible causes may be maternal fever or hyperthyroidism, or rarely, fetal anemia or infection.

If a fetal tachyarrhythmia is identified, it is important to determine whether it is *sustained*—defined as present for at least 50 percent of the time. It may be necessary to monitor the fetal heart rate for 12 to 24 hours upon initial detection, and then periodically to reassess (Srinivasan, 2008). Unsustained or intermittent tachyarrhythmias may become sustained over time. Although intermittent tachyarrhythmias do not generally require treatment, close fetal surveillance is warranted.

Sustained fetal tachyarrhythmias with ventricular rates exceeding 200 bpm impair ventricular filling to a degree that the risks for developing cardiomyopathy and hydrops are significant. With atrial flutter, lack of coordinated atrioventricular contractions may further compound this risk. Maternal administration of antiarrhythmic agents that cross the placenta may convert the rhythm to normal or may lower the baseline heart rate to forestall heart failure. Therapy can require dosages at the upper end of the therapeutic adult range. Therefore, a maternal electrocardiogram is obtained before and during therapy. Monitoring of the maternal serum level may be necessary, particularly if the dosage requires titration. If medical therapy is successful, the medication is generally continued until delivery.

Antiarrhythmic medications most commonly used include digoxin, flecainide, and sotalol. Their selection depends on the type of tachyarrhythmia and provider experience with the drug. Traditionally, digoxin was the initial preferred treatment, but its placental transfer may be poor in the setting of hydrops. Many centers now use flecainide or sotalol as first-line therapy (Ekiz, 2018; van der Heijden, 2013). A second agent is needed in more than 50 percent of cases (Jaeggi, 2011; O'Leary, 2020; Shah, 2012). With treatment, conversion to a normal rhythm or reduction in heart rate to a normal range occurs in 90 percent, including 80 percent of those with hydrops (Miyoshi, 2019; Ueda, 2018). SVT is more likely than atrial flutter to convert to a normal rhythm. The neonatal survival rate exceeds 90 percent (Ekman-Joelsson, 2015; Miyoshi, 2019; O'Leary, 2020; van der Heijden, 2013).

Bradyarrhythmia

The most common etiology of fetal bradycardia is *congenital heart block*. Approximately 50 percent of cases occur in the setting of a structural cardiac abnormality involving the conduction system. These include *heterotaxy*, in particular *left-atrial isomerism*; *endocardial cushion defect*; and less commonly *corrected transposition of the great vessels* (Srinivasan, 2008). The prognosis of heart block from a structural cardiac anomaly is extremely poor, and fetal loss rates exceed 80 percent (Glatz, 2008; Strasburger, 2010).

In a structurally normal heart, 85 percent of atrioventricular block cases are caused by transplacental passage of maternal

anti-SSA/Ro or anti-SSB/La antibodies (Buyon, 2009). Many of these women have, or subsequently develop, systemic lupus erythematosus or other autoimmune disease (Chap. 62, p. 1113). The risk of third-degree heart block with Ro antibodies is small—only approximately 2 percent. However, the risk may reach 20 percent if a prior infant has been affected. Immune-mediated congenital heart block confers a mortality rate of nearly 20 percent, requires permanent pacing in two thirds of surviving children, and also poses a risk for cardiomyopathy (Brito-Zeron, 2015; Izmirly, 2011). If associated with effusions, bradyarrhythmias, or endocardial fibroelastosis, neonatal status may progressively worsen after birth.

Research has focused on maternal corticosteroid therapy to potentially reverse fetal heart block or to forestall it. In the PR Interval and Dexamethasone (PRIDE) study, a multicenter trial of pregnancies with anti-SSA/Ro antibodies, Friedman and colleagues (2008, 2009) performed weekly fetal echocardiography to assess for development of heart block. Fetal heart block was treated with maternal oral dexamethasone, 4 mg daily. Unfortunately, therapy did not prevent progression from second- to third-degree block, and third-degree atrioventricular block was *irreversible*. In rare cases, there was a potential benefit in reversing first-degree atrioventricular block. However, first-degree block did not generally progress even without treatment. Similarly, a subsequent review of pregnancies with isolated second- or third-degree fetal heart block found that dexamethasone therapy did not affect disease progression, need for pacemaker in the neonatal period, or overall survival rates (Izmirly, 2016). Despite considerable enthusiasm for corticosteroid treatment, a systematic review of more than 700 pregnancies with treated fetal heart block demonstrated no improvement in fetal or neonatal morbidity or mortality rates (Michael, 2019). Thus, we do not recommend dexamethasone use for this indication.

More recent efforts have turned to potential therapy with hydroxychloroquine (Plaquenil), a mainstay of treatment for systemic lupus erythematosus (Chap. 62, p. 1112). In a review of more than 250 women with prior affected children, early treatment with hydroxychloroquine was associated with a significant decrease in recurrence of congenital heart block (Izmirly, 2012). A subsequent clinical trial found that treatment with hydroxychloroquine was associated with a greater than 50-percent reduction in the rate of fetal heart block (Izmirly, 2020). In each of these series, fewer than 8 percent of children from pregnancies treated with hydroxychloroquine experienced heart block. Research in this area is ongoing.

Maternal terbutaline has also been given in small cohorts with either alloimmune- or heterotaxy-mediated fetal heart block in which the fetal heart rate is persistently below 56 bpm. The terbutaline dosage is titrated to a maternal heart rate of 95 to 115 bpm. Fetal heart rate increases of 5 to 10 bpm have been reported, but resolution of hydrops has not been consistently demonstrated (Cuneo, 2007, 2010).

■ Congenital Adrenal Hyperplasia

Several autosomal recessive enzyme deficiencies impair fetal synthesis of cortisol from cholesterol by the adrenal cortex, leading to congenital adrenal hyperplasia (CAH). CAH is the most common etiology of androgen excess in those with 46,XX disorders of sex development (Chap. 3, p. 38). Lack of cortisol stimulates adrenocorticotrophic hormone (ACTH) secretion by the anterior pituitary, overproduction of androstenedione and testosterone, and subsequent virilization of female fetuses. Sequelae may include formation of labioscrotal folds, persistence of a urogenital sinus, or even creation of a penile urethra and scrotal sac (Fig. 15-55, p. 299).

More than 90 percent of CAH cases are caused by 21-hydroxylase deficiency. There are two types: classic and nonclassic. The incidence of classic CAH approximates 1 in 15,000 births worldwide but is higher in selected populations. Among Yupik Eskimos, the reported incidence is 1 in 300 births (Nimkarn, 2016). Of those with classic CAH, 75 percent require postnatal treatment with mineralocorticoids and glucocorticoids to prevent a *salt-wasting adrenal crisis*, which is characterized by hyponatremia, dehydration, hypotension, and even cardiovascular collapse. The remaining 25 percent with classic CAH have the *simple virilizing type* and also require glucocorticoid supplementation. Nonclassic CAH may present with precocious pubarche, hirsutism, or infertility. However, affected individuals also may be asymptomatic. The prevalence of nonclassic CAH approximates 1 case per 200 Caucasians and Ashkenazi Jews in the United States (Hannah-Shmouni, 2017). As discussed in Chapter 32 (p.594), all states mandate newborn screening for CAH.

For more than three decades, dexamethasone has been administered to the pregnant woman to suppress fetal androgen overproduction and either obviate or ameliorate virilization of female fetuses (David, 1984; New, 2012). Prenatal corticosteroid therapy is successful in most cases if initiated early and taken consistently. One metaanalysis found that dexamethasone treatment was associated with reduced virilization. Specifically, the Prader score, which grades genital masculinization on a scale 1 to 5, improved by 2.3 grades (Fernandez-Balselis, 2010). The alternative is consideration of postnatal genitoplasty, which may include clitoroplasty, urogenital sinus surgery, and additional vaginoplasty procedures. In a recent review, 18 percent of children treated with feminizing genitoplasty experienced postoperative complications, and 12 percent required further surgery (Baskin, 2020).

The typical preventive regimen is oral dexamethasone given to the mother at a dosage of 20 μg/kg/d—up to 1.5 mg per day, divided in three doses. The critical period for external genitalia development is 7 to 12 weeks' gestation, and treatment to prevent virilization should be initiated by 9 weeks—*before it is known whether the fetus is* affected. Because this is an autosomal recessive condition, affected females make up only 1 in 8 at-risk conceptions.

Carrier parents are typically identified after the birth of an affected child. Molecular genetic testing is clinically available in such cases and initially uses sequence analysis of the *CYP21A2* gene, which encodes the 21-hydroxylase enzyme (Nimkarn, 2016). If this is uninformative, gene-targeted deletion/duplication analysis is performed, and additional testing such as whole exome sequencing may be considered (Chap. 16, p. 327).

A goal of prenatal diagnosis is to limit dexamethasone exposure in males and in unaffected females. If both parents

are determined to be carriers, prenatal molecular genetic testing may be performed on chorionic villi—at 10 to 12 weeks' gestation—or on amniocytes after 15 weeks. Determination of fetal gender using cell-free DNA (cfDNA) may aid in avoiding dexamethasone treatment. CfDNA sensitivity to detect Y-chromosome sequences is at least 95 percent when performed at or beyond 7 weeks (Devaney, 2011; Hill, 2011). In the research setting, effective cfDNA testing using hybridization probes flanking the *CYP21A2* gene has been reported as early as $5^{6/7}$ weeks' gestation (New, 2014).

Maternal treatment with dexamethasone has become controversial. The Endocrine Society recommends that treatment be given only in the context of research protocols (Speiser, 2018). It further recommends that such protocols incorporate cfDNA screening for the Y-chromosome to avoid treatment of male fetuses. Of note, if therapy is initiated shortly before 9 weeks' gestation, the dose of dexamethasone used is not considered to have significant teratogenic potential because organogenesis of major organs has already taken place (McCullough, 2010). Ongoing concerns focus on the potential effects of either excess *endogenous* androgens or excess *exogenous* dexamethasone on the developing brain. Although maternal dexamethasone has been used for many years to prevent virilization of female fetuses with CAH, long-term safety data are relatively limited.

Congenital Cystic Adenomatoid Malformation

This well-circumscribed lung mass may appear solid and echogenic or may have one or multiple variably sized cysts (Fig. 15-33, p. 288). Lesions with one or more cysts ≥5 mm are termed macrocystic, whereas solid lesions and those with smaller cysts are microcystic (Adzick, 1985). A small subset of microcystic congenital cystic adenomatoid malformations (CCAMs) may demonstrate rapid growth, generally between 18 and 26 weeks' gestation. The mass may become so large that it causes mediastinal shift, which may compromise cardiac output and venous return, leading to hydrops (Cavoretto, 2008).

A CCAM-volume ratio (CVR) has been used to quantify size and risk for hydrops in these severe cases (Crombleholme, 2002). This ratio is an estimate of the CCAM volume using the formula for a prolate ellipse (length × width × height × π/6) divided by the head circumference. In a series of 40 pregnancies with microcystic CCAM, the mean CVR was 0.5 at 20 weeks' gestation, peaked at 1.0 by 26 weeks, and then declined sharply before delivery (Macardle, 2016). With a CVR exceeding 1.6, the risk for hydrops is as high as 60 percent. However, if the initial CVR is below 1.6, CCAM growth resulting in hydrops develops in fewer than 2 percent of cases (Ehrenberg-Buchner, 2013; Peranteau, 2016).

A CVR threshold of 1.0 also may assist counseling. In a series of 62 pregnancies with fetal lung masses, a maximal CVR >1.0 was associated with a 75-percent likelihood that the neonate would be symptomatic (Ehrenberg-Buchner, 2013). However, no fetus with a CVR ≤1.0 subsequently required surgery in the newborn period.

If the CVR exceeds 1.6 or if signs of hydrops develop, corticosteroid treatment may be beneficial. Regimens include dexamethasone—6.25 mg every 12 hours for four doses, or betamethasone—12.5 mg intramuscularly every 24 hours for two doses. A single course of corticosteroids has been associated with resolution of hydrops in approximately 80 percent of cases, and 90 percent of treated fetuses survived (Loh, 2012; Peranteau, 2016). Multiple courses of corticosteroids—generally two—have been advocated for fetuses with large CCAM lesions and with persistent or worsening hydrops or ascites despite a single course of medication (Derderian, 2015; Peranteau, 2016). Therapy for macrocystic CCAM is discussed later.

Thyroid Disease

Identification of fetal thyroid disease is rare and is usually prompted by sonographic detection of a fetal goiter. If a goiter is identified, determination of fetal hyper- or hypothyroidism is essential, and thyroid hormone levels should be measured in amnionic fluid or fetal blood. Traditionally, fetal blood sampling was preferred to amniocentesis for guiding treatment, but data are limited (Abuhamad, 1995; Ribault, 2009). Performance of these procedures is discussed in Chapter 17 (p. 347). Goals of therapy are correction of the physiological abnormality and diminished goiter size. The goiter may compress the trachea and esophagus, leading to hydramnios from impaired swallowing. Despite this, case reports attest to lack of airway compromise and favorable outcomes (Blumenfeld, 2013; Machado, 2019).

Thyrotoxicosis

Maternal Graves disease may result in transplacental passage of immunoglobulin G (IgG) thyroid-stimulating antibodies. Untreated fetal thyrotoxicosis can present with goiter, tachycardia, growth restriction, hydramnios, accelerated bone maturation, and even heart failure and hydrops (Huel, 2009; Kiefer, 2017; Peleg, 2002; van Dijk, 2018). Fetal blood sampling may be considered to confirm the diagnosis (Duncombe, 2001; Srisupundit, 2008). Maternal administration of antithyroid medication may be needed, even if the woman has had prior surgery or ablation and no longer has hyperthyroidism. If the pregnant women develops hypothyroidism, she is treated with supplemental levothyroxine (Hui, 2011).

Hypothyroidism

In a woman receiving medication for Graves disease, transplacental passage of methimazole or propylthiouracil may cause *fetal hypothyroidism* (Bliddal, 2011). Other potential causes of fetal hypothyroidism resulting in goiter include transplacental passage of thyroid peroxidase antibodies, fetal thyroid dyshormonogenesis, and maternal consumption of iodine supplements (Agrawal, 2002; Hardley, 2018; Overcash, 2016).

Goitrous hypothyroidism may lead to hydramnios, neck hyperextension, and delayed bone maturation. Treatment with intraamnionic levothyroxine should be considered. Optimal dosage and frequency have not been established but have typically ranged from 150 to 500 μg every 1 to 4 weeks (Machado, 2019; Nemescu, 2020; Ribault, 2009). If the pregnant woman is receiving antithyroid medication, it is generally discontinued.

TABLE 19-1. Guiding Principles for Fetal Surgical Procedures

Accurate prenatal diagnosis for the defect is available, with staging if applicable
The defect appears isolated, with no evidence of other abnormality or underlying genetic syndrome that would significantly worsen survival or quality of life
The defect results in a high likelihood of death or irreversible organ destruction, and postnatal therapy is inadequate
The procedure is technically feasible, and a multidisciplinary team is in agreement regarding the treatment plan
Maternal risks from the procedure are well documented and considered acceptable
There is comprehensive parental counseling
It is recommended that there be an animal model for the defect and procedure

Data from Deprest, 2010; Harrison, 1982; Vrecenak, 2013; Walsh, 2011.

SURGICAL THERAPY

Fetal surgery, also called *maternal-fetal surgery*, is offered for selected congenital abnormalities in which the likelihood of deterioration during gestation is so great that delaying treatment until after delivery would risk fetal death or substantially greater postnatal morbidity. Fetal surgical procedures are highly specialized interventions performed at relatively few centers to treat a small number of fetal conditions. They require extensive preoperative counseling and multidisciplinary care. Principles for guiding case selection are listed in Table 19-1. When considering fetal surgery, the overriding concern is the safety of the mother and fetus. Accomplishing the fetal goals of the procedure is secondary (Walsh, 2011).

Selected abnormalities amenable to fetal surgical treatment are shown in Table 19-2. An overview of some of these procedures, their indications, and complications is provided here to assist with initial patient evaluation and counseling. Additional content is also found in *Cunningham and Gilstrap's Operative Obstetrics*, 3rd edition.

Open Fetal Surgery

Fetal procedures are considered open if they are accomplished though a hysterotomy that is not performed for the purpose of delivery. Open procedures are performed under general endotracheal anesthesia to suppress uterine contractions and fetal responses. The hysterotomy is made with a stapling device, and intraoperative ultrasound is used to avoid the placental edge and to verify fetal position. The stapler seals the edges of the myometrium and membranes to achieve hemostasis and avoid chorioamnion separation. Warmed fluid is continuously infused into the uterus thorough a rapid infusion device to limit cord compression. The fetus is gently manipulated to facilitate exposure, to permit pulse oximetry monitoring, and to establish venous access in case fluids or blood are emergently needed. The surgical procedure is then performed, and the hysterotomy is closed. Prophylactic antibiotics are generally administered for 24 hours. Tocolysis typically includes intravenous magnesium sulfate for 24 hours and oral indomethacin for 48 hours. Cesarean delivery is needed later in gestation and for all future deliveries.

Risks

Open fetal surgery entails significant maternal and fetal risks. The most recent data are from studies of fetal myelomeningocele

TABLE 19-2. Selected Fetal and Placental Abnormalities Amenable to In-Utero Procedures

Open Fetal Surgery
Congenital cystic adenomatoid malformation (CCAM)
Myelomeningocele
Pulmonary sequestration
Sacrococcygeal teratoma
Fetoscopic Surgery
Amnionic band sequence: band release
Congenital diaphragmatic hernia (CDH): fetal endoscopic tracheal occlusion (FETO)
Congenital high airway obstruction sequence (CHAOS): vocal cord laser
Myelomeningocele
Posterior urethral valves: cystoscopic laser
Twin-twin transfusion: laser of placental anastomoses
Percutaneous Procedures
Cardiac catheter procedures
Aortic or pulmonic valvuloplasty for stenosis
Atrial septoplasty for hypoplastic left heart with restrictive atrial septum
Radiofrequency ablation
Twin reversed arterial perfusion (TRAP) sequence
Monochorionic twins with severe anomaly in one twin
Chorioangioma
Shunt therapy
Dominant cyst in CCAM
Thoracoamnionic shunt for pleural effusion
Vesicoamnionic shunt for bladder outlet obstruction
Ex-Utero Intrapartum Treatment (EXIT) Procedures
CDH after FETO
CHAOS
EXIT-to-extracorporeal membrane oxygenation (ECMO): CDH
EXIT-to-resection: resection of fetal thoracic or mediastinal mass
Micrognathia
Neck or airway tumors

Procedures are listed alphabetically within groupings.

TABLE 19-3. Benefits and Risks of Fetal Myelomeningocele Surgery versus Postnatal Repair

	Fetal Surgery (n = 78)	Postnatal Surgery (n = 80)	*p* value
Benefits (Primary Outcomes)			
Perinatal death or shunt by 12 months[a]	68%	98%	<0.001
Shunt placement by 12 months	40%	82%	<0.001
Composite developmental score[a,b]	149 ± 58	123 ± 57	0.007
Hindbrain herniation (any)	64%	96%	<0.001
Brainstem kinking (any)	20%	48%	<0.001
Independent walking (30 months)	42%	21%	0.01
Risks			
Maternal pulmonary edema	6%	0	0.03
Placental abruption	6%	0	0.03
Maternal transfusion at delivery	9%	1%	0.03
Oligohydramnios	21%	4%	0.001
Gestational age at delivery	34 ± 3	37 ± 1	<0.001
Preterm birth			
<37 weeks	79%	15%	<0.001
<35 weeks	46%	5%	
<30 weeks	13%	0	

[a]Each primary outcome had two components. The perinatal death components of the primary outcomes as well as the Bayley Mental Development Index at 30 months did not differ between the two study cohorts.
[b]Score derived from Bayley Mental Development Index and difference between functional and anatomical level of lesion (30 months).
Data from Adzick, 2011.

repair, which is the most commonly performed procedure. Morbidities identified in the Management of Myelomeningocele Study (MOMS) are shown in Table 19-3 (Adzick, 2011). In a review of 26 open fetal myelomeningocele cases, 15 percent experienced preterm rupture of membranes, and the mean gestational age at delivery was 35 weeks (Pruthi, 2021). Other potential risks include maternal sepsis and fetal death during or following the procedure, particularly if hydrops is present. Wilson and associates (2010) reviewed subsequent pregnancy outcomes following open fetal surgery and reported that 14 percent of women experienced uterine rupture and 14 percent had uterine dehiscence.

Myelomeningocele Surgery

Fetal myelomeningocele is the first nonlethal birth defect for which in-utero repair has been offered (Fig. 19-3). Following standard postnatal myelomeningocele repair, affected children experience varying degrees of paralysis, bladder and bowel dysfunction, developmental delays, and brainstem dysfunction from the Arnold-Chiari II malformation (Chap. 15, p. 277). Damage is postulated to result from abnormal embryonic neurulation followed by exposure of neural elements to amnionic fluid throughout pregnancy (Adzick, 2010; Meuli, 1995, 1997).

In the landmark MOMS trial, Adzick and colleagues (2011) randomized 183 pregnancies to prenatal or standard postnatal myelomeningocele repair at three centers. Criteria for trial participation included: (1) a singleton fetus at 19.0 to 25.9 weeks' gestation; (2) an upper myelomeningocele boundary between T_1 and S_1 confirmed by magnetic resonance imaging; (3) evidence of hindbrain herniation; and (4) a normal karyotype and no evidence of a fetal anomaly unrelated to the myelomeningocele. Women at risk for preterm birth or placental abruption, those with a contraindication to fetal surgery, and women with body mass index (BMI) >35 kg/m^2 were excluded.

The MOMS trial demonstrated improved early childhood outcomes in the prenatal surgery cohort (see Table 19-3). Children who had undergone fetal surgery were twice as likely to walk independently by 30 months. They had significantly less hindbrain herniation and were only half as likely to undergo ventriculoperitoneal shunting by age 1 year. A primary outcome was a composite score that was derived from the Bayley Mental Development Index and from the difference between the functional and anatomical level of the lesion at 30 months. This primary outcome was also significantly better in the prenatal surgery group.

Despite these benefits, *most* children who received fetal surgery were not able to ambulate independently, and nearly 30 percent were not able to ambulate at all. Prenatal surgery did not confer improvements in fetal or neonatal death rates or in the Bayley Mental Development Index score at age 30 months. Prenatal surgery was also associated with a small risk for placental abruption and maternal pulmonary edema. Moreover, nearly half were delivered before 34 weeks,

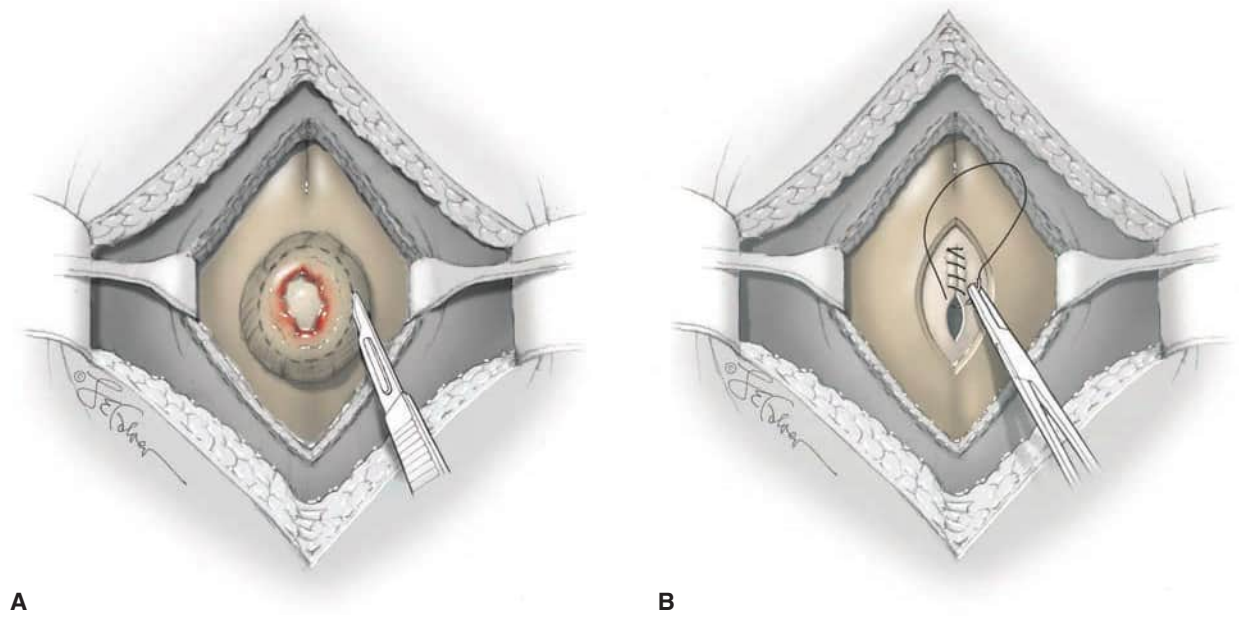

FIGURE 19-3 Fetal myelomeningocele surgery. **A.** With the edges of both the laparotomy and hysterotomy incisions retracted, the skin around the defect is incised. Subsequently, the neural placode is sharply dissected from the arachnoid membrane. **B.** The dural membrane is reflected to the midline to cover the neural placode and is reapproximated using suture. In some cases a patch is needed (not shown). The fetal skin incision is subsequently sutured. Last, hysterotomy and laparotomy are then closed. (Figures 19-3, 19-4, 19-6, and 19-8: Reproduced with permission from Shamshirsaz AA, Ramin, SM, Belfort MA: Fetal therapy. In Yeomans ER, Hoffman BL, Gilstrap LC III, et al: Cunningham and Gilstrap's Operative Obstetrics, 3rd ed. New York, McGraw Hill Education, 2017.)

which significantly increased the risk for respiratory distress syndrome (Adzick, 2011).

It is the position of the American College of Obstetricians and Gynecologists (2017) that nondirective counseling include the option of fetal surgery for all pregnancies that meet MOMS trial criteria. Study of fetal myelomeningocele repair in women with BMI up to 40 kg/m^2 has demonstrated outcomes similar to those in women of lower BMI (Hilton, 2019; Moldenhauer, 2020). Otherwise, MOMS trial criteria are strictly followed. Outcomes of children aged 6 to 10 years who previously participated in the MOMs trial are now available (Houtrow, 2020). Fetal surgery conferred a sustained benefit in the likelihood of independent ambulation. Nearly 30 percent of children were able to ambulate independently, and approximately 50 percent required ventriculoperitoneal shunt placement. Overall cognitive function was similar between cohorts (Houtrow, 2020).

Thoracic Masses

Open fetal surgery is rarely performed for thoracic masses. Most are small, and these have a good prognosis. Large CCAMs are often treated medically with a course of corticosteroids (p. 370). A dominant cyst in a CCAM may be amenable to drainage or shunt placement (p. 376). Similarly, an isolated pleural effusion surrounding a pulmonary sequestration may be amenable to drainage or shunt placement.

Fetal surgery is generally reserved for pregnancies prior to 32 weeks' gestation in which there is a large, solid-appearing or microcystic mass and hydrops is developing. In carefully selected cases, the survival rate following open lobectomy approximates 60 percent (Vrecenak, 2013). Use of the ex-utero intrapartum treatment procedure in the treatment of fetal lung masses at delivery is discussed later.

Sacrococcygeal Teratoma

The perinatal mortality rate for cases of sacrococcygeal teratoma diagnosed prenatally is 20 to 40 percent (Hedrick, 2004; Shue, 2013, Simonini, 2021). Poor prognostic factors include a solid component constituting more than 50 percent of the tumor mass and a tumor volume-to-fetal weight ratio exceeding 12 percent prior to 24 weeks' gestation (Akinkuotu, 2015). Hydramnios is common, and hydrops may develop from high-output cardiac failure, either as a consequence of tumor vascularity or secondary to bleeding within the tumor and resulting anemia. Fetal loss rates approach 100 percent in such cases. *Mirror syndrome*—maternal preeclampsia developing along with fetal hydrops—may occur in this setting (Chap. 18, p. 364).

Open fetal surgery is considered only if the tumor is completely external and high cardiac output with early hydrops has developed in the second trimester (Vrecenak, 2013). However, given the poor prognosis, rapid growth beyond 27 weeks often prompts early delivery and postnatal resection rather than open fetal surgery (Baumgarten, 2019).

■ Fetoscopic Surgery

As with open fetal surgeries, these procedures are performed at highly specialized centers. Fetoscopy is performed with fiberoptic endoscopes that measure 1 to 2 mm in diameter. Instruments such as lasers fit through a 3- to 5-mm cannula

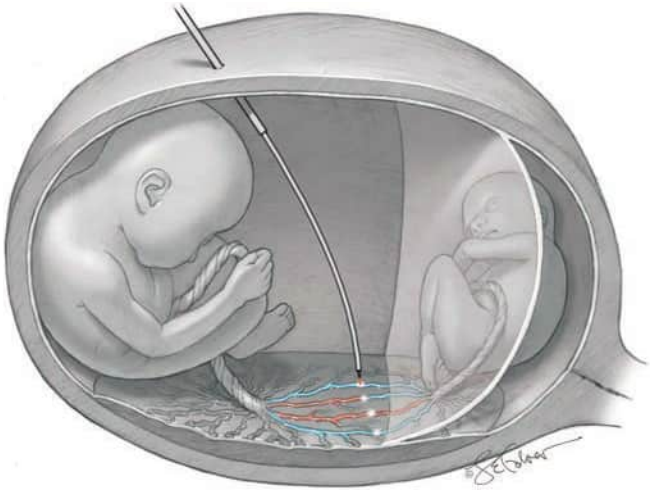

FIGURE 19-4 Selective laser photocoagulation for twin-twin transfusion syndrome. The fetoscope is inserted into the recipient-twin sac and positioned over the vascular equator, which lies in between the two placental cord insertion sites. Arteriovenous anastomoses along the placental surface are individually photocoagulated using the laser. (Reproduced with permission from Shamshirsaz AA, Ramin, SM, Belfort MA: Fetal therapy. In Yeomans ER, Hoffman BL, Gilstrap LC III, et al: Cunningham and Gilstrap's Operative Obstetrics, 3rd ed. New York, NY: McGraw Hill; 2017.)

that surrounds the endoscope. Not all fetoscopic procedures involve placing the instruments through the maternal anterior abdominal wall. In some cases, laparotomy facilitates optimal placement and maneuvering of the instruments or positioning of the fetus. Examples of conditions treated by fetoscopy are listed in Table 19-2.

Twin-Twin Transfusion Syndrome

As discussed in Chapter 48 (p. 849), fetoscopic laser ablation of placental anastomoses is the preferred management for severe twin-twin transfusion syndrome (TTTS). It is generally performed between 16 and 26 weeks' gestation for monochorionic-diamnionic twin pregnancies with stage II to stage IV TTTS (Quintero, 1999; Society for Maternal-Fetal Medicine, 2013).

A fetoscope inserted into the sac of the recipient twin is used to image the *vascular equator*. The vascular equator separates the placental cotyledons that supply each twin (Fig. 19-4). *Selective laser photocoagulation* involves individually coagulating anastomoses that cross between the twins (Ville, 1995). Arteriovenous anastomoses along the placental surface of the equator are visualized with the fetoscope and then photocoagulated using a 600-μm diameter diode laser or a 400-μm neodymium:yttrium-aluminum-garnet (Nd:YAG) laser (Fig. 19-5). The procedure is typically performed under epidural analgesia. At the end, amnioreduction is performed to decrease the single deepest pocket of amnionic fluid to below 5 cm, and antibiotics are injected into the amnionic cavity.

Unfortunately, residual anastomoses remain in up to a third of cases and may lead to TTTS recurrence or to the development of twin anemia-polycythemia sequence (TAPS). The latter is a feto-fetal transfusion characterized by large differences in hemoglobin concentrations between a pair of monochorionic twins. With the *Solomon technique*, immediately after selective photocoagulation, the laser is used to coagulate the entire vascular equator from one edge of the placenta to the other (Slaghekke, 2014a). Placental dye-injection studies confirm a significant reduction in the number of residual anastomoses following this procedure (Ruano, 2013; Slaghekke, 2014b).

Families should have reasonable expectations of procedural success and potential complications. Without treatment, the perinatal mortality rate for severe TTTS is 70 to 100 percent. Following laser therapy, the perinatal mortality rate approximates 30 to 50 percent, and the risk for long-term neurological handicap is 5 to 20 percent (Society for Maternal-Fetal Medicine, 2013). One series reported a double-twin survival rate of nearly 70 percent and survival of at least one twin in more than 90 percent of cases (Diehl, 2017). Ischemic fetal brain lesions have been identified in 2 percent of those treated by laser and include cystic periventricular leukomalacia and grade III or IV interventricular hemorrhage (Stirnemann, 2018).

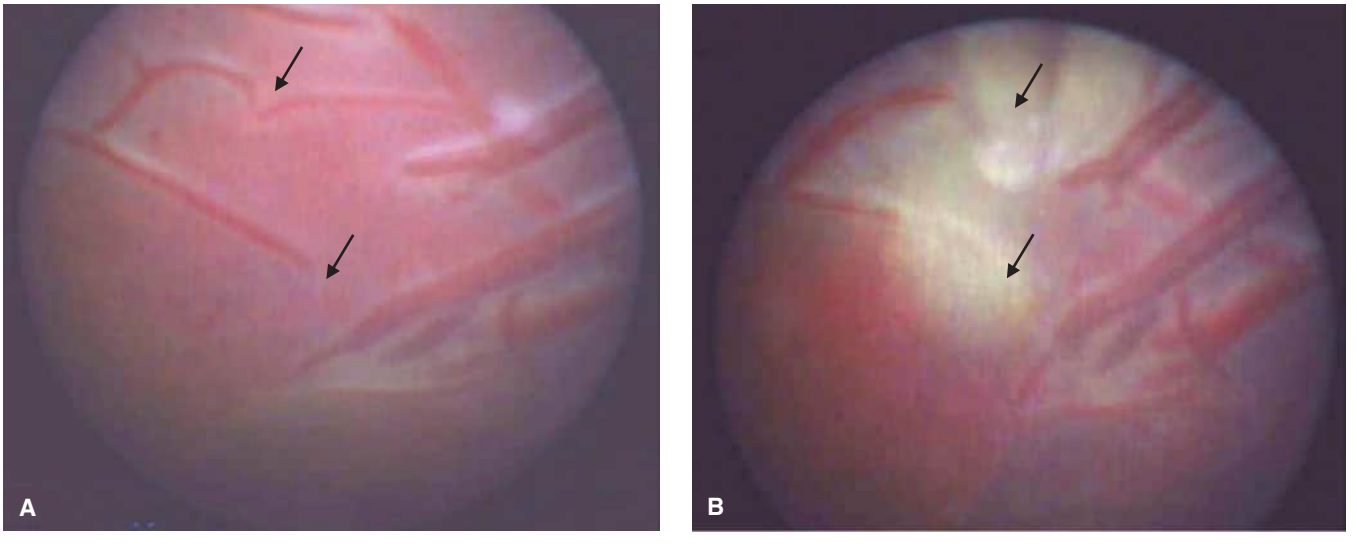

FIGURE 19-5 Fetoscopic photograph of laser photocoagulation for twin-twin transfusion syndrome. **A.** Vascular anastomoses (*arrows*) are shown before photocoagulation is performed. **B.** The ablation sites appear as blanched yellow-white areas (*arrows*). (Reproduced with permission from Dr. Timothy M. Crombleholme.)

Cerebral palsy has been reported in 5 percent of surviving children (Schou, 2019).

Procedure-related complications include preterm prelabor ruptured membranes in up to 25 percent, placental abruption in 8 percent, vascular laceration in 3 percent, and amnionic band syndrome resulting from laser laceration of the membranes in 3 percent. Additionally, TAPS complicates 16 percent of pregnancies treated with selective laser photocoagulation and 3 percent treated with the Solomon technique (Habli, 2009; Robyr, 2006; Slaghekke, 2014b). The majority of laser-treated TTTS pregnancies deliver before 34 weeks' gestation (Akkermans, 2015).

Congenital Diaphragmatic Hernia

Early attempts to treat congenital diaphragmatic hernia (CDH) used open fetal surgery to reposition the liver into the abdomen. This unfortunately kinked the umbilical vein and led to fetal demise (Harrison, 1993). Knowledge that lungs normally produce fluid and that fetuses with upper airway obstruction develop pulmonary hyperplasia formed the rationale for tracheal occlusion. The idea was to "plug the lung until it grows" (Hedrick, 1994). Initial efforts focused on occluding the trachea with an external clip (Harrison, 1993). Subsequently, a detachable silicone or latex balloon was placed within the trachea endoscopically and inflated with normal saline (Fig. 19-6). This procedure, *fetoscopic tracheal occlusion (FETO)*, is offered to selected pregnancies with isolated CDH in which the prognosis is otherwise poor based on the degree of fetal liver herniation.

FETO uses a 3-mm operating sheath and fetoscopes as small as 1 mm (Van der Veeken, 2018). The procedure is generally performed between 26 and 30 weeks' gestation. The balloon is removed after 6 weeks or at approximately 34 weeks, either through a second fetoscopic procedure or by ultrasound-guided puncture (Baschat, 2020). Fetal lamb research demonstrated that without balloon removal, the number of type II pneumocytes was markedly reduced, but that balloon removal normalized type II pneumocyte density (Flageole, 1998). Because the procedure is performed fetoscopically, vaginal delivery is not contraindicated.

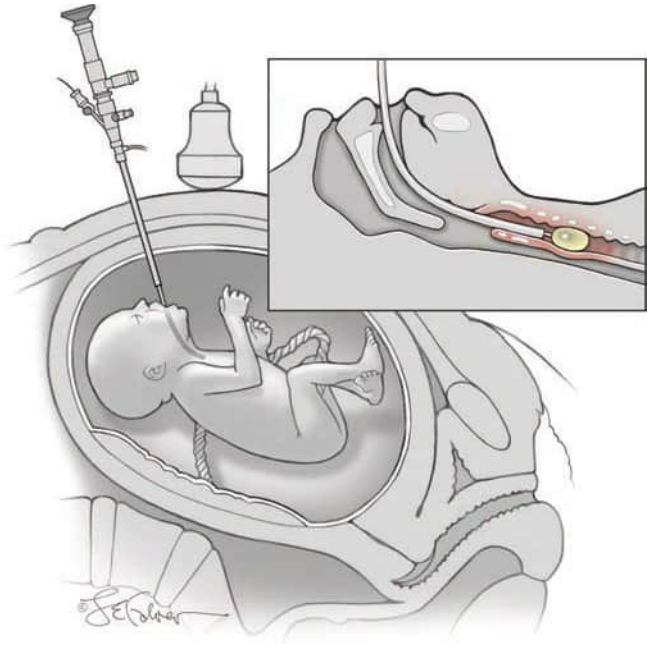

FIGURE 19-6 Fetoscopic tracheal occlusion (FETO). The endoscope enters the fetal oropharynx and advances down the trachea. Inset: The balloon is inflated to occlude the trachea, and then the endoscope is removed. (Reproduced with permission from Shamshirsaz AA, Ramin, SM, Belfort MA: Fetal therapy. In Yeomans ER, Hoffman BL, Gilstrap LC III, et al: Cunningham and Gilstrap's Operative Obstetrics, 3rd ed. New York, NY: McGraw Hill; 2017.)

In 2003, a randomized trial of the FETO procedure in pregnancies with isolated CDH, liver herniation, and lung-to-head ratio <1.4 did not identify a benefit from fetal therapy (Harrison, 2003). Survival rates 90 days after birth were unexpectedly high—75 percent—in both groups. Therefore, the lung-to-head threshold was lowered and adjusted for gestational age in an effort to improve prediction. In a metaanalysis of more than 200 pregnancies, treatment with FETO was associated with a 13-fold improvement in survival rates (Al-Maary, 2016). FETO has also been associated with improved survival rates in right-sided CDH (Russo, 2021). Although study outcomes are promising, this procedure is currently available in the United States only through a research protocol.

Lung-to-Head Ratio. This imaging index was developed to improve prediction of survival in fetuses with isolated left-sided CDH diagnosed before 25 weeks' gestation (Metkus, 1996). The lung-to-head ratio (LHR) is a semi-quantitative estimate of the right lung area divided by the head circumference. Investigators found that the neonatal survival rate was 100 percent if the LHR was >1.35 and that there were no survivors if the LHR was <0.6 (Metkus, 1996). Nearly three fourths of pregnancies had values between 0.6 and 1.35, and prediction was difficult in this group because the overall survival rate approximated 60 percent.

Modifications to the LHR have been developed in an effort to improve prediction. Jani and colleagues (2007) derived an observed-to-expected (O/E) LHR nomogram to account for differential growth of the head and torso across gestation. Lung area has been measured in 3 different ways: (1) by tracing the lung circumference, (2) by multiplying the longest diameter of the lung with its longest perpendicular diameter, and (3) by multiplying the anterior-posterior diameter of the lung at the mid-clavicular line by the perpendicular diameter at its midpoint (Jani, 2012). The North American Fetal Therapy Network found that reproducibility of the O/E LHR was highest when the lung circumference was traced, but that overall interrater agreement was lower than anticipated (Abbasi, 2019).

Fetoscopic Myelomeningocele Repair

After publication of the MOMS trial findings, research efforts focused on whether maternal morbidities associated with open fetal myelomeningocele repair might be mitigated if the procedure were accomplished fetoscopically. Araujo Junior and associates (2016) conducted a systematic review that included 456 open cases and 84 fetoscopic surgeries. The endoscopic procedures were generally performed by inserting instruments through the maternal abdominal wall and then through the uterine wall, with partial carbon dioxide insufflation of the

uterus. The rate of maternal myometrial dehiscence or attenuation was only 1 percent following endoscopy compared with 26 percent following open procedures. However, fetoscopy was associated with significantly higher rates of preterm delivery before 34 weeks—80 versus 45 percent, and of perinatal mortality—14 versus 5 percent.

More recently, investigators have performed fetoscopic myelomeningocele repair but used laparotomy and exteriorization of the uterus (Belfort 2017). The proportion of infants requiring ventriculoperitoneal shunts before age 1 year—approximately 40 percent—was similar to that with open fetal surgery in the MOMS trial (Adzick, 2011; Belfort, 2017). In one series of 34 pregnancies treated with open fetoscopic myelomeningocele repair, the median gestational age at delivery was 38 weeks, and 50 percent delivered vaginally (Kohn, 2018). Research is ongoing in this area.

Percutaneous Procedures

These procedures are performed using a shunt, angioplasty catheter, radiofrequency ablation needle, or bipolar cautery. Under ultrasound guidance, instruments are inserted through the maternal abdominal wall, uterine wall, and membranes to reach the amnionic cavity and fetus. Risks may include preterm labor, preterm prelabor ruptured membranes, placental abruption, maternal infection, and fetal injury or loss.

Thoracic Shunts

These shunts drain fetal pleural fluid into the amnionic cavity (Fig. 19-7). A large effusion may result in pulmonary hypoplasia or may cause mediastinal shift that is severe enough to result in hydrops. The most common etiology of a primary effusion is *chylothorax*, which is caused by lymphatic obstruction. Chylothorax is diagnosed if a cell count performed on the pleural fluid demonstrates that more than 80 percent of the cells are lymphocytes, and there is no evidence of infection. Pleural effusions may also form secondary to congenital viral infection or aneuploidy, or they may be associated with a malformation such as a *pulmonary sequestration*. Yinon and associates (2010) reported aneuploidy in approximately 5 percent and associated anomalies in 10 percent of cases.

Typically, the effusion is first drained using a 22-gauge needle. The fluid may be sent for chromosomal microarray analysis, infection studies, and a cell count. If the effusion recurs, a double-pigtail shunt is placed through the fetal chest wall using a trocar and cannula. For a right-sided effusion, the shunt is placed in the lower third of the chest to permit maximum expansion of the lung. If left-sided, the shunt is placed along the upper axillary line to allow the heart to return to normal position. The overall survival rate is 70 percent, and that for hydropic fetuses approximates 50 percent (Mann, 2010; Yinon, 2010). We recommend weekly surveillance following shunt placement because displacement into the amnionic cavity is common. At time of delivery, the shunt must be clamped immediately to avoid neonatal pneumothorax.

A shunt may also be used drain a dominant cyst in a fetus with *macrocystic CCAM* (Fig. 15-33, p. 288). Only rarely are such cysts large enough to confer risk for hydrops or pulmonary hypoplasia. Shunt placement may improve the survival rate to 90 percent in those without hydrops and to at least 75 percent if hydrops has developed (Litwinska, 2017).

Urinary Shunts

Vesicoamnionic shunts are offered in selected cases of fetal bladder-outlet obstruction in which the amnionic fluid volume is severely diminished. Lower urinary tract obstruction

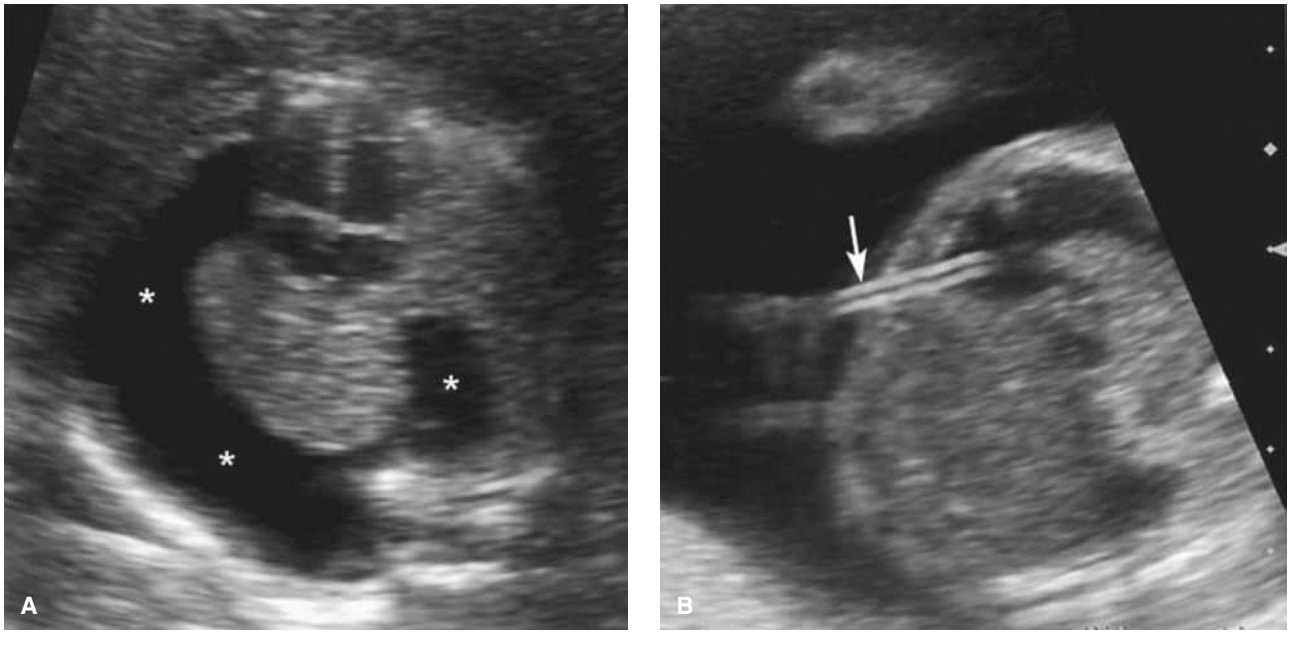

FIGURE 19-7 Thoracoamnionic shunt placement. **A.** A large, right-sided fetal pleural effusion (*asterisks*) and ascites were identified at 18 weeks' gestation. The effusion was drained but rapidly reaccumulated. The xanthochromic fluid contained 95-percent lymphocytes, consistent with chylothorax. **B.** A double-pigtail shunt (*arrow*) was inserted under ultrasound guidance. Following shunt placement, the effusion and ascites resolved.

TABLE 19-4. Fetal Urinary Analyte Values with Bladder Outlet Obstruction

Analyte	Good Prognosis	Poor Prognosis
Sodium	<90 mmol/L	>100 mmol/L
Chloride	<80 mmol/L	>90 mmol/L
Calcium	<7 mg/dL	>8 mg/dL
Osmolality	<180 mmol/L	>200 mmol/L
β_2-Microglobulin	<6 mg/L	>10 mg/L
Total protein	<20 mg/dL	>40 mg/dL

Good or poor prognosis is based on values from serial vesicocentesis performed between 18 and 22 weeks' gestation, using the last specimen obtained.
Data from Mann, 2010.

(LUTO) occurs more often in male fetuses. It is most commonly caused by posterior urethral valves but may be due to anterior urethral valves, urethral atresia or stenosis, or prune belly syndrome, which is also called Eagle-Barrett syndrome. Cases in females may be associated with complex cloacal abnormalities or the megacystis-microcolon syndrome. Ultrasound findings include dilation of the bladder and proximal urethra, termed the "keyhole" sign, along with bladder wall thickening (Fig. 15-61, p. 301). Associated oligohydramnios before midpregnancy leads to pulmonary hypoplasia. Unfortunately, postnatal renal function may be poor even when amnionic fluid volume is normal.

Evaluation includes a careful search for associated anomalies, which may occur in 40 percent of cases, and for aneuploidy, which has been reported in 5 to 8 percent (Hayden, 1988; Hobbins, 1984; Mann, 2010). Potential candidates for therapy are fetuses without other severe anomalies or genetic syndromes. Therapy is generally offered only if the fetus is male because the underlying anomaly tends to be even more severe in females. Serial bladder drainage—vesicocentesis—performed under ultrasound guidance at approximately 48-hour intervals is used to evaluate fetal urine electrolyte and protein content. Fetal urine is normally hypotonic due to tubular resorption of sodium and chloride, whereas isotonic urine in the setting of obstruction suggests renal tubular damage. Serial assessment has been used to guide candidate selection for therapy (Table 19-4). Chromosomal microarray analysis also may be performed on fetal urine.

Vesicoamnionic shunt placement allows urine to drain from the bladder into the amnionic cavity (Fig. 19-8). While this may prevent pulmonary hypoplasia, it does not reliably preserve renal function, particularly if cortical cysts are visible sonographically (Ruano, 2017). Warmed lactated Ringer solution is first infused into the amniotic cavity. Amnioinfusion improves ultrasound visualization, thereby facilitating evaluation of fetal anatomy and shunt placement. A small trocar and cannula are then inserted into the fetal bladder. A double-pigtail catheter is used, and the shunt is placed as caudal as possible within the bladder to avoid dislodgement after bladder decompression.

Complications include displacement of the shunt out of the fetal bladder in up to 40 percent of cases, urinary ascites in approximately 20 percent, and even development of bowel herniation through the abdominal wall defect—gastroschisis—in up to 10 percent (Freedman, 2000; Mann, 2010). Preterm delivery is common, and reported neonatal survival rates range from 50 to 90 percent (Biard, 2005; Walsh, 2011). A third of

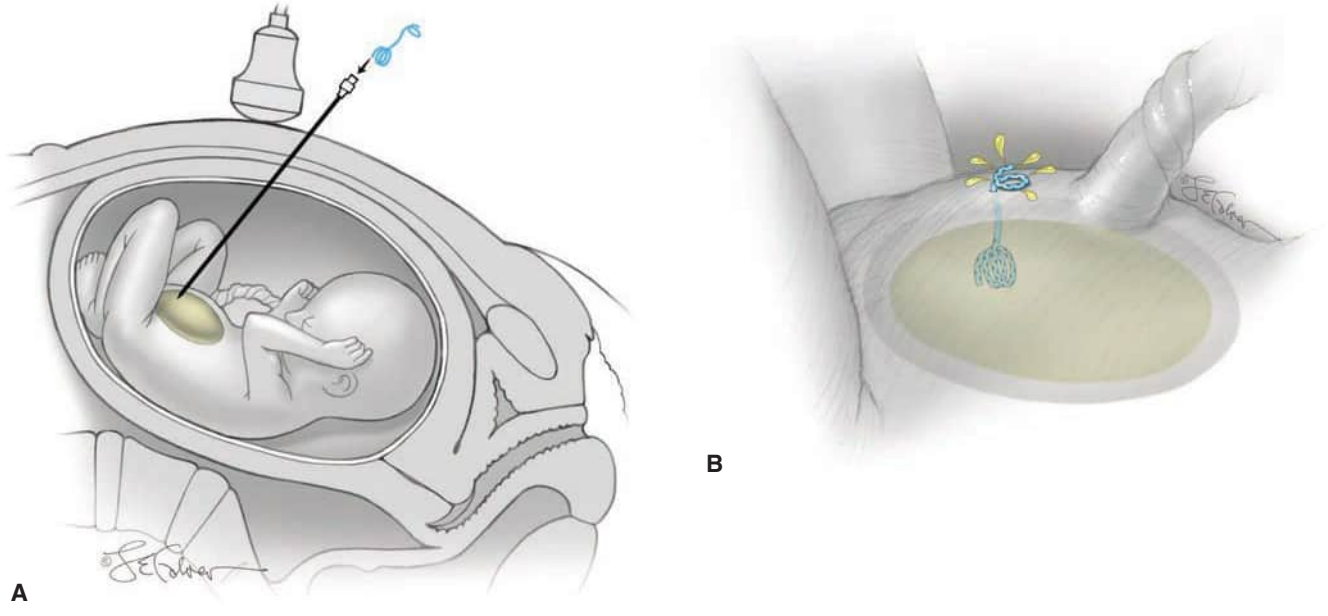

FIGURE 19-8 Vesicoamnionic shunt placement. **A.** After amnioinfusion is performed, a trocar is inserted into the distended fetal bladder under sonographic guidance. The pigtail catheter is threaded into the trocar. **B.** The double-pigtail shunt has been deployed down the trocar, and the trocar has been removed. The distal end of the shunt is coiled within the fetal bladder, and the proximal end is draining into the amnionic cavity. (Reproduced with permission from Shamshirsaz AA, Ramin, SM, Belfort MA: Fetal therapy. In Yeomans ER, Hoffman BL, Gilstrap LC III, et al: Cunningham and Gilstrap's Operative Obstetrics, 3rd ed. New York, NY: McGraw Hill; 2017.)

surviving children have required dialysis or renal transplantation, and almost half have respiratory problems (Biard, 2005). In a randomized trial comparing vesicoamnionic shunt with conservative management in 31 cases, those receiving shunts had higher survival rates. However, only two children had normal renal function at age 2 years (Morris, 2013). Similarly, a metaanalysis of LUTO studies performed between 1990 and 2015 found that vesicoamnionic shunt conferred perinatal survival benefit but no improvement in renal function or survival at age 2 years (Nassr, 2017).

Radiofrequency Ablation

With this procedure, high-frequency alternating current is used to coagulate and desiccate tissue. Radiofrequency ablation (RFA) is the favored modality for treatment of *twin reversed arterial perfusion (TRAP) sequence*, also known as *acardiac twin* (Chap. 48, p. 850). Without treatment, the mortality rate for the normal or pump twin in severe TRAP sequence exceeds 50 percent. The procedure is also used for selective termination with other monochorionic twin complications.

Under ultrasound guidance, a 17- to 19-gauge RFA needle is directed into the base of the umbilical cord within the abdomen of the acardiac twin, and a 2-cm area of coagulation is achieved. Color Doppler is used to verify absent flow into the acardius. The procedure is generally performed at 20 weeks' gestation. The neonatal survival rate of the normal or pump twin approximates 85 percent (Cabassa, 2013; Lee, 2013; Wagata, 2016). Risks are higher for monoamnionic twin pregnancies, in whom the survival rate is only 67 percent (Sugibayashi, 2016). The most common complications are preterm prelabor ruptured membranes and preterm birth.

RFA has generally been offered for TRAP sequence when the volume of the acardiac twin is large. In a series from the North American Fetal Therapy Network, the median size of the acardius relative to the pump twin was 90 percent (Lee, 2013). Considering procedure-related risks, expectant management with close fetal surveillance is often considered if the estimated weight of the acardius is below 50 percent of the estimated weight of the pump twin (Jelin, 2010).

Intracardiac Catheter Procedures

Selected fetal cardiac lesions may worsen during gestation, further complicating and even limiting options for postnatal repair. Severe narrowing of a cardiac outflow tract may result in progressive myocardial damage in utero, and a goal of fetal intervention is to permit muscle growth and preserve ventricular function. These innovative procedures include *aortic valvuloplasty* for critical aortic stenosis; *atrial septoplasty* for hypoplastic left heart syndrome with intact interatrial septum; and *pulmonary valvuloplasty* for pulmonary atresia with intact interventricular septum.

Fetal aortic valvuloplasty is the most commonly performed cardiac procedure, accounting for 75 percent of cases reported by the International Fetal Cardiac Intervention Registry (Moon-Grady, 2015). It is offered for selected cases of critical aortic stenosis in which the left ventricle is either normal sized or dilated. The goal is to prevent progression to hypoplastic left heart and to permit postnatal biventricular repair. Under sonographic guidance, an 18-gauge cannula is inserted through uterus and fetal chest wall and into the left ventricle. Although the procedure is ideally performed percutaneously—through the maternal abdominal wall—laparotomy may be needed if the fetal position is unfavorable. The cannula tip is positioned in front of the stenotic aortic valve, and a 2.5- to 4.5-mm balloon catheter is guided into the aortic annulus and then inflated. Fetal bradycardia requiring treatment may complicate a third of cases, and hemopericardium requiring drainage affects approximately 20 percent (Patel, 2020).

In a review of 108 fetuses treated with aortic valvuloplasty from 15 international centers, 75 percent survived until delivery, and biventricular repair was achieved in 32 percent (Patel, 2020). Friedman and coworkers (2018) from Boston Children's Hospital have reported improved outcomes with the procedure in recent years. Of 52 aortic valvuloplasty procedures performed between 2009 and 2015, nearly 90 percent resulted in a live birth, and more than 50 percent achieved biventricular repair. Guseh and colleagues (2020) emphasize that most children with biventricular function still require postnatal cardiac procedures. The risk for neurodevelopmental impairment in childhood appears similar to cases treated with postnatal repair (Laraja, 2017; Moon-Grady, 2015).

The subset of fetuses with hypoplastic left heart syndrome who also have an intact or restrictive interatrial septum have postnatal mortality rates of nearly 80 percent (Glantz, 2007; Jantzen, 2017). To help improve survival, fetal atrial septoplasty using a percutaneous balloon catheter has been offered. Atrial septal stent placement is often attempted at the time of septoplasty to ensure patency. Of 47 such procedures reported by the International Fetal Cardiac Intervention Registry, 35 percent of infants survived to hospital discharge (Jantzen, 2017). However, the 1-year survival rate was higher in those that had successful fetal cardiac intervention compared with those that had not undergone intervention.

Fetal pulmonary valvuloplasty has been offered in cases of pulmonary atresia with intact interventricular septum to prevent development of hypoplastic right heart syndrome and subsequent single ventricle palliation. The International Fetal Cardiac Intervention Registry reported that of 58 cases of attempted pulmonary valvuloplasty, the procedure was technically successful in 70 percent (Hogan, 2020). Those with successful in-utero procedures were twice as likely to achieve biventricular repair. However, when procedure-related losses were considered, survival to hospital discharge was similar to those who had not received fetal intervention, approximating 75 percent. Long-term benefits of the procedure have yet to be demonstrated.

■ Ex-Utero Intrapartum Treatment

This procedure allows the fetus to remain perfused by the placenta after being partially delivered, so that lifesaving treatment can be performed before completing the delivery. The technique was first developed to obtain an airway with fetal tumors involving the oropharynx and neck and is still used for this indication (Catalano, 1992; Kelly, 1990; Langer, 1992; Shamshirsaz, 2021). An ex-utero intrapartum treatment (EXIT)

TABLE 19-5. Components of the Ex-Utero Intrapartum Treatment (EXIT) Procedure

Comprehensive preoperative evaluation: specialized fetal sonography, fetal echocardiography, magnetic resonance imaging, fetal karyotype if possible
Uterine relaxation with deep general anesthesia and tocolysis
Intraoperative sonography to confirm placental margin and fetal position and to visualize vessels at planned hysterotomy site
Placement of stay-sutures followed by use of uterine stapling device to decrease hysterotomy-site bleeding
Maintenance of uterine volume during the procedure via continuous amnioinfusion of warmed physiological solution to help prevent placental separation
Delivery of the fetal head, neck, and upper torso to permit access as needed
Fetal injection of intramuscular vecuronium, fentanyl, and atropine
Fetal peripheral intravenous access, pulse oximeter, and cardiac ultrasound
Following procedure, umbilical lines placed prior to cord clamping
Uterotonic agents administered as needed

procedure is performed by a multidisciplinary team, which may include an obstetrician, maternal-fetal medicine specialist, pediatric surgeon(s), pediatric otolaryngologist, pediatric cardiologist, anesthesiologists for the mother and fetus, neonatologists, and specially trained nursing personnel. Components of the procedure are shown in Table 19-5 (Moldenhauer, 2013).

Selected indications are listed in Table 19-2. EXIT is the preferred procedure for intrapartum management of large venolymphatic malformations of the neck such as the one shown in Figure 19-9. Criteria for EXIT with a cervical venolymphatic malformation include compression, deviation, or obstruction of the airway by the mass, and also involvement of the floor of the mouth (Laje, 2015). However, a review of 112 pregnancies with fetal cervical venolymphatic malformations found that only about 10 percent met these criteria. Other indications for EXIT include severe *micrognathia* and *congenital high airway obstruction sequence (CHAOS)*, which are discussed in Chapter 15 (Figs. 15-27 and 15-35, p. 285). Criteria for an EXIT procedure for micrognathia include a fetal jaw measurement below the 5th percentile along with indirect evidence of obstruction, such as hydramnios, an absent stomach bubble, or glossoptosis (Morris, 2009b). Case selection for EXIT procedures is generally based on fetal magnetic resonance imaging findings.

In some cases, an EXIT procedure has been used as a bridge to other procedures. For example, resection of large thoracic masses may be accomplished by fetal thoracotomy performed with intact placental circulation. In a series of 16 fetuses with CCAM volume ratios >1.6 or hydrops, all of whom had mediastinal compression, Cass and colleagues (2013) reported that nine infants undergoing *EXIT-to-resection* survived. In contrast, there were no survivors with urgent postnatal surgery alone. Similarly, Moldenhauer (2013) reported that 20 of 22 newborns treated with EXIT-to-resection for lung masses survived. The EXIT procedure has also been used as a bridge to extracorporeal membrane oxygenation—EXIT-to-ECMO—in pregnancies with severe congenital diaphragmatic hernia. However,

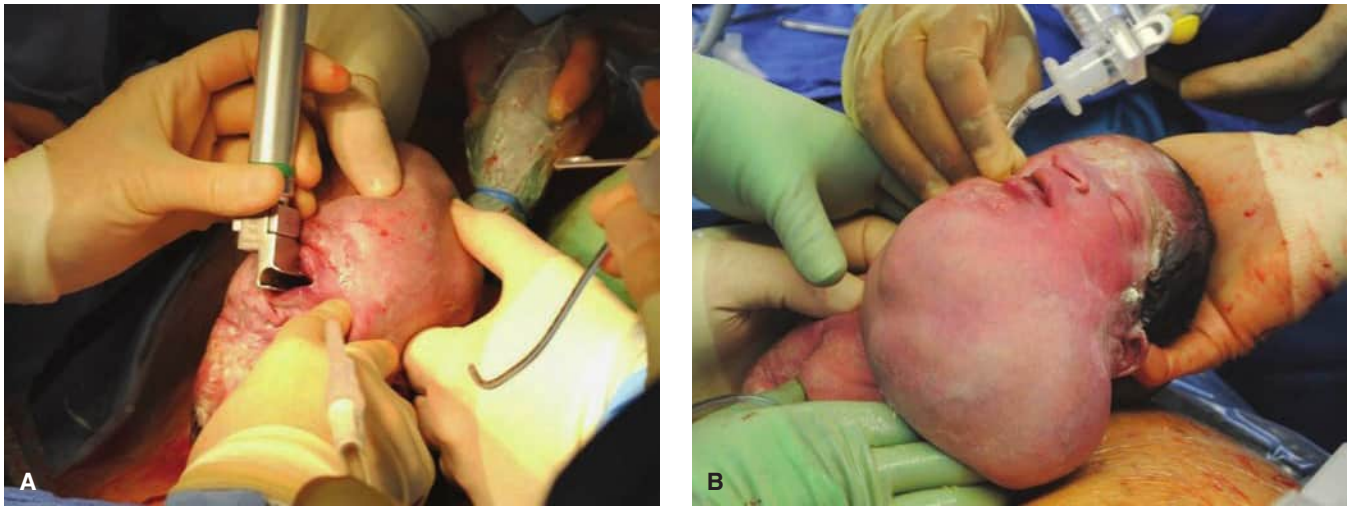

FIGURE 19-9 Ex-utero intrapartum treatment (EXIT) procedure for a venolymphatic malformation. **A.** Upon delivery of the head, placental circulation was maintained, and an airway was established over the course of 20 minutes by a team of pediatric subspecialists that included a surgeon, anesthesiologist, and otolaryngologist. **B.** Following a controlled intubation, the fetus was ready for delivery and transfer to the neonatal intensive care unit team. (Reproduced with permission from Drs. Stacey Thomas and Patricia Santiago-Muñoz.)

it has not been found to clearly confer survival benefit in such cases (Morris, 2009a; Shieh, 2017; Stoffan, 2012).

Counseling prior to an EXIT procedure includes procedure-related risks such as hemorrhage from placental abruption or uterine atony, need for cesarean delivery in future pregnancies, higher risk for subsequent uterine rupture or dehiscence, possible need for hysterectomy, and fetal death or permanent neonatal disability. Compared with cesarean delivery, the EXIT procedure is associated with greater blood loss, a higher incidence of wound complications, and a longer operating time (Noah, 2002; Shamshirsaz, 2019).

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CHAPTER 20

Antepartum Fetal Assessment

Techniques employed to evaluate fetal health focus on fetal biophysical findings that include heart rate, movement, breathing, and amnionic fluid production. Antepartum fetal surveillance aims to prevent fetal death in pregnancies with complex maternal and fetal conditions yet avoid unnecessary interventions (American College of Obstetricians and Gynecologists, 2021a).

Most fetuses will be healthy, and a normal antepartum test result is highly reassuring. Fetal death within 1 week of a normal test result is rare. Indeed, negative predictive values—true negative test results for fetal jeopardy—for most of the tests described are 99.8 percent or higher. In contrast, estimates of positive predictive values—true positive test results for fetal jeopardy—are low and range between 10 and 40 percent. The benefit of fetal surveillance is primarily based on circumstantial evidence. No definitive randomized clinical trials have been conducted for obvious ethical reasons (American College of Obstetricians and Gynecologists, 2021a).

FETAL MOVEMENTS

Fetal Behavioral States

Fetal activity commences as early as 7 weeks' gestation (Sajapala, 2017; Vindla, 1995). Between 20 and 30 weeks' gestation, general body movements become organized, and the fetus starts to show rest-activity cycles (Sorokin, 1982). These cycles reflect central nervous system development and maturation. By approximately 36 weeks' gestation, rest-activity cycles give way to behavioral states in most normal fetuses (Peirano, 2003). Four fetal behavioral states are described by Nijhuis and coworkers (1982):

- State 1F is a quiescent state—quiet sleep—with a narrow oscillatory bandwidth of the fetal heart rate.
- State 2F includes frequent gross body movements, continuous eye movements, and wider oscillation of the fetal heart rate. This state is analogous to rapid eye movement (REM) or active sleep in the neonate.
- State 3F includes continuous eye movements in the absence of body movements and no heart rate accelerations. This state is rare, and its existence is disputed (Pillai, 1990a).
- State 4F is one of vigorous body movement with continuous eye movements and heart rate accelerations. This state corresponds to the awake state in newborns.

At 28 to 30 weeks' gestation, fetuses transition to spend most of their time in states 1F and 2F, namely, in quiet or active sleep (Fig. 20-1) (Peirano 2003; Suwanrath, 2010). For example, at 38 weeks, 75 percent of time is spent in these two states. These behavioral states have been used to develop an increasingly sophisticated understanding of fetal behavior. In a study of fetal urine production, bladder volumes rose during state 1F quiet sleep and significantly declined during state 2F active sleep due to diminished urine production and infrequent fetal voiding (Oosterhof, 1993). These phenomena were

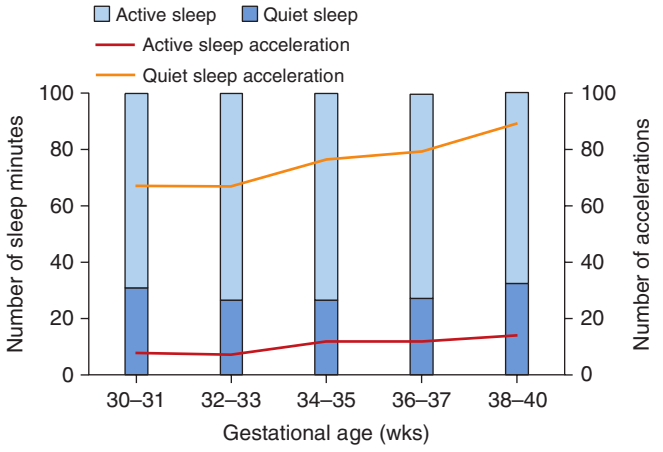

FIGURE 20-1 The change in fetal sleep patterns (*blue columns*) and corresponding number of accelerations (*graph lines*). As the third trimester advances, fetuses spend more time in active sleep and the number of accelerations per hour increases.

thought to represent reduced renal blood flow during active sleep.

Determinants of Fetal Activity

One determinant of fetal activity is the just-described sleep-awake cycles, which are independent of maternal ones. In one study of 16 near-term fetuses, the mean duration of a complete cycle, which included quiet and active states, was 60 minutes. The mean duration was 23 minutes for the quiet states and 40 minutes for the active states (Timor-Tritsch, 1978). Patrick and associates (1982) measured gross fetal body movements with real-time sonography for 24-hour periods in 31 normal near-term pregnancies and found the longest period of inactivity to be 75 minutes.

Amnionic fluid volume is another factor affecting fetal activity. Sherer and colleagues (1996) assessed the number of fetal movements in relation to amnionic fluid volume in 465 preterm pregnancies during biophysical profile testing. Fetal activity declined in those with diminished amnionic volumes, and the authors suggested that a restricted uterine space might physically limit fetal movements.

Patient habits and medications alter fetal movement. For example, maternal smoking decreases fetal activity (Coppens, 2001; Thaler, 1980). Treatment of substance abuse disorders with methadone and buprenorphine also reduces fetal movement (Jansson, 2017; Wouldes, 2004). Betamethasone administration is associated with decreased fetal movement for 24 to 72 hours, and the diurnal pattern is lost (Koenen, 2005; Mulder, 2009). The effect is less clear with dexamethasone. Maternal acetaminophen ingestion does not alter fetal movement, but a glucose load does promote activity (Aladjem, 1979; Nitsche, 2015).

Maternal Perception

Sadovsky and coworkers (1979b) classified fetal movements as weak, strong, and rolling according to maternal perceptions and independent recordings using piezoelectric sensors. As pregnancy advances, the rate of weak movements drops, and more vigorous ones rise in frequency. The latter then subside at term. Presumably, declining amnionic fluid volume and space

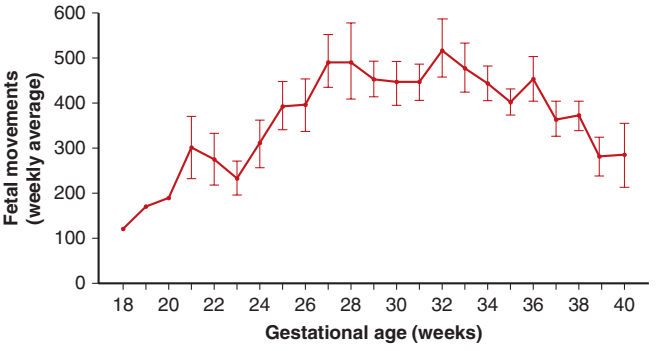

FIGURE 20-2 Graph depicts averages of fetal movements counted during 12-hour periods (mean ± SEM). (Data from Sadovsky, 1979a.)

account for diminished activity at term. Figure 20-2 shows fetal movements during the last half of gestation in 127 pregnancies with normal outcomes. The mean number of weekly movements calculated from 12-hour daily recording periods rose from approximately 200 at 20 weeks' gestation to a maximum of 575 movements at 32 weeks. Weekly fetal movement counts then declined to an average of 282 at 40 weeks. Another study of nearly 300 gravidas found a similar movement pattern across gestational ages (Bradford, 2019b). More than 90 percent of these women reported stronger movements during the evening and nighttime.

Women perceive 16 to 45 percent of fetal movements detected by sonography (Brown, 2016). A higher body mass index does not decrease maternal perception of fetal movement (Bradford, 2019a; Sasson, 2016). It remains unclear if nulliparity or anterior placental location affect maternal impression of fetal activity (Brown, 2016; Sasson, 2016).

Clinical Application

Because women may perceive a decline in fetal movement in the days to weeks preceding stillbirth, maternal perception of fetal movement has been evaluated as a preventive aid (Heazell, 2008; Stacey, 2011). However, the optimal fetal-movement protocol remains undefined (Mangesi, 2015). Some methods rely on quantitative counts, such as 10 movements in 2 hours, whereas others rely on a mother's subjective impression. In one study, more than 68,000 pregnancies were randomly assigned between 28 and 32 weeks' gestation to an objective or subjective assessment group (Grant, 1989). Women in the objective arm were instructed to record the time needed to feel 10 movements each day. This required an average of 2.7 hours daily. Women in the subjective group were informally asked about movements during prenatal visits. Reports of decreased fetal motion were then evaluated with tests of fetal well-being. Antepartum death rates for normal singleton fetuses were similar in the two study groups, and most stillborn fetuses were dead by the time the mothers reported for medical attention. Rather than concluding that maternal perceptions were meaningless, the authors concluded that informal maternal impressions were as valid as formally recorded fetal movement counts.

Women's knowledge of these protocols also vary. In one survey of more than 400 gravidas, 85 percent noted receiving

instruction from their provider regarding normal fetal movement (Pollock, 2019). However, 60 percent described it as a subjective assessment, and 40 percent reported a quantitative method. In another study, more than two thirds of women could not explain fetal movement monitoring techniques (Berndl, 2013).

Although a long-standing pillar of maternal care, fetal movement surveillance may not be as predictive as thought. Nearly 6 to 7 percent of pregnancies are complicated by decreased fetal movement, but stillbirth rates are not increased in these cases (Harrington, 1998; Scala, 2015). In one study of more than 400,000 pregnancies complicated by decreased fetal movement, directed patient and staff education coupled with a prescriptive management plan did not reduce the stillbirth incidence (Norman, 2018). Aside from stillbirth, some data show that decreased fetal movement may help identify growth-restricted fetuses before birth (Saastad, 2011; Scala, 2015). In one of these studies, nearly 1100 pregnancies were assigned to subjective or objective assessment of fetal activity. The rate of 1-minute Apgar scores ≤3 was significantly reduced (0.4 versus 2.3 percent) when counting was used (Saastad, 2011).

Thus, although most pregnancies complicated by decreased fetal movement will result in normal outcomes, maternal perception of reduced fetal activity warrants further evaluation. No consensus guides a provider's response. Care is individualized and influenced by gestational age and pregnancy comorbidities. In low-risk pregnancies, documenting fetal heart tones and adequate amnionic fluid volume may be sufficient. For older fetuses, tests described in the upcoming sections are typically added. Our practice is a nonstress test and sonographic measurement of amnionic fluid volume.

Many women report excessive fetal movement in the third trimester. Its risk, if any, is poorly understood. Stacey and colleagues (2011) reported that a single episode of vigorous fetal activity is associated with a greater risk for fetal death. Similarly, others have described maternal perception of a single episode of excessive of fetal movement in the weeks prior to a stillbirth diagnosis (Heazell, 2017; Whitehead, 2020). More research is needed prior to recommending intervention.

FETAL BREATHING

Small inward and outward flow of tracheal fluid, indicating thoracic movement, was first identified in fetal sheep (Dawes, 1972). These chest wall movements differ from those following birth in that they are discontinuous. Another feature of fetal respiration is *paradoxical chest wall movement* (Fig. 20-3) (Johnson, 1988). In the newborn or adult, the opposite occurs. One interpretation of paradoxical respiratory motion might be coughing to clear amnionic fluid debris. Although the physiological basis for the breathing reflex is not completely understood, such exchange of amnionic fluid appears to be essential for normal lung development (Chap. 7, p. 130). Dawes (1974) identified two types of respiratory movements. The first are *gasps* or *sighs,* which occurred at a frequency of 1 to 4 per minute. The second, *irregular bursts of breathing,* occurred at rates up to 240 cycles per minute. These latter rapid respiratory movements were associated with rapid eye movement. Badalian

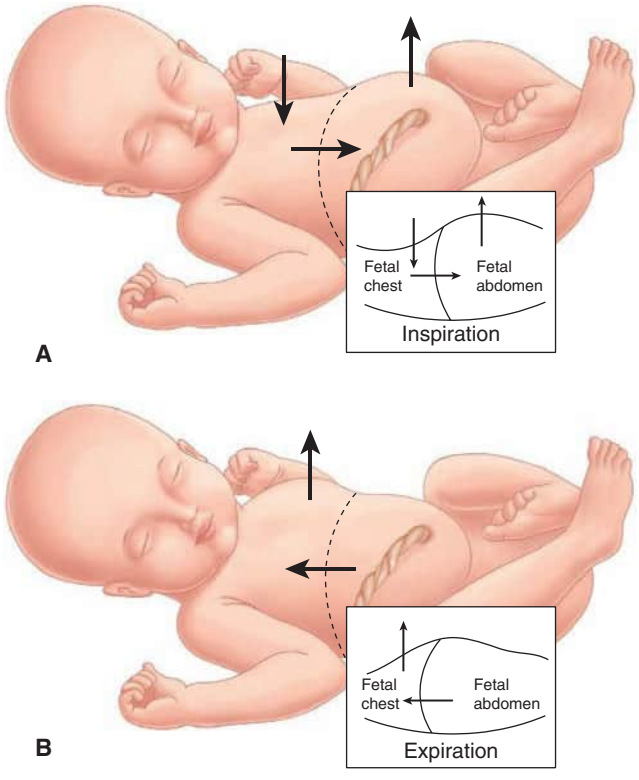

FIGURE 20-3 Paradoxical chest movement with fetal respiration. During inspiration **(A)**, the chest wall paradoxically *collapses* and the abdomen protrudes, whereas during expiration **(B)**, the chest wall *expands*.

and associates (1993) studied the maturation of normal fetal breathing using color flow and spectral Doppler analysis of nasal fluid flow as an index of lung function. They suggested that fetal respiratory rate declined in conjunction with increasing respiratory volume at 33 to 36 weeks' gestation and coincided with lung maturation.

Many investigators have used sonography to determine whether chest wall movements might reflect fetal health. Several variables in addition to hypoxia affect these movements. These include maternal hypoglycemia, sound stimuli, cigarette smoking, amniocentesis, impending preterm labor, gestational age, fetal heart rate, and labor—during which it is normal for fetal respiration to cease.

Because fetal breathing movements are episodic, interpretation of fetal health when respirations are absent may be difficult. Patrick and coworkers (1980) performed continuous 24-hour observation using sonography to characterize fetal breathing patterns during the last 10 weeks of pregnancy. A total of 1224 hours of fetal observation in 51 pregnancies were collected. Figure 20-4 displays the percentages of time spent breathing near term. Substantively diminished breathing during the night suggests a diurnal pattern. In addition, breathing activity is enhanced somewhat following maternal meals. Total absence of breathing was observed in some of these normal fetuses for up to 122 minutes, indicating that fetal evaluation to diagnose absent respiratory motion may require long periods of observation.

The potential for breathing activity to be an important sole marker of fetal health is unfulfilled because of the multiple

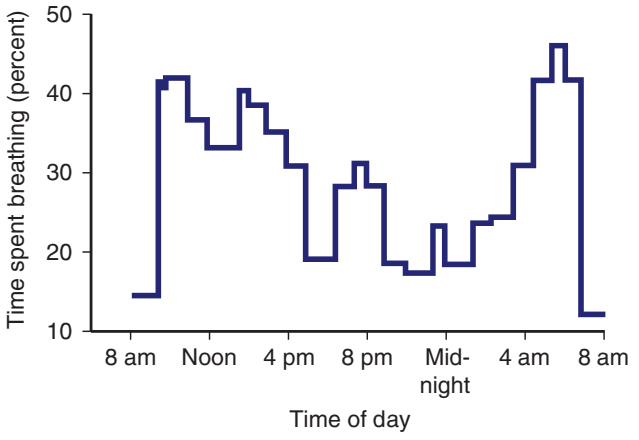

FIGURE 20-4 The percentage of time spent breathing by 11 fetuses at 38 to 39 weeks' gestation. Fetal breathing activity significantly increases after breakfast. Breathing activity diminished during the day and reached its minimum between 20:00 and 24:00 hours. The percentage of time spent breathing rose significantly between 04:00 and 07:00 hours, when mothers were asleep. (Adapted with permission from Patrick J, Campbell K, Carmichael L, et al: Patterns of human fetal breathing during the last 10 weeks of pregnancy, Obstet Gynecol. 1980 Jul;56(1):24–30.)

factors that affect breathing. Most clinical applications couple fetal breathing with other biophysical indices. For example, fetal breathing is one component of the biophysical profile (p. 389).

CONTRACTION STRESS TEST

During a uterine contraction, pressures generated by the myometrium exceed the collapsing pressure of the vessels coursing through it. This ultimately lowers blood flow to the placenta's intervillous space. Brief periods of impaired oxygen exchange result. If uteroplacental pathology is present, oxygen exchange to the fetus is further diminished, and *late fetal heart rate decelerations* appear (Chap. 24, p. 452). These downward-sloping heart-rate waveforms begin with the onset of the uterine contraction waveform or just beyond its acme. Instead, contractions may produce variable decelerations as a result of cord compression. This suggests oligohydramnios, which is often comorbid with placental insufficiency.

Ray and associates (1972) used this concept in 66 complicated pregnancies and developed the *oxytocin challenge test,* which was later called the *contraction stress test (CST).* A positive test result, that is, an abnormal result, is uniform repetitive late fetal heart rate decelerations. In their study, the tests were repeated weekly, and the authors concluded that negative CST results, that is, normal results, forecasted fetal health.

To perform the test, contractions are induced with either intravenous oxytocin or nipple stimulation. If at least three spontaneous contractions of 40 seconds or longer are present in a 10-minute span, no uterine stimulation is necessary (American College of Obstetricians and Gynecologists, 2021a). The fetal heart rate and uterine contractions are recorded simultaneously by external monitors. With oxytocin, a dilute intravenous infusion is used to establish a satisfactory contraction pattern (Freeman, 1975). At Parkland Hospital, 20 units of oxytocin are mixed in 1 liter of Ringer solution and initiated at a rate of 6 mU/min. The rate is increased by 6 mU/min every 40 minutes to achieve the just-discussed contraction pattern.

Nipple stimulation to induce uterine contractions for a CST is usually successful (Huddleston, 1984). One method involves a woman rubbing one nipple through her clothing for 2 minutes or until a contraction begins. This 2-minute nipple stimulation ideally will induce a pattern of three contractions per 10 minutes. If not, after a 5-minute rest interval, she is instructed to retry nipple stimulation to achieve the desired pattern. If this is unsuccessful, dilute oxytocin may be used.

CST results are interpreted according to the criteria shown in Table 20-1. Disadvantageously, the average CST requires 90 minutes to complete. Compared with oxytocin, nipple stimulation shortens testing time and costs less. During a CST, some have reported unpredictable uterine hyperstimulation and fetal distress, whereas others did not find excessive activity to be harmful (Frager, 1987; Schellpfeffer, 1985). Relative contraindications to a CST include those conditions that contraindicate vaginal delivery.

NONSTRESS TEST

The *nonstress test (NST)* also is used to assess fetal well-being and employs the phenomenon of fetal heart rate acceleration in response to fetal movement (Freeman, 1975; Lee, 1975). During an NST, these accelerations are correlated with fetal movements perceived by the mother.

Compared with a CST, an NST is easier to perform, and normal results can be used to further define false-positive CST results. Simplistically, the NST is primarily a test of *fetal condition,* and it differs from the CST, which is considered a test of *uteroplacental function.* Currently, NST is the most widely used primary testing method for assessment of fetal well-being. It has also been incorporated into the biophysical profile, discussed later (p. 389).

TABLE 20-1. Criteria for Interpretation of the Contraction Stress Test

Negative: no late or significant variable decelerations
Positive: late decelerations following 50% or more of contractions (even if the contraction frequency is fewer than three in 10 minutes)
Equivocal-suspicious: intermittent late decelerations or significant variable decelerations
Equivocal-hyperstimulatory: fetal heart rate decelerations that occur in the presence of contractions more frequent than every 2 minutes or lasting longer than 90 seconds
Unsatisfactory: fewer than three contractions in 10 minutes or an uninterpretable tracing

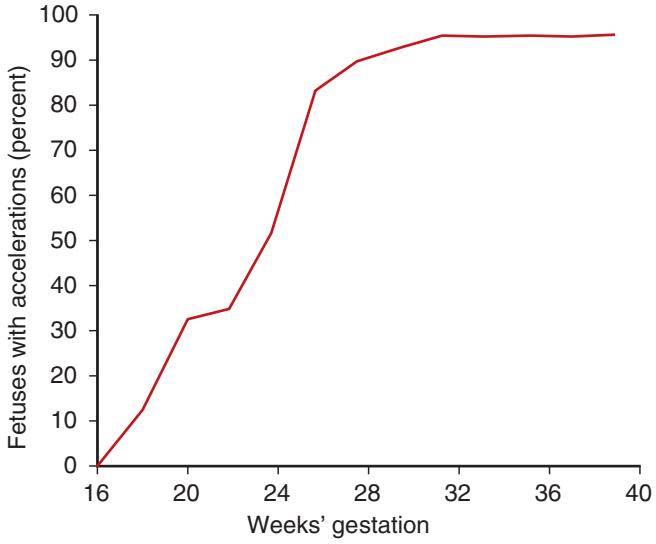

FIGURE 20-5 Percentage of fetuses with at least one acceleration of 15 bpm sustained for 15 seconds concurrent with fetal movement. (Redrawn from Pillai M, James D: The development of fetal heart rate patterns during normal pregnancy, Obstet Gynecol. 1990 Nov;76(5 Pt 1):812–816.)

Fetal Heart Rate Acceleration

Autonomic influences are mediated by sympathetic or parasympathetic impulses from brainstem centers to normally raise or slow the fetal heart rate. The NST is based on the hypothesis that the heart rate of a fetus that is not acidemic as a result of hypoxia or neurological depression will temporarily accelerate in response to fetal movement (American College of Obstetricians and Gynecologists, 2019; Lee, 1975). Fetal movements during testing are identified by maternal perception and self-recorded. As hypoxia develops, fetal heart rate accelerations diminish (Smith, 1988).

Gestational age influences acceleration of the fetal heart rate. Pillai and James (1990b) studied patterns of fetal heart rate acceleration during normal pregnancy. The percentage of body movements accompanied by accelerations and the amplitude of these waveforms both increase with gestational age (Fig. 20-5).

Accordingly, the National Institute of Child Health and Human Development Fetal Monitoring Workshop defined acceleration waveforms based on gestational age (Macones, 2008). In fetuses at or beyond 32 weeks' gestation, the acceleration acme is ≥15 beats per minute (bpm) above the baseline rate, and the acceleration lasts ≥15 seconds but <2 minutes. Before 32 weeks, accelerations are defined as having a rise ≥10 bpm above baseline for ≥10 seconds. In one study of 188 normal fetuses at 25 and 28 weeks' gestation, only 70 percent demonstrated the required ≥15 bpm during heart rate accelerations. Accelerations of 10 bpm occurred in 90 percent (Guinn, 1998). Cousins and associates (2012) compared the Workshop criteria recommended before 32 weeks with the standard 15 bpm/15 second criteria in a randomized trial of 143 women. They found no differences in perinatal outcomes.

Reactive (Normal) Nonstress Tests

A normal NST is termed *reactive* and requires two or more accelerations within 20 minutes of beginning the test (Fig. 20-6) (American College of Obstetricians and Gynecologists, 2021a). Accelerations are accepted irrespective of fetal movement. Before concluding that a test is *nonreactive*, a 40-minute or longer tracing should be performed. This threshold accounts for fetal sleep cycles (Paul, 1995). Miller and coworkers (1996b) reviewed outcomes in fetuses with NST results that were considered nonreactive because only one acceleration was recorded. They concluded that one acceleration was as reliable as two in predicting healthy fetal status. NSTs are more likely to be reactive and have a shorter testing time in the evening compared with the morning (Babazadeh, 2005; Petrikovsky, 1996).

Loud external sounds have been used to startle the fetus and thereby provoke heart rate acceleration. A commercially available acoustic stimulator is positioned on the maternal abdomen, and a stimulus of 1 to 2 seconds is applied (Eller, 1995). This may be repeated up to three times for up to 3 seconds (American College of Obstetricians and Gynecologists, 2021a). In a randomized trial of 113 women undergoing NST, vibroacoustic stimulation lowered the average testing time and incidence of nonreactive test results (Perez-Delboy, 2002; Turitz, 2012). One case report described a fetal tachyarrhythmia that was provoked with vibroacoustic stimulation in a fetus with known premature atrial contractions (Laventhal, 2003).

Although a normal number and amplitude of accelerations seems to reflect fetal well-being, their absence does not

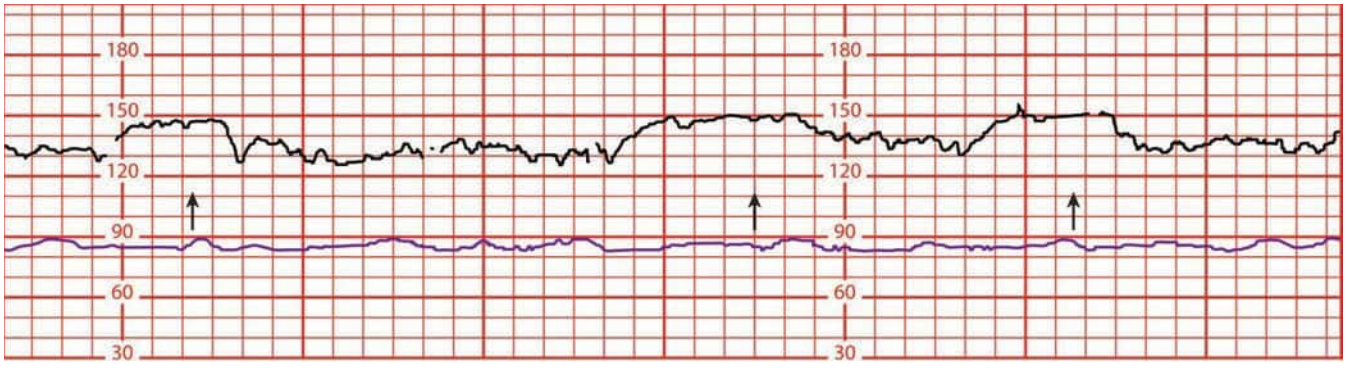

FIGURE 20-6 Reactive nonstress test. Notice there are at least two fetal heart rate accelerations (*arrows*) of more than 15 beats/min for longer than 15 seconds. The black line reflects fetal heart rate, whereas the purple line reflects the mother's.

invariably predict fetal compromise. Indeed, some investigators have reported false-positive rates ≥90 percent (Devoe, 1986). Because healthy fetuses may not move for up to 75 minutes, some have considered that a longer NST duration might increase the positive predictive value of the NST (Brown, 1981). In this scheme, either the test became reactive during a period up to 80 minutes or the test remained nonreactive for 120 minutes, which indicated a very ill fetus. Therefore, prolonged fetal heart rate monitoring is undertaken if an NST remains nonreactive after 40 minutes.

Nonreactive (Abnormal) Nonstress Tests

Based on the foregoing, a nonreactive NST is not always ominous and can be seen with a sleeping fetus. An NST result can also revert to normal as the fetal condition changes. An example is shown in Figure 20-7. Instead, a reactive NST result can become abnormal if the fetal condition deteriorates.

Some abnormal patterns reliably forecast severe fetal jeopardy (Fig. 20-8). For example, Devoe and colleagues (1985) concluded that >90 percent of NST results that were nonreactive for 90 minutes or more were associated with significant perinatal pathology. Specifically, Visser and associates (1980) described a *terminal cardiotocogram,* which included:

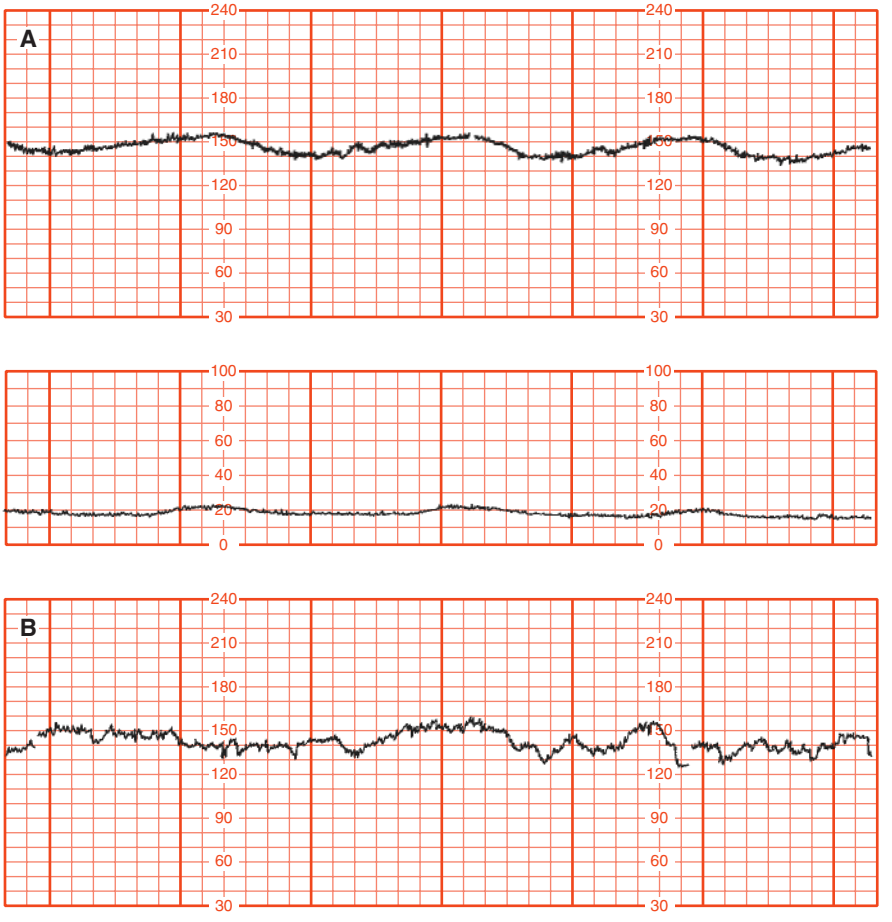

FIGURE 20-7 Two antepartum fetal heart rate (FHR) tracings in a 28-week pregnant woman with diabetic ketoacidosis. **A.** FHR tracing (*upper panel*) and accompanying contraction tracing (*second panel*). Tracing, obtained during maternal and fetal acidemia, shows absence of accelerations, diminished variability, and late decelerations with weak spontaneous contractions. **B.** Fetal heart rate tracing shows return of normal accelerations and variability of the fetal heart rate following correction of maternal acidemia.

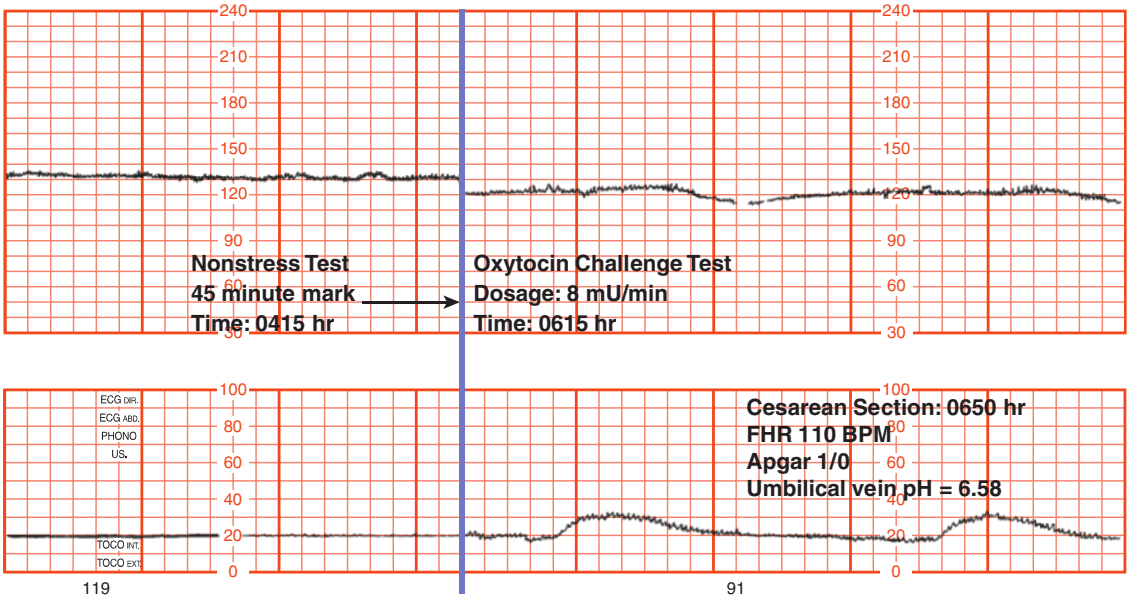

FIGURE 20-8 Nonreactive nonstress test (*left side of tracing*) followed by contraction stress test showing mild, late decelerations (*right side of tracing*). Cesarean delivery was performed, and the severely acidemic fetus could not be resuscitated.

(1) baseline variability <5 bpm, (2) absent accelerations, and (3) late decelerations with spontaneous uterine contractions. These mirrored experiences from Parkland Hospital in which absence of accelerations during an 80-minute recording period in 27 fetuses was associated consistently with evidence of uteroplacental pathology (Leveno, 1983). The latter included fetal-growth restriction in 75 percent, oligohydramnios in 80 percent, fetal acidemia in 40 percent, meconium in 30 percent, and placental infarction in 93 percent.

Interval Between Testing

Set originally and arbitrarily at 7 days, the interval between NSTs varies based on indication (Paul, 1995). According to the American College of Obstetricians and Gynecologists (2021a), weekly testing is undertaken in the setting of stable maternal medical conditions such as pregestational diabetes, chronic hypertension, or lupus. For high-risk conditions such as preeclampsia remote from term, some perform NSTs daily. Fetal conditions require individualized periodic testing based on the fetal complication. Fetal-growth restriction is a common indication for which testing intervals vary (Fig. 47-6, p. 829).

Decelerations During Nonstress Testing

Fetal movements commonly produce heart rate decelerations. In one study of 16 near-term fetuses, one half to two thirds of NST tracings had decelerations, depending on the vigor of the fetal motion (Timor-Tritsch, 1978). This high incidence of decelerations inevitably makes interpretation of their significance problematic. Indeed, Meis and coworkers (1986) reported that variable fetal heart rate decelerations during NSTs were not a sign of fetal compromise. The American College of Obstetricians and Gynecologists (2021a) has concluded that variable decelerations, if nonrepetitive and brief—less than 30 seconds—do not indicate fetal compromise or the need for obstetrical intervention. Repetitive variable decelerations—at least three in 20 minutes—have been associated with a greater risk of cesarean delivery for fetal distress. Decelerations lasting ≥1 minute are reported to have an even worse fetal prognosis (Bourgeois, 1984; Druzin, 1981; Pazos, 1982).

Hoskins and associates (1991) attempted to refine interpretation of tests that showed variable decelerations by adding sonographic estimation of amnionic fluid volume. The incidence of cesarean delivery for intrapartum fetal distress progressively rose concurrently with the decline of amnionic fluid volume. Variable decelerations during an NST plus oligohydramnios resulted in a 75-percent cesarean delivery rate. Fetal distress in labor, however, also frequently developed in those pregnancies with variable decelerations but with normal amounts of amnionic fluid. Others report similar results (Grubb, 1992).

False-reactive Nonstress Tests

In one review of fetal death within 7 days of a reactive NST, the most frequent indication for testing was postterm pregnancy (Smith, 1987). The mean interval between testing and death was 4 days, with a range of 1 to 7 days. The single most common autopsy finding was meconium aspiration, often associated with some type of umbilical cord abnormality. The authors concluded that acute asphyxia had provoked fetal gasping. They considered an NST inadequate to preclude an acute asphyxial event, but viewed amnionic fluid volume assessment as valuable. Other ascribed frequent causes of fetal death despite a false-reactive NST included intrauterine infection, abnormal cord position, fetal malformations, and placental abruption.

BIOPHYSICAL PROFILE

Assessing five specific fetal biophysical variables more accurately predicts fetal health (Manning, 1980). These include heart rate acceleration, breathing, movement, tone, and amnionic fluid volume (Table 20-2). In the commonly used *biophysical profile (BPP)*, each normal variable is assigned a score of 2, and abnormal variables are given a score of 0. Thus, the highest score possible for a normal fetus is 10. Because fetal breathing and movement are episodic, 30 minutes are allotted to perform a BPP before a score of 0 is assigned to any component. Figure 20-9 shows color Doppler evidence of amnionic fluid flowing through the nares with fetal breathing. In one study, BPP scores were higher if a test was performed in late evening compared with the morning (Ozkaya, 2012). Narcotics and sedatives can significantly lower the score (Kopecky, 2000).

Using the BPP interpretation and management strategy shown in Table 20-3, Manning and colleagues (1987) evaluated more than 19,000 pregnancies. Greater than 97 percent of the tested pregnancies had normal results. They reported a

TABLE 20-2. Components and Scores for the Biophysical Profile

Component	Score 2	Score 0
Nonstress test[a]	≥2 accelerations within 20–40 min	0 or 1 acceleration within 20–40 min
Fetal breathing	≥1 episode of rhythmic breathing lasting ≥30 sec	<30 sec of breathing
Fetal movement	≥3 discrete body or limb movements	<3 discrete movements
Fetal tone	≥1 episode of extremity extension and subsequent return to flexion	0 extension/flexion events
Amnionic fluid volume[b]	A pocket of amnionic fluid that measures at least 2 cm in two planes perpendicular to each other (2 × 2 cm pocket)	Deepest single vertical pocket ≤2 cm

[a]May be omitted if all four sonographic components are normal.
[b]Further evaluation warranted, regardless of biophysical composite score, if deepest vertical amnionic fluid pocket ≤2 cm.

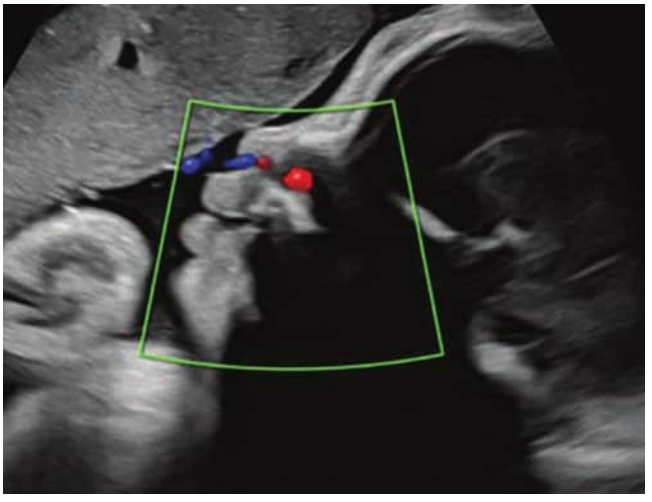

FIGURE 20-9 A sagittal color Doppler image displays the movement of amnionic fluid through the nares during fetal breathing.

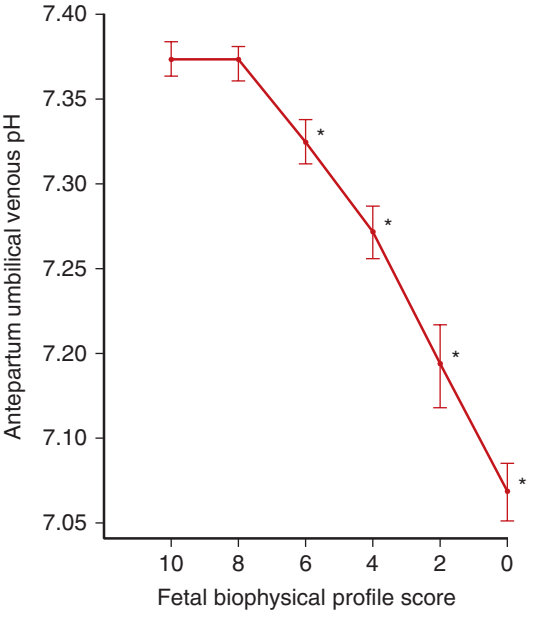

FIGURE 20-10 Mean umbilical vein pH (±2 SD) obtained by cordocentesis in relation to fetal biophysical profile score category. (Data from Manning, 1993.)

false-normal test rate—defined by an antepartum death of a structurally normal fetus—that approximated 1 per 1000. The most common identifiable causes of fetal death after a normal BPP score include fetomaternal hemorrhage, umbilical cord accident, and placental abruption (Dayal, 1999).

Subsequently, Manning and associates (1993) published a remarkable description of 493 fetuses in which BPP scores were correlated with umbilical venous blood pH values. This blood was being obtained via antepartum cordocentesis for other specific fetal indications. Namely, karyotyping of fetal-growth restricted fetuses constituted 20 percent, and the remainder had alloimmune hemolytic anemia requiring hemoglobin measurement. As shown in Figure 20-10, a BPP score of 0 was almost invariably associated with significant fetal acidemia, whereas a normal score of 8 or 10 was associated with normal pH. An equivocal test result—a score of 6—was a poor predictor of an abnormal outcome. A drop in the BPP score from 2 or 4 down to 0 more accurately predicted an abnormal fetal outcome. Overall, BPP scores provided poor sensitivity to predict cord blood pH. Similar studies have concluded the same (Salvesan, 1993; Weiner, 1996). Kaur and colleagues (2008) performed daily BPPs to ascertain the optimal delivery time in 48 growth-restricted preterm fetuses that weighed <1000 g. Despite scores of 8 in 27 fetuses and 6 in 13 others, 6 died and 21 were acidemic.

Modified Biophysical Profile

BPP performance is labor intensive and requires a trained sonographer. In response, Clark and coworkers (1989) created

TABLE 20-3. Interpretation of Biophysical Profile Score

Biophysical Profile Score	Interpretation	Recommended Management
10	Normal, nonasphyxiated fetus	No fetal indication for intervention; repeat test weekly
8/10 (Normal AFV) 8/8 (NST not done)	Normal, nonasphyxiated fetus	No fetal indication for intervention; repeat test weekly
8/10 (Decreased AFV)	Chronic fetal asphyxia suspected	If ≥36 weeks, deliver If <36 weeks, monitor per institution's protocol
6 (Normal AFV)	Equivocal	If ≥37 weeks, deliver If <37 weeks and normal fluid, repeat test in 24 hours If repeat test >6, monitor per institution's protocol
6 (Decreased AFV)	Possible fetal asphyxia	If 36–37 weeks, deliver If <36 weeks, monitor per institution's protocol
4	Probable fetal asphyxia	If ≥32 weeks, deliver If <32 weeks, individualize management based on maternal and fetal conditions
0 or 2	Almost certain fetal asphyxia	Deliver

AFV = amnionic fluid volume; NST = nonstress test.
Adapted from American College of Obstetricians and Gynecologists, 2021a; Liston, 2018; Manning, 2018.

an abbreviated BPP, in which an NST was coupled with amnionic fluid volume assessment. In 2628 singleton pregnancies, the NST was performed twice weekly. Described in the next section, amnionic fluid volume was measured by the amnionic fluid index (AFI), and values ≤5 cm were considered abnormal. This abbreviated BPP required approximately 10 minutes to perform. The authors considered it a superb antepartum surveillance method because no fetuses died unexpectedly.

From another study of 17,429 modified BPPs in 2774 women, investigators concluded that such testing was an excellent fetal surveillance tool (Nageotte, 1994). Miller and associates (1996a) reported results of more than 54,000 modified BPPs performed in 15,400 high-risk pregnancies. They described a false-negative rate of 0.8 per 1000 and a false-positive rate of 1.5 percent. The American College of Obstetricians and Gynecologists (2021a) has concluded that the BPP and modified BPP are comparable to other biophysical fetal surveillance approaches in predicting fetal well-being.

AMNIONIC FLUID VOLUME

The importance of amnionic fluid volume estimation is indicated by its inclusion into virtually all schemes of fetal health assessment (Frøen, 2008). Physiologically, diminished uteroplacental perfusion may lead to lower fetal renal blood flow, decreased urine production, and ultimately, oligohydramnios (Chap. 14, p. 260). Amnionic fluid volume is measured either by the AFI or by the single deepest vertical pocket (DVP). In one study of more than 1000 women in which both methods were compared, AFI led to a higher rate of oligohydramnios diagnoses and induction of labor. Despite this, perinatal outcomes were not improved (Kehl, 2016). The American College of Obstetricians and Gynecologists (2021a) concludes that DVP measurement, as opposed to AFI, is associated with fewer unnecessary interventions but comparable perinatal outcomes (Nabhan, 2008; Reddy, 2014). An AFI ≤5 cm and a DVP ≤2 cm is considered abnormal.

DOPPLER VELOCIMETRY

Blood flow velocity measured by Doppler ultrasound reflects downstream impedance (Chap. 14, p. 261). This Doppler velocimetry has been used to interrogate the umbilical artery, middle cerebral artery (MCA), and ductus venosus. With umbilical artery studies, abnormal waveforms correlated with placental villous hypovascularity. Specifically, of the small placental arterial channels, 60 to 70 percent must be obliterated before the umbilical artery Doppler waveform becomes abnormal. Such extensive placental vascular pathology has a major effect on fetal circulation. According to Trudinger (2007), because more than 40 percent of the combined fetal ventricular output is directed to the placenta, obliteration of placental vascular channel increases afterload and leads to fetal hypoxemia. This in turn leads to ventricular dilation and redistribution of MCA blood flow. Ultimately, pressure rises in the ductus venosus due to afterload in the right side of the fetal heart (Baschat, 2004). Clinically, abnormal Doppler waveforms in the ductus venosus are a late finding in the progression of fetal deterioration due to chronic hypoxemia. To predict placental dysfunction, maternal uterine artery Doppler velocimetry also has been assessed, with the goal to balance stillbirth against the risks of preterm delivery (Ghidini, 2007).

Umbilical Artery

The umbilical artery systolic-diastolic (S/D) ratio is considered abnormal if it is above the 95th percentile for gestational age or if diastolic flow is either absent or reversed (Chap. 14, p. 262). Absent or reversed end-diastolic flow signifies greater impedance to umbilical artery blood flow (Fig. 47-7, p. 830). It is reported to result from poorly vascularized placental villi and is seen in extreme cases of fetal-growth restriction (Todros, 1999). The perinatal mortality rate is increased when absent or reversed end-diastolic flow is present (Viero, 2004).

Umbilical artery Doppler velocimetry to evaluate fetal health has been extensively assessed in randomized trials. In one, 1360 women with a high risk for stillbirth underwent either an NST or Doppler velocimetry, and abnormal results prompted labor induction. More patients in the Doppler group required induction, yet the cesarean delivery rate for intrapartum fetal distress was 4.6 percent. This rate was significantly lower than the 8.7-percent cesarean rate for those receiving an NST (Williams, 2003). The authors believed that Doppler assessment, compared with an NST, identified a higher proportion of patients with early placental compromise. Identified early, these fetuses experienced less distress, which yielded a lower cesarean delivery rate. Similarly, Yoon and coworkers (1992) found that the BPP and umbilical artery Doppler measurements are comparable indicators of fetal acidosis. Introduction of Doppler velocimetry as a primary screening test must balance any advantages against its necessary training and associated costs.

In addition, umbilical artery Doppler velocimetry does not effectively predict fetal health in normal pregnancies (Alfirevic, 2015; Page, 2017). Gonzalez and associates (2007) found that abnormal umbilical artery Doppler findings in a cohort of growth-restricted fetuses were the best predictors of perinatal outcomes. The American College of Obstetricians and Gynecologists (2021a) has concluded that umbilical artery Doppler velocimetry has not proved valuable as a screening test, except in cases of fetal-growth restriction (Chap. 47, p. 830).

Ductus Venosus

Doppler ultrasound can also assess the fetal venous circulation, and as discussed earlier, an abnormal ductus venosus Doppler waveform indicates cardiac dysfunction. However, its routine use in surveillance of fetal-growth restriction is not recommended (Society for Maternal-Fetal Medicine, 2020).

Ductus venosus Doppler is also used in the staging of twin-twin transfusion syndrome (Quintero, 1999). Abnormal Doppler indices reflect myocardial dysfunction and predict a poorer outcome (Banek, 2003). Additionally, this Doppler method can help monitor fetuses with congenital heart defects and supraventricular tachycardia (SVT) (Seravalli, 2016). Namely, SVT can induce a reversible cardiomyopathy that may lead to hydrops.

Ductus venosus Doppler patterns may aid prediction and monitor improvement following treatment. Thus, ductus venosus Doppler may have a role in monitoring pregnancies at increased risk for fetal cardiovascular decline (Baschat, 2010).

Middle Cerebral Artery

Doppler velocimetry of the MCA is the primary method of detecting fetal anemia (Chap. 14, p. 263). With fetal anemia, the *peak systolic velocity* is enhanced due to greater cardiac output and decreased blood viscosity. However, to detect fetal compromise, Doppler velocimetry of the MCA is not recommended (Morris, 2012). In one randomized study of 665 women assigned to modified BPP alone or to modified BPP plus MCA and umbilical artery Doppler velocimetry, pregnancy outcomes did not differ (Ott, 1998).

Uterine Artery

Vascular resistance in the uterine circulation normally declines in the first half of pregnancy. This stems from trophoblast invasion and remodeling of maternal uterine vessels (Chap. 5, p. 90). Uterine artery Doppler velocimetry may be most helpful in assessing pregnancies at high risk of uteroplacental insufficiency (Abramowicz, 2008). Persistence or development of high-resistance patterns has been linked to various pregnancy complications (Sciscione, 2009; Velathur, 2014). In a study of 30,519 unselected British women, uterine artery velocimetry was assessed at 22 to 24 weeks' gestation (Smith, 2007). The risk of fetal death before 32 weeks, when associated with abruption, preeclampsia, or fetal-growth restriction, was significantly linked to high-resistance flow. However, technique standards and criteria to define an abnormal test are lacking. Thus, uterine artery Doppler studies are not considered standard practice in either low- or high-risk populations (Society for Maternal-Fetal Medicine, 2020).

ANTENATAL TESTING SUMMARY

Despite a continuous evolution of options, the precision of any given method is limited. Moreover, the wide range of normal biological fetal variation makes interpretation of test results challenging. This prompts many clinicians to use antenatal testing to forecast fetal *wellness* rather than *illness.*

Antenatal testing efficacy was reviewed between 1971 and 1985 at Los Angeles County Hospital (Platt, 1987). Nearly 17,000 women underwent antepartum testing of various types. Fetal surveillance rose from <1 percent of pregnancies in the early 1970s to 15 percent in the mid-1980s. These authors concluded that such testing was clearly beneficial because the fetal death rate was significantly less in the tested high-risk pregnancies compared with the rate in those not tested. The study, however, did not consider other innovations incorporated into practice during those years. Results from Ghana suggest that NSTs may be beneficial in low-resource countries (Lawrence, 2016). Namely, in an observational study of 316 pregnancies complicated by gestational hypertension, women undergoing an NST had a nonsignificant decreased risk for stillbirth compared with those not tested—3.6 versus 9.2 percent, respectively. However, the benefits of antenatal fetal testing have not been sufficiently evaluated in randomized trials.

Another important and unanswered question is whether antepartum fetal surveillance identifies fetal asphyxia early enough to prevent brain damage. Manning and associates (1998) studied the incidence of cerebral palsy in 26,290 high-risk pregnancies managed with serial BPP testing. These outcomes were compared with those of 58,657 low-risk pregnancies in which antepartum testing was not performed. The rate of cerebral palsy was 1.3 per 1000 in tested pregnancies compared with 4.7 per 1000 in untested women. Todd and colleagues (1992) attempted to correlate cognitive development in infants up to age 2 years following abnormal umbilical artery Doppler velocimetry or NST results. Only abnormal NST results were associated with marginally poorer cognitive outcomes. These investigators concluded that by the time fetal compromise is diagnosed with antenatal testing, fetal damage has already been sustained. Low and coworkers (2003) reached a similar conclusion.

Indications for antepartum testing include fetal and maternal conditions that increase the risk for stillbirth (Table 20-4) (American College of Obstetricians and Gynecologists, 2021b). According to the American College of Obstetricians and Gynecologists (2021a), a *normal* antepartum fetal test result is highly reassuring that a stillbirth will not occur within 1 week. This conclusion was reached after an analysis of reports of stillbirth rates associated with the various antepartum fetal heart rate tests (Table 20-5).

The most important consideration in deciding when to begin antepartum testing is the prognosis for neonatal survival. The severity of maternal disease is another. In general, with most high-risk pregnancies, testing begins by 32 to 34 weeks' gestation. Pregnancies with severe complications, such as

TABLE 20-4. Indications for Antepartum Testing

Maternal	Pregnancy-related
Chronic hypertension	Gestational hypertension
Pregestational DM	Preeclampsia
SLE	Insulin-requiring gestational DM
Antiphospholipid syndrome	Oligohydramnios
Hemoglobinopathies	Polyhydramnios
Cyanotic heart disease	Postterm pregnancy
Cardiomyopathy	Prior stillbirth
Cystic fibrosis	Isoimmunization
Restrictive lung disease	Cholestasis
Chronic renal disease	Velamentous cord insertion
Hyperthyroidism	Single umbilical artery
In vitro fertilization	**Fetal**
Substance abuse	Fetal-growth restriction
Chemotherapy (current)	Decreased fetal movement
Prepregnancy BMI ≥35	Multifetal gestation
Maternal age >35	

BMI = body mass index; DM = diabetes mellitus; SLE = systemic lupus erythematosus.

TABLE 20-5. Stillbirth Rates within 1 Week of a Normal Antepartum Fetal Surveillance Test

Antepartum Fetal Test	Stillbirth[a] Rate/1000	Number
Nonstress test	1.9	5861
Contraction stress test	0.3	12,656
Biophysical profile	0.8	44,828
Modified biophysical profile	0.8	54,617

[a]Corrected for lethal anomalies and unpredictable causes of fetal death such as abruption or cord accident.

fetal-growth restriction, might require testing as early as 26 to 28 weeks. The frequency for repeating tests is arbitrarily set at 7 days, but more frequent testing is often done.

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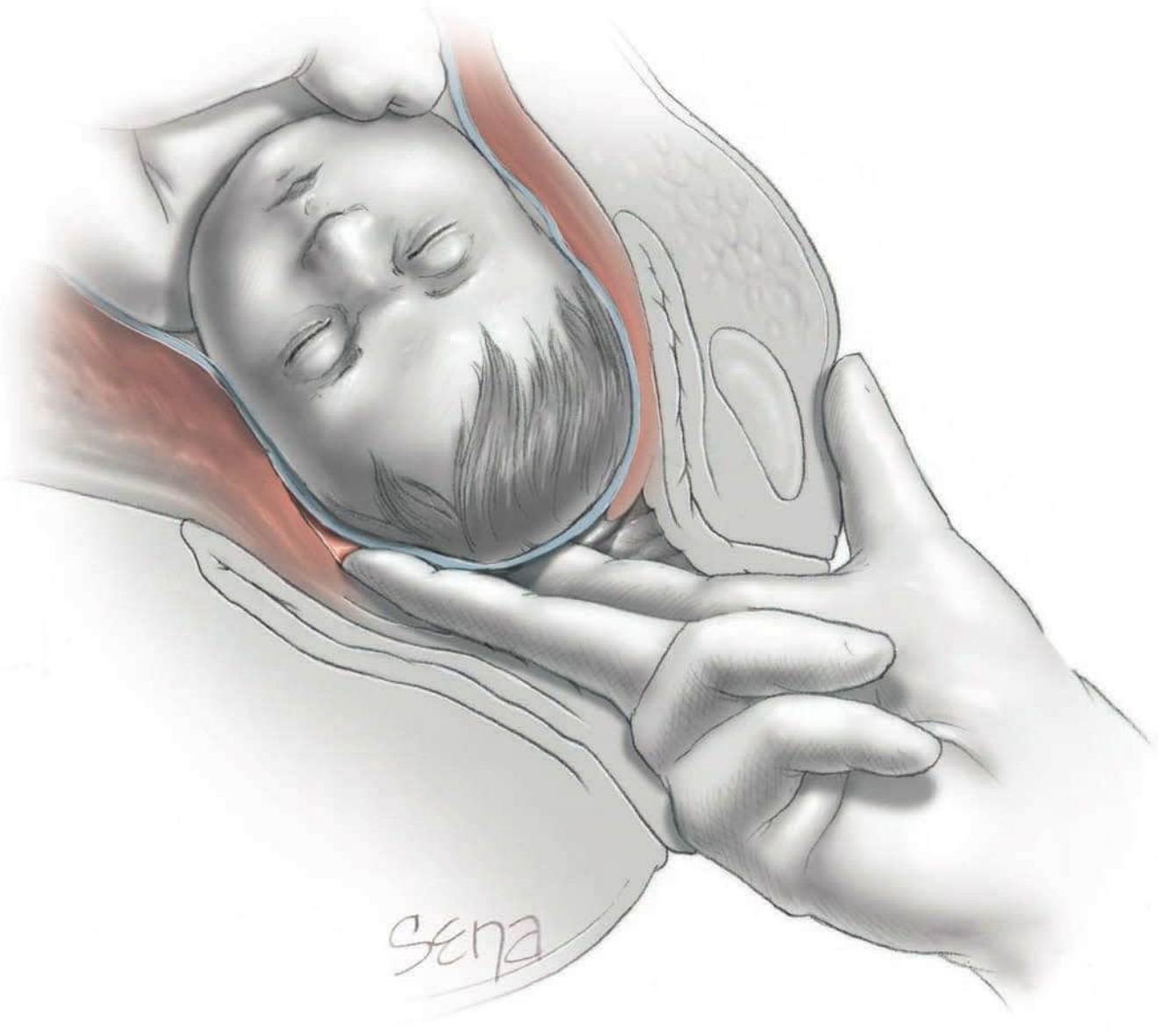
SECTION 7

LABOR



CHAPTER 21

Physiology of Labor

Labor is characterized by forceful and painful uterine contractions that effect cervical dilation and cause the fetus to descend through the birth canal. However, extensive preparations take place in both the uterus and cervix long before this. During the first 36 to 38 weeks of normal gestation, the myometrium is in a preparatory yet unresponsive state. Concurrently, the cervix begins an early stage of remodeling yet maintains structural integrity. Following uterine quiescence, a transitional phase begins during which myometrial unresponsiveness is suspended and the cervix undergoes ripening, effacement, and loss of structural cohesion.

The physiological processes that regulate *parturition* and the onset of labor continue to be defined. Three theories describe labor initiation. Viewed simplistically, the first is the *functional loss of pregnancy maintenance factors.* The second focuses on *synthesis of factors that induce parturition*. The third suggests that the mature fetus is the source of the initial *signal for parturition commencement*. Research supports a model that draws from all three themes. Thus, labor onset represents the culmination of a series of biochemical changes in the uterus and cervix. These result from endocrine and paracrine signals emanating from both mother and fetus. Their relative contributions vary between species, and it is these differences that complicate elucidation of the exact factors that regulate human parturition. When parturition is abnormal, preterm labor, dystocia, or postterm pregnancy may result.

MATERNAL AND FETAL COMPARTMENTS

Uterus and Cervix

The myometrial layer of the uterus is composed of bundles of smooth muscle cells surrounded by connective tissue. In contrast to skeletal or cardiac muscle, the smooth muscle cell is not terminally differentiated and therefore is readily adaptable to environmental changes. Varied stimuli such as mechanical stretch, inflammation, and endocrine and paracrine signals modulate the transition of the smooth muscle cell into phenotypes that provide cell growth, proliferation, secretion, and contractility.

Additionally, several smooth muscle qualities confer advantages for uterine contraction efficiency and fetal delivery. First, the degree of smooth muscle cell shortening with contractions may be one order of magnitude greater than that attained in striated muscle cells. Second, forces can be exerted in smooth muscle cells in multiple directions. This differs from the contraction force generated by skeletal muscle, which is always aligned with the axis of the muscle fibers. Third, the thick and thin filaments of smooth muscle are found in long, random bundles throughout the cells. This plexiform arrangement aids augmented shortening and force-generating capacity. Last, greater multidirectional force generation in the uterine fundus

compared with that of the lower uterine segment helps optimize expulsive force vectors.

Lining the thick muscular uterine walls, the endometrium is transformed by pregnancy hormones and is then termed *decidua*. Composed of stromal cells and maternal immune cells, the decidua serves to maintain the pregnancy via unique immunoregulatory functions that suppress inflammatory signals during gestation. However, at the end of pregnancy, the decidua transitions to induce inflammatory signals and withdraw active immunosuppression, contributing to parturition initiation.

During pregnancy, the cervix has multiple functions that include: (1) maintaining the epithelial barrier to protect the reproductive tract from infection, (2) sustaining cervical competence despite greater gravitational forces as the fetus grows, and (3) orchestrating extracellular matrix (ECM) changes that allow progressively greater tissue compliance.

In nonpregnant women, the cervix is closed and firm, and its consistency is similar to nasal cartilage. By the end of pregnancy, the cervix is easily distensible, and its consistency is similar to the lips of the oral cavity. The cervix has a high ratio of fibroblasts to smooth muscle cells, and ECM contributes significantly to overall tissue mass. Vink and colleagues (2016) showed that the smooth muscle cells in the cervix have a spatial gradient. Specifically, smooth muscle cells make up approximately 50 percent of stromal cells at the internal os but only 10 percent at the external os. Also, three-dimensional sonography and magnetic resonance imaging show increases in the cross-sectional area of the cervical canal and changes in ECM structure from early to late pregnancy (House, 2009; Lang, 2010; Pizzella, 2020). Concurrent with expansion of the stroma, the cervical epithelia proliferate and exert a pregnancy-specific immunoprotection.

Placenta

In addition to providing the exchange of nutrients and waste between mother and fetus, the placenta is a key source of steroid hormones, growth factors, and other mediators that maintain pregnancy and potentially aid the transition to parturition. The fetal membranes—amnion and chorion—and adjacent decidua serve as a physiologic, immunologic, and metabolic shield to protect against untimely parturition initiation.

The amnion provides virtually all of the fetal membranes' tensile strength to resist membrane tearing and rupture (Chap. 5, p. 94). This avascular tissue is highly resistant to penetration by leukocytes, microorganisms, and neoplastic cells (Fig. 21-1). It also constitutes a selective filter to prevent fetal particulate-bound lung and skin secretions from reaching the maternal compartment. In this manner, maternal tissues are protected from amnionic fluid constituents that could prematurely accelerate decidual or myometrial activation or could promote adverse events such as amnionic fluid embolism.

The chorion is a primarily protective tissue layer and provides immunological acceptance. It is also enriched with enzymes that inactivate *uterotonins*, which are agents that stimulate contractions. Inactivating enzymes include prostaglandin dehydrogenase, oxytocinase, and enkephalinase (Cheung, 1990; Germain, 1994; Mizutani, 2011).

SEX STEROID HORMONE ROLE

In many species, the role of sex steroid hormones is clear—estrogen promotes and progesterone inhibits the events leading to parturition. The removal of progesterone, that is, *progesterone withdrawal*, directly precedes progression of parturition. In addition, providing progesterone to some species will delay parturition via a decline in myometrial activity and continued cervical competency (Challis, 1994). In humans, however, both estrogen and progesterone are components of a broader molecular system that maintains uterine quiescence.

Plasma levels of estrogen and progesterone in normal pregnancy are enormous and in great excess of the affinity constants for their receptors. For this reason, it is difficult to comprehend how relatively subtle changes in the ratio of their concentrations could modulate physiological processes during pregnancy. The evidence, however, for an increased progesterone-to-estrogen ratio in the maintenance of pregnancy and a decline in this ratio for parturition is overwhelming. In all species studied, including humans, administration of the progesterone-receptor antagonists *mifepristone (RU-486)* or *onapristone* will promote some or all key features of parturition. These include cervical ripening, greater cervical distensibility, and augmented uterine sensitivity to uterotonins (Bygdeman, 1994; Chwalisz, 1994b; Wolf, 1993). The exact role of estrogen in regulation of human uterine quiescence and cervical competency is less well understood. That said, estrogen can advance progesterone responsiveness and, at the end of pregnancy, aid in processes that mediate uterine activation and cervical ripening.

Both progesterone and estrogen bind to nuclear receptors that regulate gene transcription. Two nuclear receptors for estrogen are estrogen receptor α (ERα) and estrogen receptor

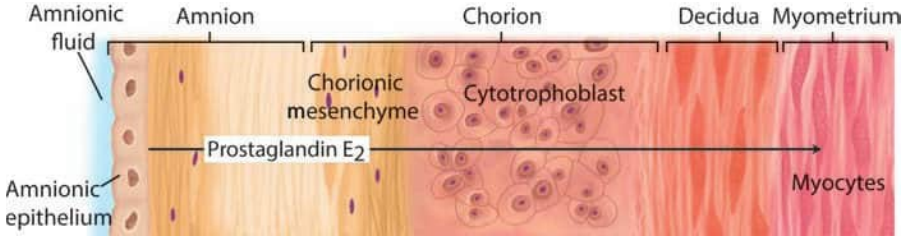


FIGURE 21-1 The amnion synthesizes prostaglandins, and late in pregnancy, synthesis is augmented by increased phospholipase A_2 and prostaglandin H synthase, type 2 (PGHS-2) activity. The transport of prostaglandins from the amnion to maternal tissues is limited by expression of the inactivating enzyme, prostaglandin dehydrogenase (PGDH), in the chorion. During labor, PGDH levels decline, and amnion-derived prostaglandins can influence membrane rupture and uterine contractility. The role of decidual activation in parturition is unclear but may involve local progesterone metabolism and higher prostaglandin receptor concentrations, thus enhancing uterine prostaglandin actions and cytokine production. (Redrawn from Smith R: Parturition. N Engl J Med. 2007 Jan 18;356(3):271–283.)

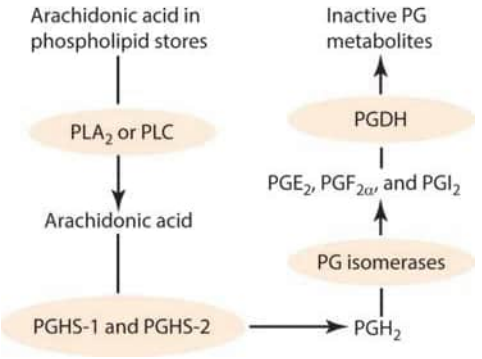


FIGURE 21-2 Overview of the prostaglandin biosynthetic pathway. PG = prostaglandin; PGDH = prostaglandin dehydrogenase; PGE_2 = prostaglandin E_2; $PGF_{2\alpha}$ = prostaglandin $F_{2\alpha}$; PGH_2 = prostaglandin H_2; PGHS = prostaglandin H synthase; PGI_2 = prostaglandin I_2; PLA_2 = phospholipase A_2; PLC = phospholipase C.

β (ERβ). Nuclear receptor isoforms of the progesterone receptor (PR-A and PR-B) are encoded by differing transcripts from a single gene (Patel, 2015).

PROSTAGLANDINS ROLE

Prostaglandins are lipid molecules with varied hormone-like actions. In parturition, they play a prominent role in myometrial contractility, relaxation, and inflammation. Prostaglandins interact with a family of eight different G protein–coupled receptors (p. 403), several of which are expressed in the myometrium and the cervix (Konopka, 2015; Myatt, 2004).

The major synthetic pathway involved in prostaglandin biosynthesis is shown in Figure 21-2. Prostaglandins are produced using plasma membrane–derived arachidonic acid, which usually is released by the action of phospholipase A_2 or C. The enzymes type 1 and 2 prostaglandin H synthase (PGHS-1 and -2), also known as cyclooxygenase 1 and 2 (COX-1 and -2), convert arachidonic acid to prostaglandin H_2 (PGH_2). These enzymes are the target of many nonsteroidal antiinflammatory drugs (NSAIDs). The tocolytic actions of specific COX inhibitors, as discussed in Chapter 45 (p. 806), were considered promising until they were shown to have adverse fetal effects (Loudon, 2003; Olson, 2007).

Through prostaglandin isomerases, PGH_2 is converted to active prostaglandins. These include prostaglandins E_2 (PGE_2), $F_{2\alpha}$ ($PGF_{2\alpha}$), and I_2 (PGI_2). Isomerase expression is tissue-specific and thereby controls the relative production of various prostaglandins. Another important control point for prostaglandin activity is its metabolism, which most often is through the action of 15-hydroxyprostaglandin dehydrogenase (PGDH). Expression of this enzyme is upregulated during pregnancy in the uterus and cervix, which provides the important ability to rapidly inactivate prostaglandins (Giannoulias, 2002; Kishore, 2017). Thus, myometrial responses to prostaglandins stem from a balance between prostaglandin synthesis versus metabolism, from the relative expression of various prostaglandin receptors, or from a switch in receptor-signaling pathways (Kandola, 2014; Lyall, 2002; Olson, 2007; Smith, 2001). It is possible that prostanoids contribute to myometrial relaxation at one stage of pregnancy and to myometrial contractions after parturition initiation (Myatt, 2004).

In addition to the myometrium, the amnion synthesizes several bioactive peptides and prostaglandins that cause myometrial relaxation or contraction (see Fig. 21-1). Late in pregnancy, amnionic prostaglandin biosynthesis of PGE_2 and $PGF_{2\alpha}$ is increased, and phospholipase A_2 and PGHS-2 show greater activity (Peiris, 2020). The amnion is likely the major source for amnionic fluid prostaglandins, and their role in the activation of cascades that promote membrane rupture is clear. However, the influence of amnion-derived prostaglandins on uterine quiescence and activation is less clear because their access to maternal tissues is limited by expression of PGDH.

PHASE 1: UTERINE QUIESCENCE AND CERVICAL SOFTENING

Parturition can be arbitrarily divided into four overlapping phases that correspond to the major physiological transitions of the myometrium and cervix during pregnancy (Fig. 21-3) (Casey, 1997; Shynlova, 2020; Vink, 2018). These include: (1) the prelude, (2) the preparation, (3) the process itself, and (4) the recovery. Importantly, the *phases of parturition* should not be confused with the *clinical stages of labor*. The first, second, and third stages of labor make up phase 3 of parturition (Fig. 21-4).

Beginning even before implantation, a remarkably effective period of myometrial quiescence is imposed. This phase 1 normally constitutes 95 percent of pregnancy and is characterized by uterine smooth muscle tranquility with maintenance of cervical structural integrity (Fig. 21-5). All manner of molecular systems—neural, endocrine, paracrine, and autocrine—are likely called to implement and coordinate a state of relative uterine unresponsiveness. Moreover, a complementary "fail-safe" system that protects the uterus against agents that could perturb the tranquility of phase 1 also must be in place.

During phase 1, the uterus must initiate extensive changes in its size and vascularity to accommodate fetal growth. Concurrently, myometrial cells undergo

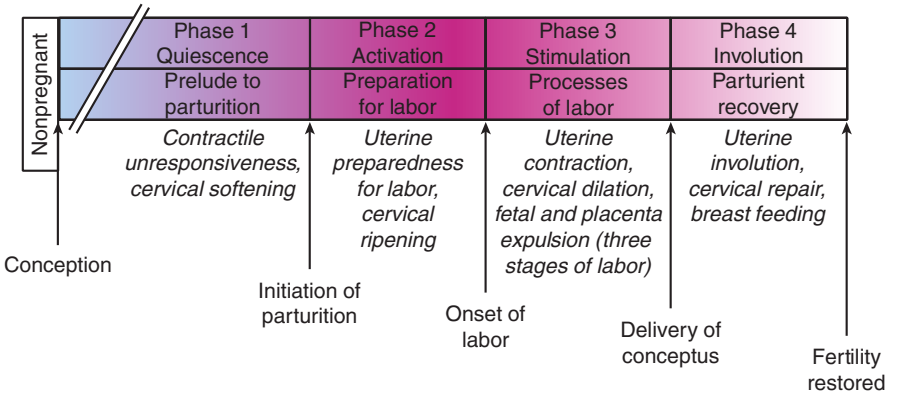


FIGURE 21-3 The phases of parturition.

a phenotypic modification to a noncontractile state, and uterine muscle is rendered unresponsive to natural stimuli. Although this unresponsiveness continues until near the end of pregnancy, some low-intensity myometrial contractions are felt during the quiescent phase. These contractions do not normally cause cervical dilation, and they are common toward the end of pregnancy, especially in multiparas. They are referred to as *Braxton Hicks contractions* or *false labor* (Chap. 4, p. 52).

The quiescence of phase 1 likely stems from: (1) actions of estrogen and progesterone via intracellular receptors, (2) myometrial-cell plasma membrane receptor–mediated increases in cyclic adenosine monophosphate (cAMP), (3) generation of cyclic guanosine monophosphate, and (4) other systems, including modification of myometrial-cell ion channels.

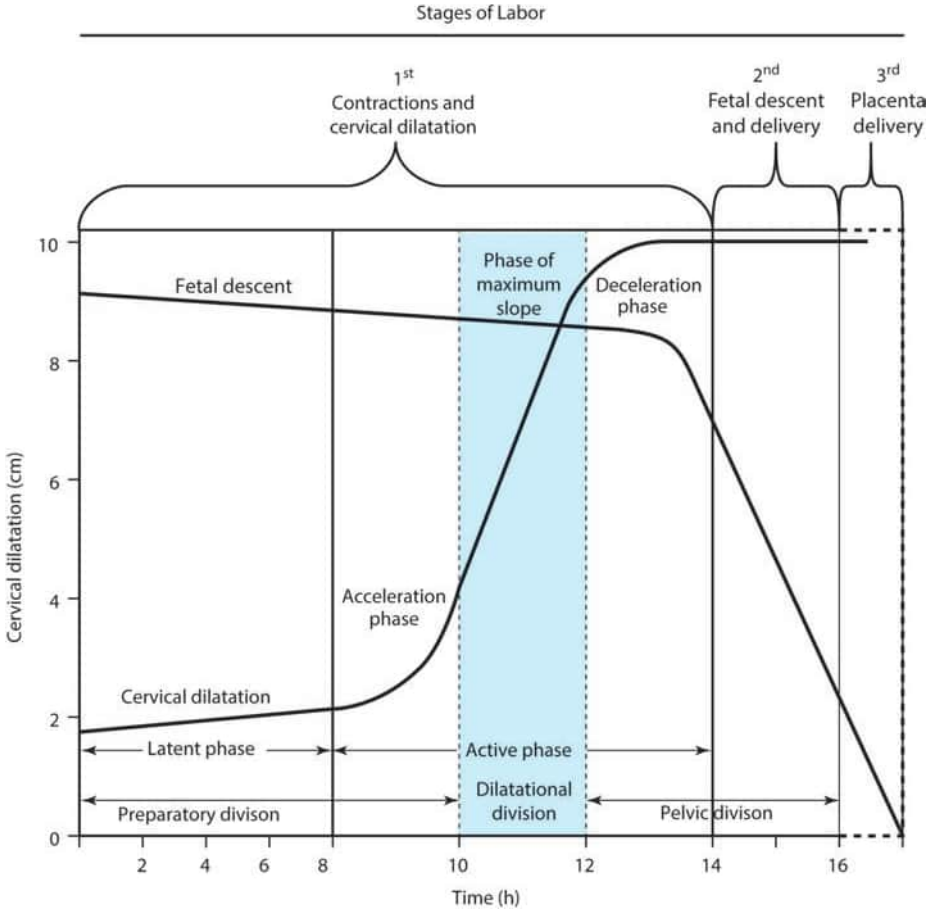


FIGURE 21-4 Labor course divided on the basis of expected evolution of the dilatation and descent curves into three functional divisions. The preparatory division includes the latent and active phases. The dilatational division is the phase of maximum slope of dilatation. The pelvic division encompasses both the deceleration phase and the second stage, which is concurrent with the phase of maximum slope of fetal descent. (Redrawn from Friedman EA: Labor: Clinical Evaluation and Management, 2nd ed. New York, Appleton-Century-Crofts, 1978.)

Myometrial Relaxation and Contraction

The balance between myometrial relaxation and contraction is controlled by steroid- and peptide-hormone transcriptional regulation of key genes and their protein products (Wray, 2019). Quiescence is achieved in part by: (1) diminished intracellular crosstalk and reduced intracellular Ca^{2+} ($[Ca^{2+}]_i$) levels, (2) ion-channel regulation of cell membrane potential, (3) activation of the stress–unfolded protein response by the uterine endoplasmic reticulum, and (4) uterotonin degradation. In contrast, contractility results from: (1) enhanced interactions between the actin and myosin proteins, (2) heightened excitability of individual myometrial cells, and (3) promotion of intracellular crosstalk that allows synchronous contractions to develop.

Actin–Myosin Interactions

Actin and myosin proteins are essential to muscle contraction. For this, actin must be converted from a globular to a filamentous form. Indeed, a potential mechanism for maintenance of relaxation is the promotion of actin into a globular form rather than into fibrils, which are required for contraction. Moreover, actin must be attached to the cytoskeleton at focal points in the cell membrane to allow tension to develop.

Actin must partner with myosin, which is composed of multiple light and heavy chains (Fig. 21-6). This interaction is brought about by enzymatic phosphorylation of the 20-kDa light chain of myosin (Stull, 1998). This is catalyzed by the enzyme *myosin light-chain kinase*, which is activated by calcium (Ca^{2+}).

Thus, logically, uterine relaxation ordinarily is promoted by conditions that lower concentrations of $(Ca^{2+})_i$. In contrast, agents that prompt contraction act on myometrial cells to augment $(Ca^{2+})_i$ levels. Or, they allow an influx of extracellular calcium through ligand- or voltage-regulated calcium channels (see Fig. 21-6). For example, $PGF_{2\alpha}$ and oxytocin bind their respective receptors during labor to open ligand-activated calcium channels. Activation of these receptors also releases calcium from the sarcoplasmic reticulum. Additionally, greater localization of nonselective cation channels on the cell membrane promotes Ca^{2+} entry (Ying, 2015). The rise in $(Ca^{2+})_i$ levels is often transient. But, contractions can be prolonged by inhibition of myosin phosphatase, an enzyme that dephosphorylates myosin (Woodcock, 2004).

Regulation of Membrane Potentials

As just noted, myocyte excitability is regulated in part by changes in the electrochemical potential gradient across the plasma membrane. Before labor, myocytes maintain a relatively high interior electronegativity. Maintenance of a hyperpolarized membrane potential attenuates smooth muscle cell excitation and is regulated by ion channels.

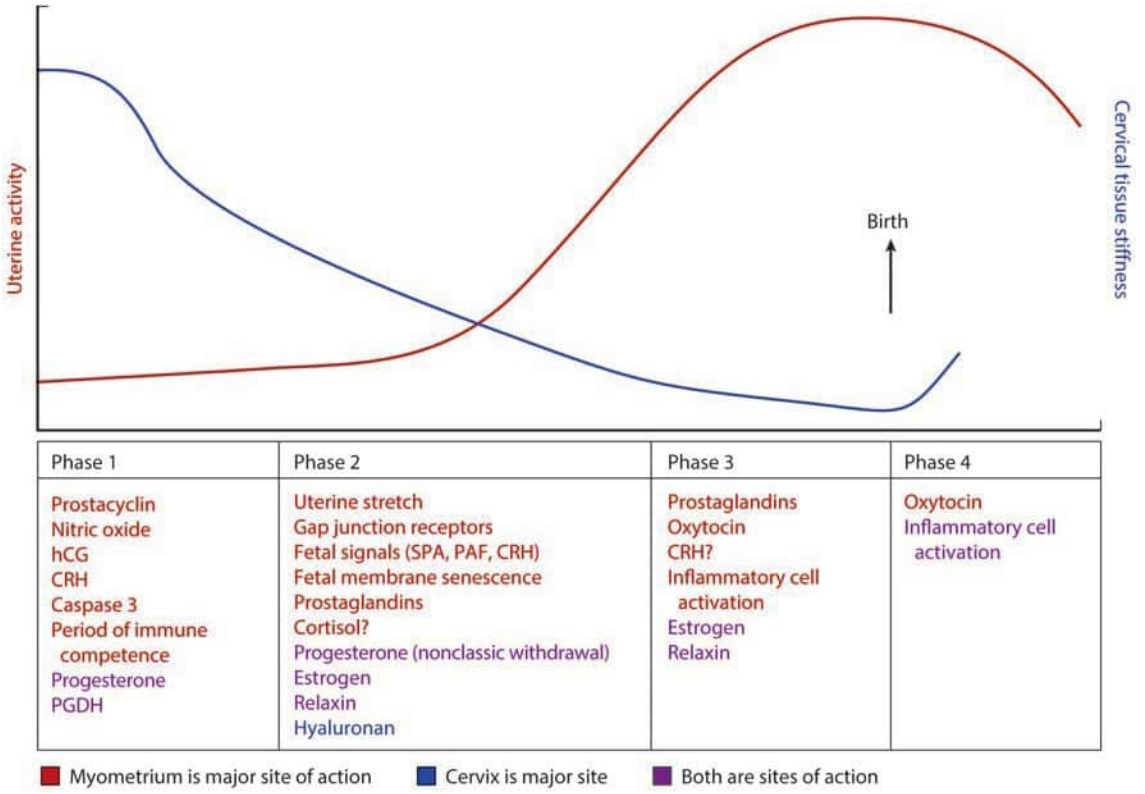


FIGURE 21-5 The key factors thought to regulate the phases of human parturition. CRH = corticotropin-releasing hormone; hCG = human chorionic gonadotropin; PAF = platelet-activating factor; PGDH = prostaglandin dehydrogenase; SPA = surfactant protein A.

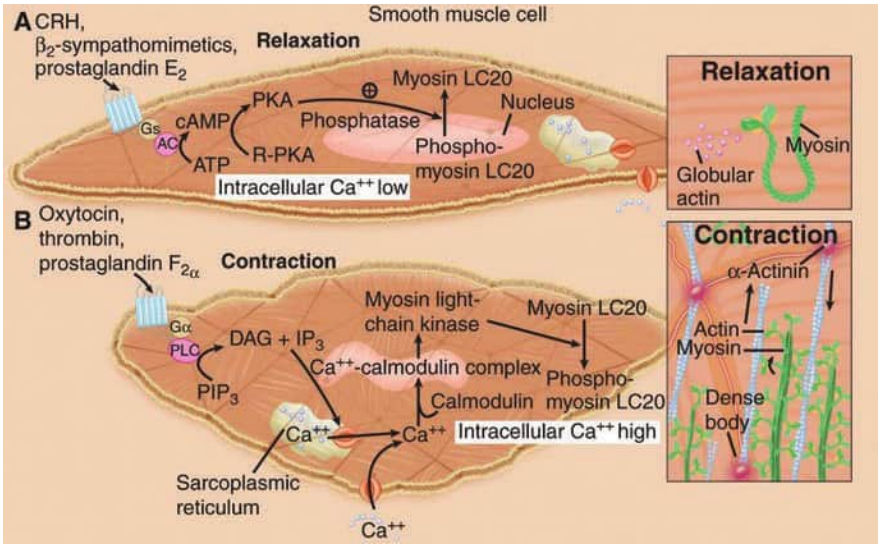


FIGURE 21-6 Uterine myocyte relaxation and contraction. **A.** Uterine relaxation is maintained by factors that increase myocyte cyclic adenosine monophosphate (cAMP) levels. This activates protein kinase A (PKA) to promote phosphodiesterase activity with dephosphorylation of myosin light-chain kinase (MLCK). Other processes serve to maintain actin in a globular form and thus to prevent the fibril formation necessary for contractions. **B.** Uterine contractions result from reversal of these sequences. Actin now assumes a fibrillar form, and calcium enters the cell to combine with calmodulin to form complexes. These complexes activate MLCK to bring about phosphorylation of the myosin light chains. This generates ATPase activity to cause sliding of myosin over the actin fibrils, which is a uterine contraction. AC = adenylyl cyclase; Ca^{2+} = calcium; DAG = diacylglycerol; Gs and Gα = G-receptor proteins; IP_3 = inositol triphosphate; LC20 = light chain 20; PIP_3 = phosphatidylinositol 3,4,5–triphosphate; PLC = phospholipase C; R-PKA = inactive protein kinase. (Redrawn from Smith R: Parturition. N Engl J Med. 2007 Jan 18;356(3):271–283.)

Numerous ion channels control sodium (Na^+) and calcium (Ca^{2+}) influx and potassium (K^+) efflux to collectively regulate membrane potential. Sodium leak channels (NALCN) are important to normal uterine function (Reinl, 2018). Another key regulator is the large-conductance voltage- and Ca^{2+}-activated K^+ channel (BK_{Ca}) (Pérez, 1993). The BK_{Ca} channel is abundantly expressed in the myometrium and plays dual promoting and opposing roles to maintain a balance between uterine quiescence and contractility. Opening the BK_{Ca} channel allows potassium to leave the cell to maintain interior electronegativity, thus preventing voltage-gated Ca^{2+} influx and contraction. Inhibition of the BK_{Ca} channel augments myometrial contractility. Regulation of uterine contractility from early to late gestation may result from temporal changes in expression of the BK_{Ca} channel and/or BK_{Ca} interacting partners (Wakle-Prabagaran, 2016).

Myometrial Gap Junctions

Cellular signals that control myometrial contraction and relaxation can be effectively transferred between cells through

intercellular junctional channels. Communication is established between myocytes by gap junctions, which aid the passage of electrical or ionic coupling currents as well as metabolite coupling. The connexin family of proteins form cell-type specific gap junctions (Solan, 2018). Connexin-43 is expressed in the myometrium, and concentrations rise near labor onset. Six connexin subunits form a *connexon*, and two adjacent connexons establish a conduit between communicating cells. This permits exchange of small molecules that can be nutrients, waste, metabolites, second messengers, or ions. Optimal numbers and types of gap junctions are believed to be important for electrical myometrial synchrony.

Progesterone promotes uterine quiescence in part by lowering expression of contraction-associated proteins (CAPs) and maintaining expression of anticontractile agents such as *caspase 3* (Ingles, 2018; Kyathanahalli, 2015). CAPs include the oxytocin receptor, prostaglandin F receptor, and connexin-43. Also, at the end of pregnancy, increased stretch, metabolism of progesterone by the enzyme 20α-hydroxysteroid dehydrogenase (20α-HSD), loss of progesterone-mediated repression of CAP genes, and greater estrogen dominance raise CAP levels. Integration of diverse regulatory pathways culminates in released inhibition of connexin-43 and oxytocin receptor levels to promote greater uterine contractility (Anamthathmakula, 2019; Mendelson, 2019; Peavey, 2021).

G Protein–Coupled Receptors

In addition to ion-channel linked receptors, G protein–coupled receptors regulate myocyte contractility. These receptors together with appropriate ligands may act with sex steroid hormones to maintain uterine quiescence (Price, 2000; Sanborn, 1998). Examples are the luteinizing hormone (LH) receptor and corticotropin-releasing hormone receptor 1 (CRHR1), both described in this section (Fig. 21-7). Other G protein–coupled myometrial receptors, instead, are associated with uterine contractility. G protein–mediated activation of phospholipase C, which releases arachidonic acid, is one example. Ligands for the G protein–coupled receptors include numerous neuropeptides, hormones, and autacoids. Many of these are available to the myometrium during pregnancy in high concentration via *endocrine* or *autocrine* mechanisms.

LH and human chorionic gonadotropin (hCG) hormones share the same LH-hCG receptor. This G protein–coupled receptor is found in myometrial smooth muscle and blood vessels, and levels during pregnancy are greater before labor (Ziecik, 1992). hCG acts to activate adenylyl cyclase by way of a plasma membrane receptor $G_{\alpha s}$-linked system. This lessens contraction frequency and force and lowers the number of tissue-specific myometrial cell gap junctions (Ambrus, 1994; Eta, 1994). Thus, high circulating levels of hCG may be one mechanism of uterine quiescence. β-Adrenergic receptors mediate $G_{\alpha s}$-stimulated myometrial cell relaxation. Agents binding to these receptors have been used for tocolysis of preterm labor and include ritodrine and terbutaline (Chap. 45, p. 805). The rate-limiting factor is likely the number of receptors expressed and the level of adenylyl cyclase expression.

Prostaglandin E_2 mediates its diverse cellular effects through four G protein–coupled receptors. Specifically, prostaglandin E receptors 1 through 4 (EP_1-EP_4) are expressed in the

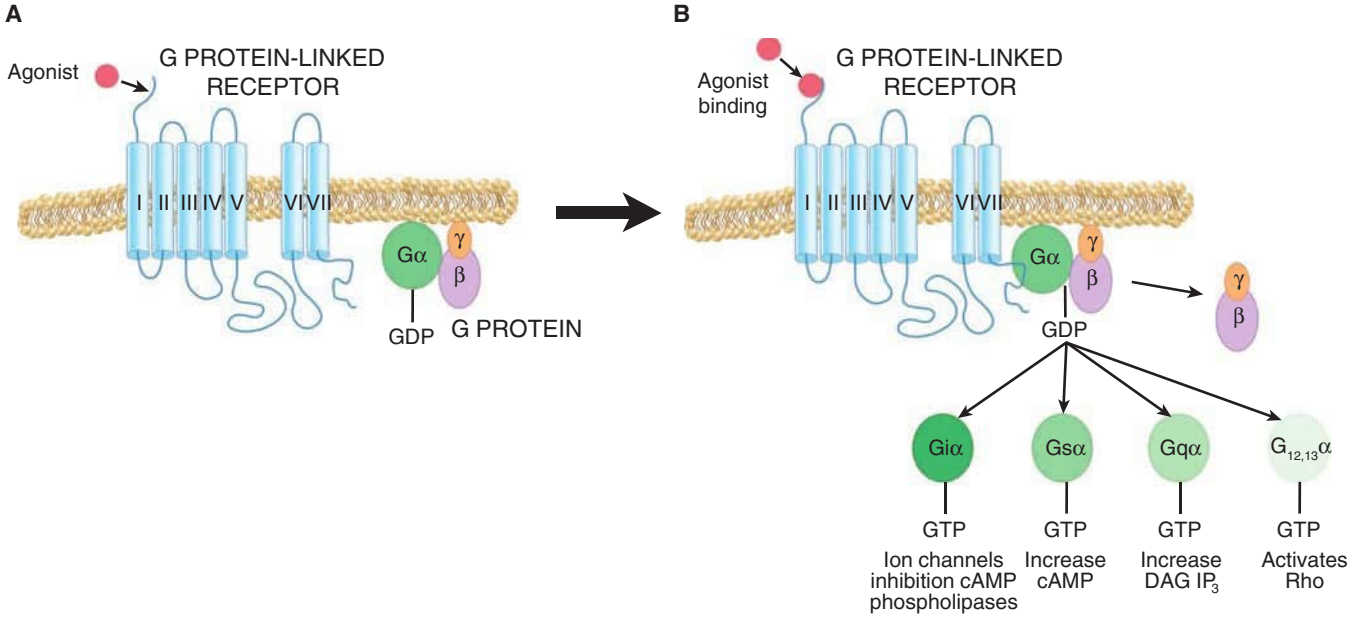


FIGURE 21-7 G protein–coupled receptor signal transduction pathways. **A.** Receptors coupled to heterotrimeric guanosine-triphosphate (GTP)-binding proteins (G proteins) are integral transmembrane proteins that transduce extracellular signals to the cell interior. G protein–coupled receptors exhibit a common structural motif consisting of seven membrane-spanning regions. **B.** Receptor occupation promotes interaction between the receptor and the G protein on the interior surface of the membrane. An exchange of guanosine diphosphate (GDP) for GTP on the G protein α subunit and dissociation of the α subunit from the βγ heterodimer occurs. Depending on its isoform, the GTP-α subunit complex mediates intracellular signaling either indirectly by acting on effector molecules such as adenylyl cyclase (AC) or phospholipase C (PLC), or directly by regulating ion channel or kinase function. cAMP = cyclic adenosine monophosphate; DAG = diacylglycerol; IP_3 = inositol triphosphate.

myometrium during pregnancy and with labor onset (Astle, 2005; Leonhardt, 2003). EP_2 and EP_4 act through $G_\alpha s$ to maintain myometrial cell quiescence but switch to a $G_\alpha q/11$ calcium-activating pathway during labor (Kandola, 2014). EP_1 and EP_3 receptors act through $G_\alpha q$ and $G_\alpha i$ to augment intracellular Ca^{2+} and contractility.

The peptide hormone relaxin binds to the G protein–coupled receptor named *relaxin family peptide receptor 1 (RXFP1)*. Binding activates adenylyl cyclase, which in turn prevents increased intracellular Ca^{2+}, and thus promotes uterine quiescence (Downing, 1993; Meera, 1995). The *H1* relaxin gene is primarily expressed in the decidua, trophoblast, and prostate, whereas the *H2* gene is primarily expressed in the corpus luteum. Relaxin plasma levels peak at approximately 1 ng/mL between 8 and 12 weeks' gestation. Thereafter, they decline until term.

Corticotropin-releasing hormone (CRH) is synthesized in the placenta and hypothalamus. Discussed on page 408, CRH plasma levels rise dramatically during the final 6 to 8 weeks of normal pregnancy and are implicated in mechanisms that control the timing of human parturition (Smith, 2007; Wadhwa, 1998; Wang, 2019). CRH appears to promote myometrial quiescence during most of pregnancy but then aids contractions with parturition onset. Studies suggest that these opposing actions are achieved by differential actions of CRH via its receptor CRHR1. In nonlaboring myometrium at term, the interaction of CRH with CRHR1 activates the Gs-adenylate cyclase-cAMP signaling pathway. This results in inhibition of inositol triphosphate (IP_3) and stabilization of $(Ca^{2+})_i$ levels (You, 2012). However, in term laboring myometrium, $(Ca^{2+})_i$ concentrations are augmented by CRH activation of G proteins Gq and Gi and prompts stimulation of IP_3 production and greater contractility.

Cyclic Guanosine Monophosphate

As noted, cAMP is an important mediator of myometrial relaxation. However, activation of guanylyl cyclase raises intracellular cyclic guanosine monophosphate (cGMP) levels. This also promotes smooth muscle relaxation (Word, 1993). Intracellular cGMP levels are increased in the pregnant myometrium and can be stimulated by atrial natriuretic peptide, brain natriuretic peptide, and nitric oxide (Guerra, 2019; Telfer, 2001). All of these factors and their receptors are expressed in the pregnant uterus.

Accelerated Uterotonin Degradation

The activity of enzymes that degrade or inactivate endogenously produced uterotonins also is strikingly increased in phase 1. Pairs of some degrading enzymes and their respective targets include PGDH and prostaglandins; enkephalinase and endothelins; oxytocinase and oxytocin; diamine oxidase and histamine; catechol *O*-methyltransferase and catecholamines; angiotensinases and angiotensin II; and platelet-activating factor (PAF) and PAF acetylhydrolase. Levels of several of these enzymes decline late in gestation (Germain, 1994).

Decidua

To ensure uterine quiescence, the synthesis in the decidua of prostaglandins, in particular $PGF_{2\alpha}$, is markedly suppressed. Suppression of prostaglandin production here persists throughout most of pregnancy, and suppression withdrawal is a prerequisite for parturition (Norwitz, 2015).

The mother and fetus come in direct contact at the decidua basalis and decidua parietalis. At this interface, myeloid and lymphoid immune cells such as natural killer cells, macrophages, dendritic cells, and T cells undergo dynamic changes in number and phenotype to achieve a balanced microenvironment (Ander, 2019; Solano, 2019; van der Zwan, 2020). This is a critical site for immune tolerance in phase 1 and for decidual activation in phase 2 of parturition (see Fig. 21-5). In phase 1 of parturition, these cells, in collaboration with decidual cells, promote an environment of immune tolerance to protect the fetus. Immune cells with innate and adaptive immune responses support vascular and tissue remodeling, immune surveillance and defense, and trophoblast invasion in phase 1 (Fig. 21-8).

During phase 2, decidual stromal cells and fetal membranes undergo an aging process termed cellular senescence. Noninflammatory signals precipitate senescence, which in turn leads to synthesis of proinflammatory cytokines, augmented

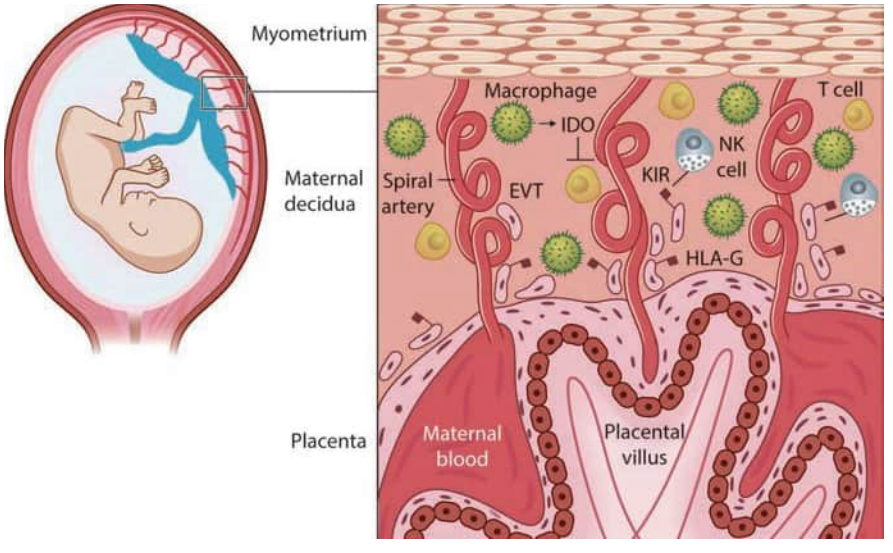


FIGURE 21-8 Immune tolerance and activation at the maternal fetal interface. In the antepartum period, dNK cells are abundant and their maturation is promoted by release of uterine IL-15. These cells promote decidual remodeling, blastocyst implantation, and EVT invasion. The cytotoxicity of dNK cells is regulated by the interaction of its KIR receptor with HLA-G on EVTs. Decidual macrophages—primary antigen-presenting cells—produce the enzyme IDO, which limits T cell activation. Changes in the intrapartum period are less understood, but the number of dNK cells decline and decidual macrophages are activated to a proinflammatory phenotype. dNK = decidual natural killer; EVT = extravillous trophoblasts; HLA = human leukocyte antigen; IL = interleukin; IDO = indoleamine 2,3-dioxygenase; KIR = killer-cell immunoglobulin-like receptors.

prostaglandin production, and increased protease expression. These proteins and hormones break down fetal membranes.

Cervical Softening

The initial stage of cervical remodeling—termed *softening*—begins in phase 1 of parturition. It is characterized by greater tissue compliance, yet the cervix remains firm and unyielding. Hegar (1895) first described palpable softening of the lower uterine segment at 4 to 6 weeks' gestation, and this sign was once used to diagnose pregnancy. Clinically, the maintenance of cervical anatomical and structural integrity is essential for pregnancy to continue to term. Preterm cervical dilation, structural insufficiency, or both may forecast delivery.

Cervical Connective Tissue

Cervical softening is an active molecular process that balances tissue competence against slow, progressive compositional and structural changes in the extracellular matrix (ECM) to increase compliance (Myers, 2015; Nallasamy, 2017; Vink, 2018). Constituents of the ECM include type I and III fibrillar collagens, matricellular proteins, glycosaminoglycans, proteoglycans, and elastic fibers. Key to matrix changes, collagen, which is the main structural protein in the cervix, undergoes conformational changes that alter tissue stiffness and flexibility (Zhang, 2012). Specifically, collagen processing and the number or type of stable covalent cross-links between collagen's triple helices are altered. Beginning in early pregnancy, mature cross-links between newly synthesized collagen monomers are reduced due to diminished expression and activity of the cross-link-forming enzymes (Akins, 2011; Yoshida, 2014). These enzymes are lysyl hydroxylase and lysyl oxidase. Gradual turnover of collagen during pregnancy replaces mature cross-linked collagen fibrils with poorly linked fibrils. The result is a collagen with reduced stiffness. The collagen-binding proteoglycans—decorin and biglycan—ensure the new, poorly cross-linked collagen is appropriately assembled and deposited in the ECM. Data from human and mouse studies support the theory that a balance in the synthesis and breakdown of collagen, rather than loss of collagen, achieves cervical remodeling (Fig. 21-9) (Akins, 2011; Myers, 2008; Read, 2007; Yoshida, 2014).

Clinical evidence for the importance of matrix changes to cervical softening is supported by in vivo mechanical evaluation of the cervix (Badir, 2013; Parra-Saavedra, 2011). The prevalence of cervical insufficiency is also higher in those with inherited defects in the synthesis or assembly of collagen or elastic fibers (Anum, 2009; Hermanns-Le, 2005; Volozonoka, 2020).

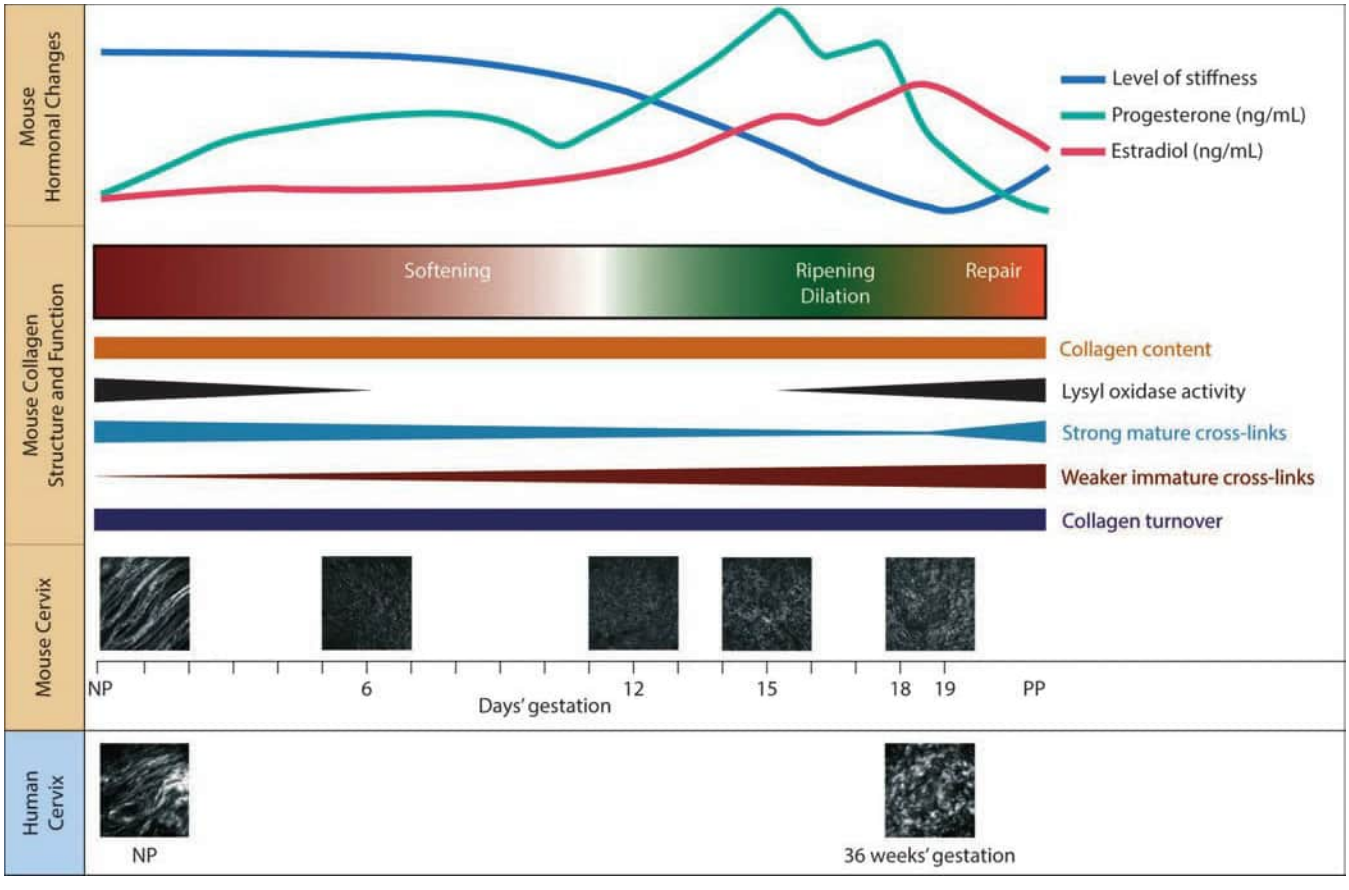


FIGURE 21-9 Mouse studies identify molecular changes in collagen structure and function during cervical remodeling. These changes are regulated by steroid hormones and result in a gradual loss of tissue stiffness. During the softening phase, the decline in lysyl oxidase activity in conjunction with high collagen turnover results in the replacement of strong cross-linked collagen fibers with weakly cross-linked collagen fibers. Second harmonic generation images in the mouse and human cervix show the corresponding gradual decline in mechanical function of the cervix. (Compiled from Akins, 2010, 2011; Ozasa, 1981; Read, 2007; Yoshida, 2014; Zhang, 2012.)

Examples are Ehlers-Danlos and Marfan syndromes, discussed in Chapter 62 (p. 1121). Concurrent with matrix remodeling in the softening period, genes involved in cervical dilation and parturition are actively repressed (Kishore, 2012).

PHASE 2: PREPARATION FOR LABOR

To prepare for labor, the myometrial tranquility of phase 1 of parturition must be suspended. This so-called *uterine awakening* or *activation* in phase 2 of parturition is a progression of uterine changes during the last few weeks of pregnancy. Importantly, shifting events associated with phase 2 can cause either preterm or delayed labor.

Progesterone Withdrawal

Key factors in uterine activation are depicted in Figure 21-5. In species that exhibit progesterone withdrawal, parturition progression to labor can be blocked by administering progesterone to the mother. Whether progesterone administration in the absence of classic progesterone withdrawal can delay the timely onset of parturition or prevent preterm labor remains unclear. The possibility that progesterone may prevent preterm labor has been studied, but its use in preventing preterm birth continues to be debated (Chap. 45, p. 795).

Classic progesterone withdrawal from decreased secretion does not occur in human parturition. However, a mechanism for progesterone inactivation, whereby the myometrium and cervix become refractory to progesterone's inhibitory actions, is supported by studies using progesterone-receptor antagonists. Mifepristone is a classic steroid antagonist, acting at the level of the progesterone receptor. Although less effective in inducing abortion or labor later in pregnancy, mifepristone appears to have some effect on cervical ripening and on increasing myometrial sensitivity to uterotonins (Berkane, 2005; Chwalisz, 1994a).

The diverse mechanisms by which functional progesterone withdrawal or antagonism is achieved is an active area of research. These include: (1) changes in the relative expression of the nuclear progesterone-receptor (PR) isoforms, (2) differential interaction of PR isoforms A and B with enhancers and inhibitors of gene expression, (3) altered PR activity through changes in the expression of coactivators or corepressors of receptor function, (4) local progesterone inactivation by steroid-metabolizing enzymes or synthesis of a natural antagonist, and (5) microRNA regulation of progesterone-metabolizing enzymes and transcription factors that modulate uterine quiescence (Chen, 2017; Condon, 2003; Mahendroo, 1999; Mesiano, 2002; Nadeem, 2016; Peavey, 2021; Renthal, 2010; Williams, 2012). Thus, multiple pathways exist to create functional progesterone withdrawal.

Myometrial Changes

Phase 2 changes in the myometrium prepare it for labor contractions. Changes result from a shift in the expression of proteins that control uterine quiescence to an expression of CAPs, described earlier (p. 403) (Mendelson, 2019; Renthal, 2015; Stanfield, 2019). These CAPs increase uterine responsiveness to uterotonins.

Another critical change in phase 2 is formation of the lower uterine segment from the isthmus. With this development, the fetal head often descends to or even through the pelvic inlet—*lightening*. The abdomen commonly undergoes a shape change, sometimes described by women as "the baby dropped." It is also likely that the lower segment myometrium is unique from that in the upper uterine segment, and leads to distinct roles for each near term and during labor. This is supported by human studies that demonstrate differential expression of prostaglandin receptors and CAPs within the upper- and lower-segment myometrial regions (Astle, 2005; Blanks, 2003; Sparey, 1999). Near term, elevated expression of the *HoxA13* gene in the lower myometrial segment compared with the upper segment also induces CAP expression and regionalized contractility of the lower segment (Li, 2016).

Oxytocin Receptors

Because of its long-standing application for labor induction, it seemed logical that oxytocin must play a central role in spontaneous human labor. Myometrial oxytocin receptor levels do rise during phase 2 of parturition, and the level of oxytocin receptor mRNA in human myometrium at term is greater than that found in preterm myometrium (Wathes, 1999). However, it is unclear whether oxytocin plays a role in the early phases of uterine activation or whether its sole function is in the expulsive phase of labor. Most studies of regulation of myometrial oxytocin receptor synthesis have been performed in rodents. Disruption of the oxytocin receptor gene in the mouse does not affect parturition. This suggests that, at least in this species, multiple systems likely ensure that parturition occurs.

Progesterone inhibits and estradiol induces oxytocin receptor expression. Through interaction with PR-B, progesterone regulates numerous genes in the oxytocin signaling pathway (Peavey, 2021). Progesterone may also act within the myometrial cell to enhance oxytocin receptor degradation (Bogacki, 2002). These data indicate that one of the mechanisms whereby progesterone maintains uterine quiescence is through inhibition of a myometrial oxytocin signaling pathway.

Cervical Ripening

Before contractions begin, the cervix must shift from a state of competence to one of compliance. This eventually leads to the cervix yielding and dilating from forceful uterine contractions. Cervical modifications during phase 2 principally involve connective tissue changes—termed *cervical ripening*. The transition from the softening to the ripening phase begins weeks or days before labor. The understanding of this cervical matrix transformation remains incomplete. However, it is clear that levels of *glycosaminoglycans*, which are large linear polysaccharides, are uniquely increased in phase 2.

Glycosaminoglycans and Proteoglycans

Hyaluronan is a high-molecular-weight polysaccharide that functions alone, but most other glycosaminoglycans (GAGs)

complex with proteins to form proteoglycans. Hyaluronan is a hydrophilic, space-filling molecule, and thus greater hyaluronan production during cervical ripening is thought to increase viscoelasticity, hydration, and matrix disorganization. Hyaluronan synthesis is carried out by hyaluronan synthase isoenzymes, and expression of these enzymes is elevated in the cervix during ripening (Akgul, 2012; Straach, 2005).

Inflammatory Changes

In phase 2, resident immune cells are localized to the cervical stroma, although a functional role for them in this phase has not been demonstrated. For example, studies of gene expression patterns at term both before and after cervical ripening show little rise in proinflammatory gene expression. However, once labor is underway, activation of neutrophils, proinflammatory M1 macrophages, and tissue repair M2 macrophages in the cervix is augmented. Moreover, proinflammatory and immunosuppressive gene expression in the cervix increases markedly after delivery (Bollapragada, 2009; Hassan, 2006, 2009). This suggests a role for inflammatory cells in postpartum cervical remodeling and repair (Mahendroo, 2012).

Induction of Cervical Ripening

No therapies prevent premature cervical ripening. In contrast, treatment to promote cervical ripening for labor induction includes direct application of PGE_2 and $PGF_{2\alpha}$ (Chap. 26, p. 489). Prostaglandins likely modify ECM structure to aid ripening, although their role in the normal physiology of cervical ripening remains unclear.

In some nonhuman species, events that allow cervical ripening are induced by dropping serum progesterone concentrations. And in humans, administration of progesterone antagonists causes cervical ripening.

Endocervical Epithelia

In addition to matrix changes during pregnancy, endocervical epithelial cells proliferate such that endocervical glands account for a significant percentage of cervical mass. The endocervical canal is lined with mucus-secreting columnar and stratified squamous epithelia. These cells form both a mucosal barrier and a tight junctional barrier that protect against microbial invasion (Akgul, 2014; Blaskewicz, 2011; Timmons, 2007). The mucosal epithelium recognizes and deters pathogen invasion via expression of toll-like receptors that identify pathogens and via antimicrobial peptides and protease inhibitors. These epithelia also express signals to underlying immune cells when a pathogenic challenge exceeds their protective capacity (Wira, 2005).

■ Fetal Contributions to Parturition

It is intriguing to envision that the mature human fetus provides the signal to initiate parturition, and evidence for fetal signaling is mounting (Mendelson, 2017). The fetus may give signals through blood-borne agents that act on the placenta or through secretion into the amniotic fluid.

Uterine Stretch

Fetal growth is an important component of uterine activation in phase 2 of parturition. With uterine activation, stretch is required for induction of specific CAPs. Namely, stretch increases expression of connexin-43 and oxytocin receptors. Levels of gastrin-releasing peptide, a stimulatory agonist for smooth muscle, also are augmented by stretch in the myometrium (Tattersall, 2012).

Clinical clues for a role of stretch come from the observation that multifetal pregnancies carry a much greater risk for preterm labor than singleton ones. Preterm labor is also more common in pregnancies complicated by hydramnios. Although the mechanisms causing preterm birth in these two are debated, a role for uterine stretch must be considered.

Cell signaling systems are influenced by stretch to regulate the myometrial cell. This process—*mechanotransduction*—may include activation of cell-surface receptors or ion channels, transmission of signals through ECM, or release of autocrine molecules that act directly on myometrium (Shynlova, 2007; Young, 2011).

Fetal Endocrine Cascades

The ability of the fetus to provide endocrine signals that initiate parturition has been demonstrated in several species. However, evidence suggests that it is not regulated in the same manner in humans. That said, the human fetal hypothalamic-pituitary-adrenal-placental axis is considered a critical component of normal parturition. Moreover, premature activation of this axis is considered to prompt many cases of preterm labor (Challis, 2000, 2001). Steroid products of the human fetal adrenal gland are believed to have effects on the placenta and membranes that eventually transform the myometrium from a quiescent to a contractile state.

A key component in the human may be the unique ability of the placenta to produce large amounts of CRH that is identical to maternal and fetal hypothalamic CRH (Grino, 1987; Saijonmaa, 1988) (Fig. 21-10). However, unlike hypothalamic CRH, which is under glucocorticoid negative feedback, cortisol

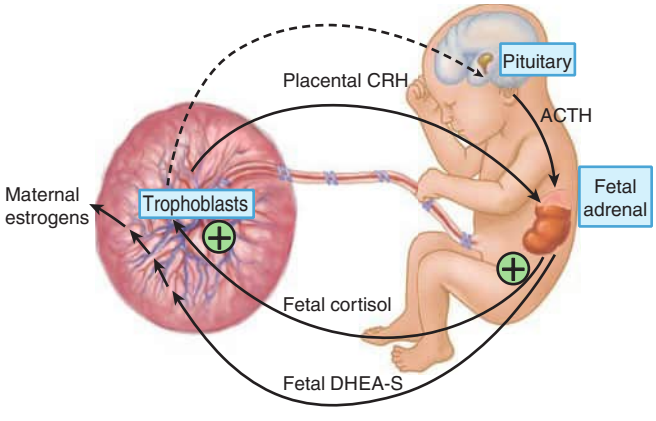


FIGURE 21-10 The placental–fetal adrenal endocrine cascade. In late gestation, placental corticotropin-releasing hormone (CRH) stimulates fetal adrenal production of dehydroepiandrosterone sulfate (DHEA-S) and cortisol. The latter stimulates production of placental CRH, which leads to a feed-forward cascade that enhances adrenal steroid hormone production. ACTH = adrenocorticotropic hormone.

instead *stimulates* placental CRH production. This ability makes it possible to create a feed-forward endocrine cascade that does not end until delivery.

Maternal plasma CRH levels are low in the first trimester and rise from midgestation to term. In the last 12 weeks, CRH plasma levels rise exponentially, peak during labor, and then fall precipitously after delivery (Frim, 1988; Sasaki, 1987). Amnionic fluid CRH concentrations similarly increase in late gestation. CRH is the only trophic hormone-releasing factor to have a specific serum binding protein. During most of pregnancy, CRH-binding protein (CRH-BP) binds most maternal circulating CRH, and this inactivates it (Lowry, 1993). During later pregnancy, however, CRH-BP levels in both maternal plasma and amnionic fluid decline, leading to markedly greater levels of bioavailable CRH (Perkins, 1995; Petraglia, 1997).

In pregnancies in which the fetus can be considered "stressed" from various complications, concentrations of CRH in fetal plasma, amnionic fluid, and maternal plasma are greater than those seen in normal gestation (Berkowitz, 1996; McGrath, 2002). The placenta is the likely source of this elevated CRH concentration. For example, placental CRH content is fourfold higher in placentas from women with preeclampsia than in those from normal pregnancies (Perkins, 1995).

Placental CRH is thought to play several roles in parturition regulation. It may enhance fetal cortisol production to provide positive feedback so that the placenta produces more CRH. Late in pregnancy—phase 2 or 3 of parturition—modification in the CRH receptor favors a switch from cAMP formation instead to increased myometrial cell calcium levels via protein kinase C activation (You, 2012). Oxytocin acts to attenuate CRH-stimulated accumulation of cAMP in myometrial tissue. CRH acts to augment myometrial contractile force in response to $PGF_{2\alpha}$ (Benedetto, 1994). Last, CRH stimulates fetal adrenal C_{19}-steroid synthesis, thereby increasing substrate for placental aromatization.

Some have proposed that the rising CRH level at the end of gestation reflects a *fetal-placental clock* (McLean, 1995). CRH concentrations vary greatly among women, and the rate of rise in maternal CRH levels is a more accurate predictor of pregnancy outcome than is a single measurement (Leung, 2001; McGrath, 2002). In this regard, the placenta and fetus, through endocrinological events, influence parturition timing at the end of normal gestation.

Fetal Lung Surfactant and Platelet-activating Factor

Surfactant protein A (SP-A) produced by the fetal lung is required for lung maturation. SP-A is expressed by the human amnion and decidua, is present in the amnionic fluid, and prompts signaling pathways in human myometrial cells (Garcia-Verdugo, 2008; Lee, 2010; Snegovskikh, 2011). The exact mechanisms by which SP-A activates myometrial contractility in women, however, remain to be clarified. One mode may be its effects on prostaglandins. Namely, SP-A selectively inhibits $PGF_{2\alpha}$ in the term decidua, but SP-A levels drop in the amnionic fluid at term (Chaiworapongsa, 2008). The fetal lung also makes the uterotonic agent platelet-activating factor (Frenkel, 1996; Toyoshima, 1995). This factor and SP-A play a role in fetal–maternal signaling for parturition (Gao, 2015).

Fetal Membrane Senescence

Toward the end of pregnancy, fetal membranes undergo cellular senescence (Menon, 2016). In human and animal fetal membranes, stretch and oxidative stress induce senescent fetal membrane to manifest a form of sterile inflammation termed senescent-associated secretory phenotype (SASP). This in turn propagates inflammatory signals that further weaken the fetal membrane and activate signals in the decidua and myometrium to initiate parturition. Thus, as the functional necessity of fetal membranes declines at term, they are able to promote signals that contribute to parturition initiation.

Fetal Anomalies and Delayed Parturition

Some evidence shows that pregnancies with markedly diminished estrogen production may be associated with prolonged gestation. These include women with inherited placental sulfatase deficiency and fetal anencephaly with adrenal hypoplasia. The broad range of gestational length seen with these disorders, however, calls into question the exact role of estrogen in human parturition initiation.

Some brain anomalies of the fetal calf, fetal lamb, and sometimes the human fetus delay the normal timing of parturition. In particular, the association between fetal anencephaly and prolonged gestation is well described (Rea, 1898; Malpas, 1933). Malpas concluded that the prolonged gestation was attributable to anomalous fetal brain-pituitary-adrenal function. Indeed, the adrenal glands of the anencephalic fetus are very small and, at term, may be only 5 to 10 percent as large as those of a normal fetus. This is caused by developmental failure of the fetal zone that normally accounts for most of fetal adrenal mass and production of C_{19}-steroid hormones (Chap. 5, p. 101). Such pregnancies are associated with delayed labor and suggest that the fetal adrenal glands are important for the timely onset of parturition.

Other fetal abnormalities that prevent or severely reduce the entry of fetal urine or lung secretions into amnionic fluid do not prolong human pregnancy. Examples are renal agenesis and pulmonary hypoplasia, respectively. Thus, a fetal signal through the paracrine arm of the fetal–maternal communication system does not appear to be mandated for parturition initiation.

PHASE 3: LABOR

This phase is synonymous with active labor, which is customarily divided into three stages (see Figure 21-4). The first stage begins when spaced uterine contractions of sufficient frequency, intensity, and duration are attained to bring about cervical thinning, termed *effacement*. Several uterotonins may be important to the success of this stage of active labor (see Fig. 21-5). These have been shown to stimulate smooth muscle contraction through G-protein coupling. This labor stage ends when the cervix is fully dilated—about 10 cm—to allow passage of the term-sized fetus. The first stage of labor, therefore, is the *stage of cervical effacement and dilation*. The second stage begins when cervical dilation is complete and ends with delivery. Thus, the second stage of labor is the *stage of fetal expulsion*. Last, the third stage begins immediately after delivery of the

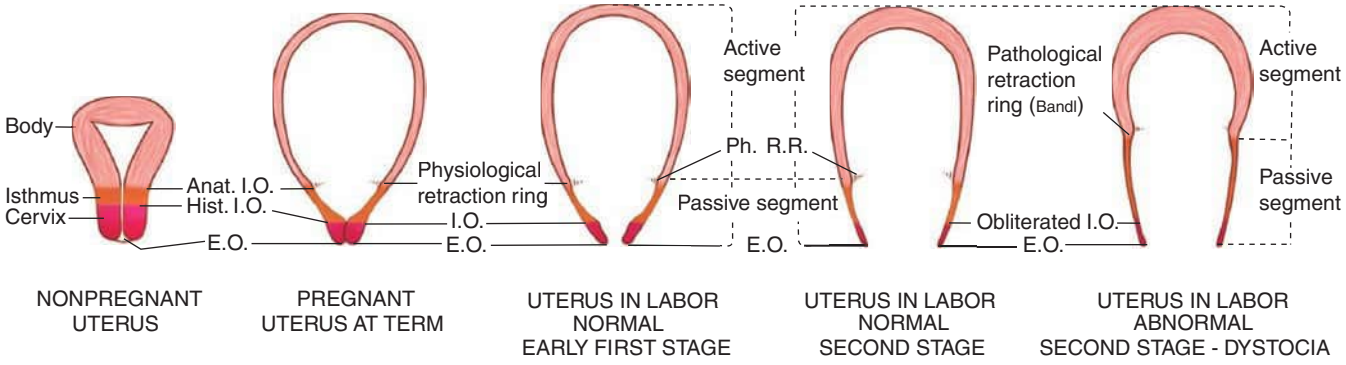


FIGURE 21-11 Sequence of development of the segments and rings in the uterus at term and in labor. Note comparison between the nonpregnant uterus, the uterus at term, and the uterus during labor. The passive lower uterine segment is derived from the isthmus, and the physiological retraction ring develops at the junction of the upper and lower uterine segments. The pathological retraction ring develops from the physiological ring. Anat. I.O. = anatomical internal os; E.O. = external os; Hist. I.O. = histological internal os; Ph.R.R. = physiological retraction ring.

fetus and ends with the delivery of the placenta. This stage of labor is the *stage of placental separation and expulsion*.

First Stage: Clinical Onset of Labor

Uterine Labor Contractions

In some women, forceful uterine contractions that effect delivery begin suddenly. In others, labor initiation is heralded by spontaneous release of a small amount of blood-tinged mucus from the vagina. This extrusion of the mucus plug that had previously filled the cervical canal during pregnancy is referred to as "bloody show." Its passage indicates that labor is already in progress or likely will ensue in hours to days.

Unique among physiological muscular contractions, those of uterine smooth muscle during labor are painful. Suggested causes are: (1) hypoxia of the contracted myometrium—such as that with angina pectoris; (2) compression of nerve ganglia in the cervix and lower uterus by contracted interlocking muscle bundles; (3) cervical stretching during dilation; and (4) stretching of the peritoneum overlying the fundus.

Of these, compression of nerve ganglia in the cervix and lower uterine segment by the contracting myometrium is an especially attractive hypothesis. Paracervical infiltration with local anesthetic usually produces appreciable pain relief with contractions (Chap. 25, p. 472). Uterine contractions are involuntary and, for the most part, independent of extrauterine control. Neural blockade from epidural analgesia does not diminish their frequency or intensity. In other examples, myometrial contractions in paraplegic women and in women after bilateral lumbar sympathectomy are normal but painless.

Mechanical stretching of the cervix enhances uterine activity in several species, including humans. This phenomenon is the *Ferguson reflex* (Ferguson, 1941). Its exact mechanism is unclear, and release of oxytocin has been suggested but not proven. Manipulation of the cervix and "stripping" the fetal membranes are associated with a rise in blood levels of prostaglandin $F_{2\alpha}$ metabolites.

The interval between contractions narrows gradually from approximately 10 minutes at the onset of first-stage labor to as little as 1 minute or less in the second stage. Periods of relaxation between contractions, however, are essential for fetal welfare. Unremitting contractions compromise uteroplacental blood flow sufficiently to cause fetal hypoxemia. In active-phase labor, the duration of each contraction ranges from 30 to 90 seconds and averages 1 minute. Contraction intensity varies appreciably during normal labor. Specifically, amnionic fluid pressures generated by contractions during spontaneous labor average 40 mm Hg, but vary from 20 to 60 mm Hg (Chap. 24, p. 462).

Distinct Lower and Upper Uterine Segments

During active labor, the anatomical uterine divisions that were initiated in phase 2 of parturition become increasingly evident (Figs. 21-11 and 21-12). By abdominal palpation, even before membrane rupture, the two segments can sometimes be

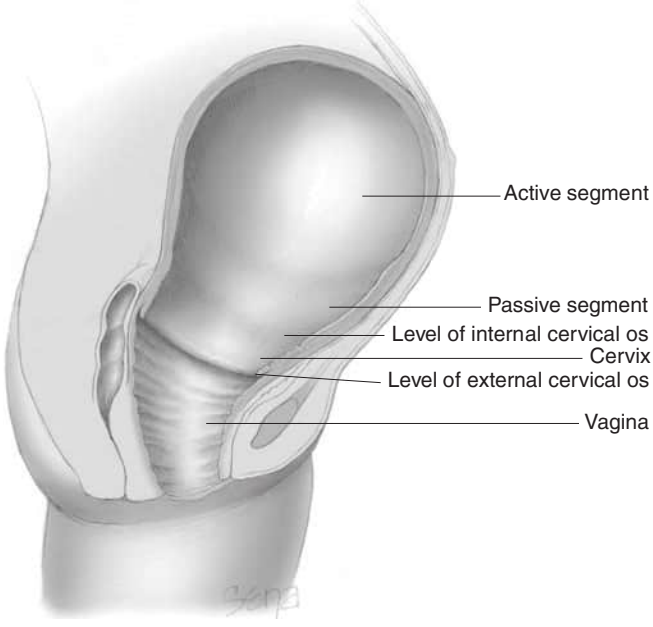


FIGURE 21-12 The uterus at the time of vaginal delivery. The active upper segment retracts around the presenting part as the fetus descends through the birth canal. In the passive lower segment, there is considerably less myometrial tone.

differentiated. The upper segment is firm during contractions, whereas the lower segment is softer, distended, and more passive. This mechanism is imperative because if the entire myometrium, including the lower uterine segment and cervix, were to contract simultaneously and with equal intensity, the net expulsive force would markedly decline. Thus, the upper segment contracts, retracts, and expels the fetus. In response to these contractions, the softened lower uterine segment and cervix dilate and thereby form a greatly expanded, thinned-out tube through which the fetus can pass.

The myometrium of the upper segment does not relax to its original length after contractions. Instead, it becomes relatively fixed at a shorter length. The upper active uterine segment contracts down on its diminishing contents, but myometrial tension remains constant. The net effect is to take up slack, thus maintaining the advantage gained in expulsion of the fetus. Concurrently, the uterine musculature is kept in firm contact with the uterine contents. As the consequence of retraction, each successive contraction commences where its predecessor left off. Thus, the upper part of the uterine cavity becomes slightly smaller with each successive contraction. Because of the successive shortening of the muscular fibers, the upper active segment becomes progressively thickened throughout first- and second-stage labor (see Fig. 21-11). This process continues and results in a tremendously thickened upper uterine segment immediately after delivery.

Clinically, it is important to understand that the phenomenon of upper segment retraction is contingent on a decrease in the volume of its contents. For this to happen, particularly early in labor when the entire uterus is virtually a closed sac with only minimal cervical dilation, the musculature of the lower segment must stretch. This permits a greater portion of the uterine contents to occupy the lower segment. The upper segment retracts only to the extent that the lower segment distends and the cervix dilates.

Relaxation of the lower uterine segment mirrors the same gradual progression of retraction. In the lower segment, successive lengthening of the fibers with labor is accompanied by thinning, normally to only a few millimeters in the thinnest part. With lower segment thinning and concomitant upper segment thickening, a boundary between the two is marked by a ridge on the inner uterine surface—the *physiological retraction ring*. When the thinning of the lower uterine segment is extreme, as in obstructed labor, the ring is prominent and forms a *pathological retraction ring*. This abnormal condition is also known as the *Bandl ring,* which is discussed further in Chapter 23 (p. 442).

Changes in Uterine Shape

Each contraction gradually elongates the ovoid uterine shape an estimated 5 to 10 cm and thereby narrows the horizontal diameter. This *fetal axis pressure* straightens the fetal vertebral column. It also presses the upper pole of the fetus firmly against the fundus, whereas the lower pole is thrust farther downward. With uterine lengthening, the longitudinal muscle fibers are drawn taut. As a result, the lower segment and cervix are the only parts of the uterus that are flexible, and these are pulled upward and around the lower pole of the fetus.

Ancillary Forces

After the cervix is dilated fully, the most important force in fetal expulsion is produced by maternal intraabdominal pressure. Contraction of the abdominal muscles simultaneously with forced respiratory efforts with the glottis closed is referred to as *pushing*. The force is similar to that with defecation, but the intensity usually is much greater. The importance of intraabdominal pressure is shown by the prolonged descent during labor in paraplegic women and in those with a dense epidural block.

Cervical Changes

As the result of contraction forces, two fundamental changes—effacement and dilation—occur in the ripened cervix. For an average-sized fetal head to pass through the cervix, it must completely or fully dilate to a diameter of approximately 10 cm. The fetus may not descend during cervical effacement. However, as the cervix dilates, the presenting fetal part typically does descend somewhat.

Cervical effacement is "obliteration" or "taking up" of the cervix. It is manifest clinically by shortening of the cervical canal from a length of approximately 3 cm to a mere circular orifice with almost paper-thin edges. The muscular fibers at the level of the internal cervical os are pulled upward, or "taken up," into the lower uterine segment. The condition of the external os remains temporarily unchanged (Fig. 21-13). Because of

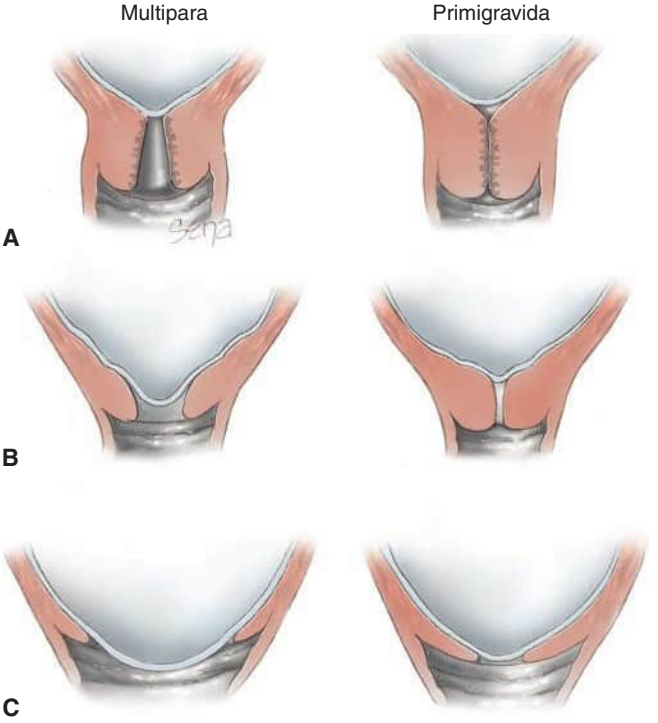


FIGURE 21-13 Schematic showing effacement and dilation. **A.** Before labor, the primigravid cervix is long and undilated in contrast to that of the multipara, which has dilation of the internal and external os. **B.** As effacement begins, the multiparous cervix shows more dilation and funneling of the internal os compared with the primigravid cervix. **C.** As complete effacement is achieved in the primigravid cervix, dilation is minimal. The reverse is true in the multipara.

growing myometrial activity during uterine preparedness for labor, appreciable effacement of a softened cervix sometimes is accomplished before active labor begins. Effacement causes expulsion of the mucous plug as the cervical canal is shortened.

Because the lower segment and cervix have less resistance during a contraction, a centrifugal pull is exerted on the cervix and creates *cervical dilation* (Fig. 21-14). As uterine contractions cause pressure on the membranes, the hydrostatic action of the amnionic sac in turn dilates the cervical canal like a wedge. The process of cervical effacement and dilation causes formation of the *forebag* of amnionic fluid. This is the leading portion of fluid and amnionic sac located in front of the presenting part. In the absence of intact membranes, the pressure of the presenting fetal part against the cervix and lower uterine segment is a similar wedge. Early rupture of the membranes does not retard cervical dilation so long as the presenting fetal part is positioned to exert pressure against the cervix and lower segment.

Referring back to Figure 21-4, recall that cervical dilation is divided into latent and active phases. The duration of the latent phase is more variable and sensitive to extraneous factors. For example, sedation may prolong the latent phase, and myometrial stimulation shortens it. The latent phase duration has little bearing on the subsequent course of labor, whereas the characteristics of the active phase are usually predictive of labor outcome. Normal and abnormal labor curves are fully described in Chapters 22 and 23.

Second Stage: Fetal Descent

In many nulliparas, engagement of the head is accomplished before labor begins. That said, the head may not descend further until late in labor. In the descent pattern of normal labor, a typical hyperbolic curve is formed when the station of the fetal head is plotted as a function of labor duration (see Fig. 21-4). *Station* describes descent of the fetal biparietal diameter in relation to a line drawn between maternal ischial spines (Chap. 22, p. 427). Active descent usually takes place after dilation has progressed for some time. During second-stage labor, the speed of descent is maximal and is maintained until the presenting part reaches the perineal floor (Friedman, 1978). In nulliparas, the presenting part typically descends slowly and steadily. In multiparas, however, descent may be rapid.

Pelvic Floor Changes

The birth canal is supported and functionally closed by the pelvic floor (Chap. 2, p. 19). The most important component of the floor is the levator ani muscle and the fibromuscular connective tissue that covers its upper and lower surfaces. The biomechanical properties of these structures and of the vaginal wall change markedly during parturition. These result from altered ECM structure or composition (Alperin, 2015; Lowder, 2007; Rahn, 2008).

In the first stage of labor, the membranes, when intact, and the fetal presenting part serve to dilate the upper vagina. The most marked change consists of stretching levator ani muscle fibers. This is accompanied by thinning of the central portion

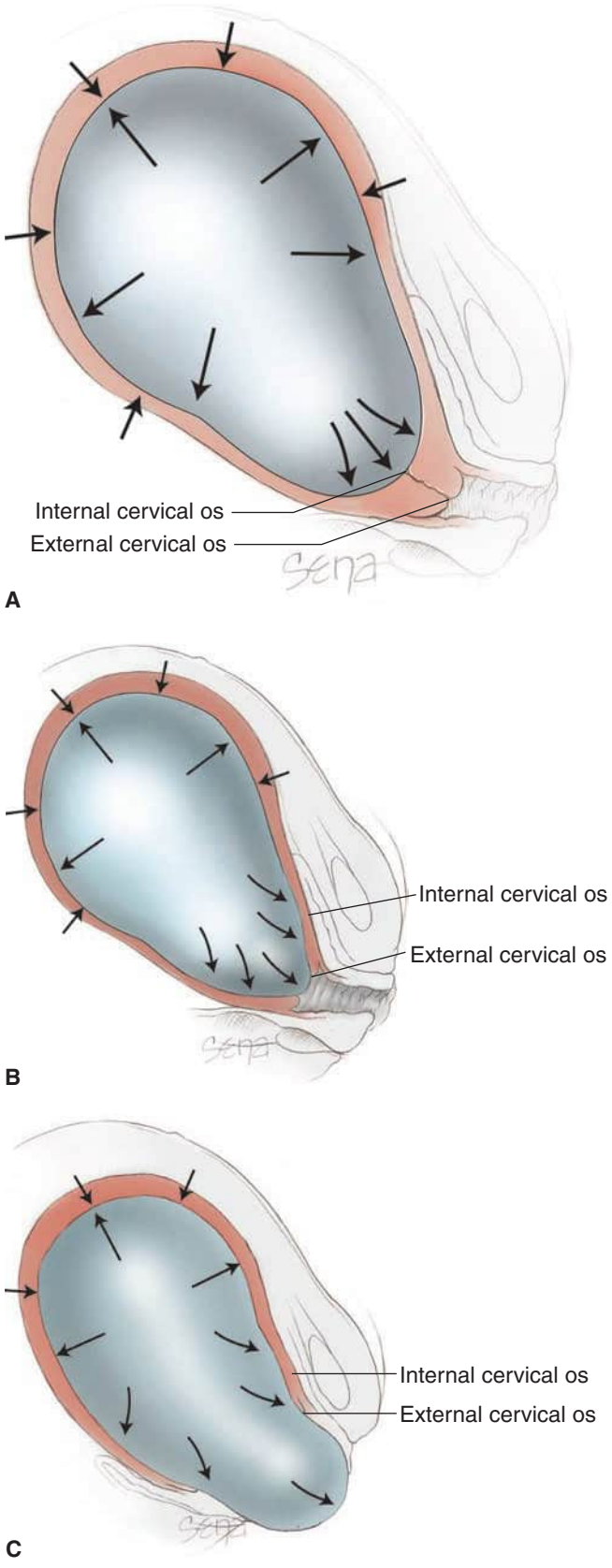


FIGURE 21-14 Hydrostatic action of membranes in effecting cervical effacement and dilation. With labor progression, note the changing relations of the internal and external os in **(A)**, **(B)**, and **(C)**. Although not shown in this diagram, with membrane rupture, the presenting part, applied to the cervix and the forming lower uterine segment, acts similarly.

of the perineum, which becomes transformed from a wedge-shaped, 5-cm-thick tissue mass to a thin, almost transparent membranous structure less than 1 cm thick. When the perineum is distended maximally, the anus becomes markedly dilated and presents an opening that varies from 2 to 3 cm in diameter and through which the anterior wall of the rectum bulges.

Third Stage: Delivery of Placenta and Membranes

This stage begins immediately after fetal delivery and involves separation and expulsion of the placenta and membranes. Normally, by the time the newborn is delivered, the uterine cavity is nearly obliterated and is an almost solid mass of muscle, several centimeters thick, above the thinner lower segment. The uterine fundus now lies just below the level of the umbilicus.

This sudden diminution in uterine size is inevitably accompanied by a decrease in the area of the placental implantation site (Fig. 21-15). For the placenta to accommodate itself to this reduced area, it thickens, but because of limited placental elasticity, it buckles. The resulting tension pulls the weakest layer—decidua spongiosa—from that site. Thus, placental separation follows the disproportion created between the relatively unchanged placental size and the reduced implantation site size.

Cleavage of the placenta is aided greatly by the loose structure of the spongy decidua. As detachment proceeds, a hematoma forms between the separating placenta and the adjacent decidua, which remains attached to the myometrium. The hematoma is usually the result rather than the cause of the separation, because in some cases bleeding is negligible.

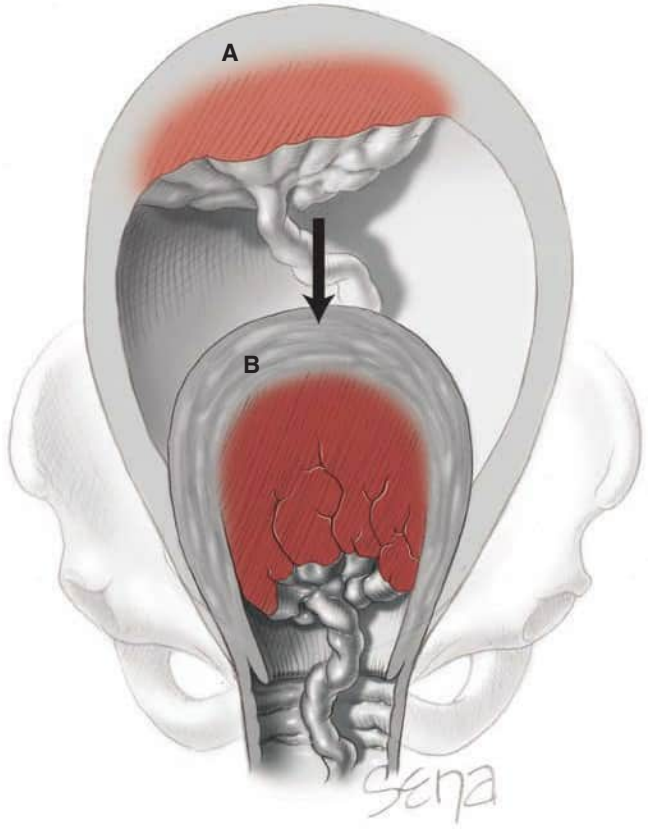


FIGURE 21-15 Diminution in size of the placental site after birth of the newborn. **A.** Spatial relations before birth. **B.** Placental spatial relations after birth.

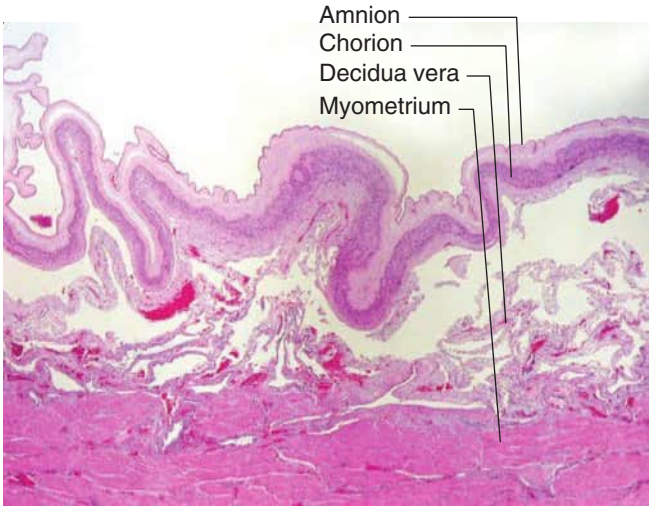


FIGURE 21-16 Postpartum, membranes are thrown up into folds as the uterine cavity decreases in size. (Reproduced with permission from Dr. Kelley S. Carrick.)

The great decline in uterine cavity surface area simultaneously throws the fetal membranes—the amniochorion and the parietal decidua—into innumerable folds (Fig. 21-16). Membranes usually remain in situ until placental separation is nearly completed. These are then peeled off the uterine wall, partly by further contraction of the myometrium and partly by traction that is exerted by the separated placenta as it descends during expulsion.

After the placenta has detached, it can be expelled by increased abdominal pressure. Completion of the third stage is also accomplished by alternately compressing and elevating the fundus, while exerting minimal traction on the umbilical cord. The retroplacental hematoma either follows the placenta or is found within the inverted sac formed by the membranes. In this process, known as the *Schultze mechanism* of placental expulsion, blood from the placental site pours into the membrane sac and does not escape externally until after extrusion of the placenta. In the other form of placental extrusion, known as the *Duncan mechanism*, the placenta separates first at the periphery and blood collects between the membranes and the uterine wall and escapes from the vagina. In this circumstance, the placenta descends sideways, and its maternal surface appears first.

UTEROTONINS IN PARTURITION PHASE 3

Oxytocin

This nanopeptide is synthesized in the magnocellular neurons of the supraoptic and paraventricular neurons. The prohormone is transported with its carrier protein, neurophysin, along the axons to the neural lobe of the posterior pituitary gland in membrane-bound vesicles for storage and later release. The prohormone is converted enzymatically to oxytocin during transport (Gainer, 1988; Leake, 1990).

Oxytocin—literally, *quick birth*—was the first uterotonin to be implicated in parturition initiation. Support for this role includes: (1) oxytocin receptor numbers strikingly rising in myometrial and decidual tissues near the end of gestation; (2) oxytocin acting on decidual tissue to promote prostaglandin release; and (3) oxytocin synthesis directly in decidual and extraembryonic fetal tissues and in the placenta (Chibbar, 1993; Zingg, 1995). Moreover, abundant data support oxytocin's important role during second-stage labor and in the puerperium, which is phase 4 of parturition. Specifically, maternal serum oxytocin levels are elevated: (1) during second-stage labor, which is the end of phase 3 of parturition; (2) in the early puerperium; and (3) during breastfeeding (Nissen, 1995). Immediately after delivery of the fetus and placenta, which completes parturition phase 3, firm and persistent uterine contractions induced by oxytocin are essential to prevent postpartum hemorrhage.

Prostaglandins

Prostaglandins play a critical role in phase 3 of parturition (MacDonald, 1993). First, levels of prostaglandins—or their metabolites—in amnionic fluid, maternal plasma, and maternal urine are increased during labor. Second, receptors for PGE_2 and $PGF_{2\alpha}$ are expressed in the uterus and cervix. Thus, if these tissues are exposed to prostaglandins, they will respond. Third, treatment of pregnant women with prostaglandins, by any of several administration routes, causes abortion or labor at all gestational ages. Moreover, administration of prostaglandin H synthase type 2 inhibitors to pregnant women will delay spontaneous labor onset and sometimes arrest preterm labor (Loudon, 2003).

During labor, prostaglandin production within the myometrium and decidua is an efficient mechanism of activating contractions. For example, prostaglandin synthesis is high and unchanging in the decidua during phase 2 and 3 of parturition. Moreover, the receptor level for $PGF_{2\alpha}$ is augmented in the decidua at term, and this increase most likely is the regulatory step in prostaglandin action in the uterus.

The fetal membranes and placenta also produce prostaglandins. Primarily PGE_2, but also $PGF_{2\alpha}$, are detected in amnionic fluid at all gestational ages. As the fetus grows, prostaglandin levels in the amnionic fluid rise gradually. Their greatest elevation in concentration within amnionic fluid, however, is demonstrable after labor begins. These higher levels likely result as the cervix dilates and exposes decidual tissue (Fig. 21-17). These higher levels in the forebag, compared with those in the upper compartment, are believed to follow an inflammatory response that signals the events leading to active labor. Together, the rise in cytokine and prostaglandin concentrations further degrade the ECM, thus weakening fetal membranes.

Endothelin 1

The endothelins are a family of 21-amino-acid peptides that powerfully induce myometrial contraction (Word, 1990). The endothelin A receptor is preferentially expressed in smooth muscle, and when activated, it effects a rise in intracellular calcium.

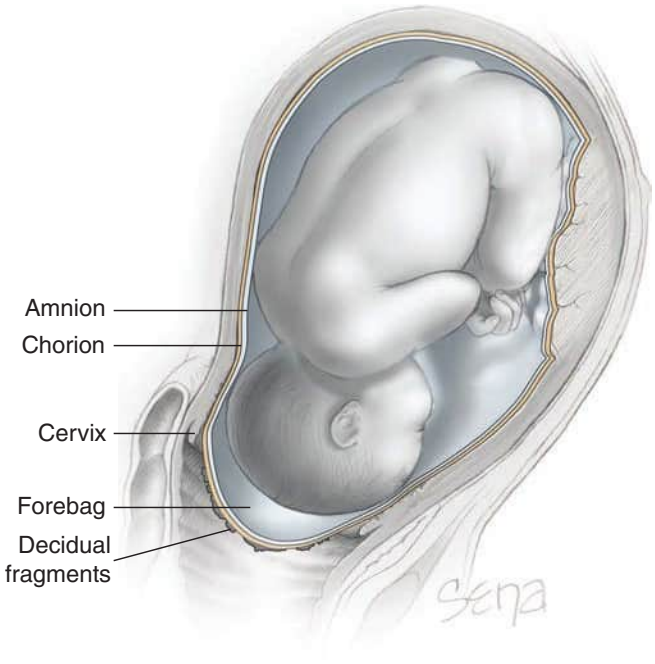


FIGURE 21-17 Sagittal view of the exposed forebag and attached decidual fragments after cervical dilation during labor. (Redrawn from MacDonald PC, Casey ML: Preterm birth. Sci Am 3:42, 1996.)

Endothelin 1 is produced in myometrium of term gestations and is able to induce synthesis of other contractile factors such as prostaglandins and inflammatory mediators (Momohara, 2004; Sutcliffe, 2009). The requirement of endothelin 1 in normal parturition physiology remains to be established.

Angiotensin II

Modulation of uteroplacental blood flow is regulated by angiotensin II, a potent vasoconstrictor. Although, in pregnancy, circulating levels of angiotensin II are increased, vascular resistance is reduced and vasodilation is enhanced. Two angiotensin II receptors are expressed in the uterus—AT_1R and AT_2R. In nonpregnant women, the AT_1R receptor predominates, but the AT_2R receptor is preferentially expressed in gravidas (Cox, 1993). During normotensive pregnancy, AT_2R-mediated effects on vascular smooth muscle lead to vasodilation, which contributes to the pregnancy-associated rise in uterine arterial blood flow. Decreased AT_2R expression is associated with preeclamptic pregnancies (Mishra, 2018; Rosenfeld, 2012) (Chap. 4, p. 65).

PHASE 4: THE PUERPERIUM

Immediately and for about an hour after delivery, the myometrium remains persistently contracted. This directly compresses large uterine vessels and allows thrombosis of their lumens to prevent hemorrhage. This is typically augmented by endogenous and pharmacological uterotonic agents (Chap. 27, p. 507).

Uterine involution and cervical repair are prompt remodeling processes that restore these organs to the nonpregnant state. These protect the reproductive tract from invasion by commensal microorganisms and restore endometrial responsiveness to normal hormonal cyclicity.

During the early puerperium, lactogenesis and milk let-down begin in mammary glands (Chap. 36, p. 639). Reinstitution of ovulation signals preparation for the next pregnancy. Ovulation generally occurs within 4 to 6 weeks after birth. However, it is dependent on the duration of breastfeeding and lactation-induced, prolactin-mediated anovulation and amenorrhea.

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CHAPTER 22

Normal Labor

Labor is the process that leads to childbirth. It begins with the onset of regular uterine contractions and ends with delivery of the newborn and expulsion of the placenta. Pregnancy and birth are physiological processes. Thus, labor and delivery should be considered normal for most women.

FETAL ORIENTATION

Fetal Lie

Fetal position within the birth canal is critical to labor progress and to the delivery route. It should be determined in early labor, and sonography can be implemented for unclear cases. Important relationships include fetal lie, presentation, attitude, and position.

Of these, *fetal lie* describes the relationship of the fetal long axis to that of the mother. In more than 99 percent of labors at term, the fetal lie is *longitudinal*. A *transverse lie* is less frequent. Occasionally, the fetal and maternal axes may cross at a 45-degree angle to form an *oblique lie*. This is unstable and becomes longitudinal or transverse during labor.

Fetal Presentation

The *presenting part* is the portion of the fetal body either within or in closest proximity to the birth canal. It usually can be felt through the cervix on vaginal examination. In longitudinal lies, the presenting part is either the fetal head or the breech, creating cephalic and breech presentations, respectively. When the fetus lies with the long axis transversely, the shoulder is considered the presenting part.

Cephalic presentations are subclassified according to the relationship between the head and body of the fetus (Fig. 22-1). Ordinarily, the head is flexed sharply so that the chin contacts the thorax. The occipital fontanel is the presenting part, and this presentation is referred to as a *vertex* or *occiput presentation*. Much less often, the fetal neck may be sharply extended so that the occiput and back come into contact, and the face is foremost in the birth canal—*face presentation*. The fetal head may assume a position between these extremes. When the neck is only partly flexed, the anterior (large) fontanel may present—*sinciput presentation*. When the neck is only partially extended, the brow may emerge—*brow presentation*. These latter two are usually transient. As labor progresses, sinciput and brow presentations almost always convert into occiput or face presentations by neck flexion or extension, respectively. If not, dystocia can develop (Chap. 23, p. 441).

The fetus at term usually presents occiput rather than breech. Although the fetal head at term is slightly larger than the breech, the entire *podalic pole* of the fetus—that is, the breech and extremities—is bulkier and more mobile than the cephalic pole. The *cephalic pole* is composed of the fetal head only. Logically, the fetus orients its polarity to make use of the roomier fundus for its bulkier and more mobile podalic pole. The breech presentation rate drops with gestational age, but 2

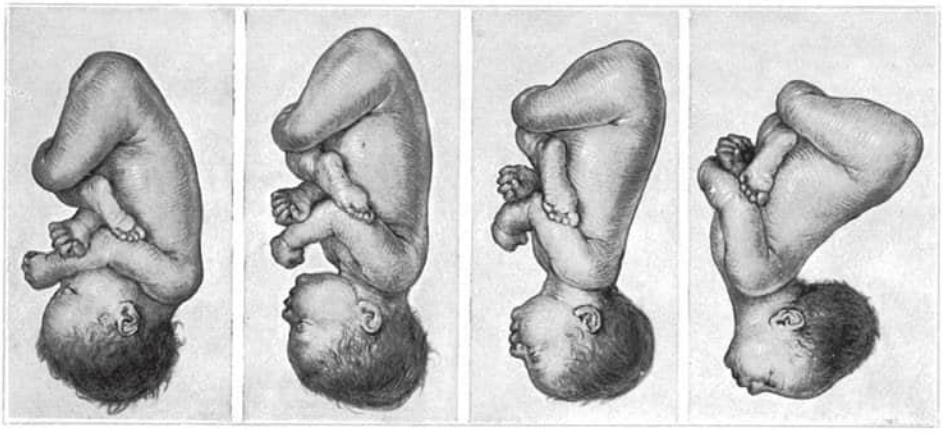


FIGURE 22-1 Longitudinal lie, cephalic presentation. Differences in attitude of the fetal body in **(A)** occiput, **(B)** sinciput, **(C)** brow, and **(D)** face presentations. Note changes in fetal attitude as the fetal head becomes less flexed.

to 3 percent of singletons are breech at delivery (Bin, 2016; Toijonen, 2020). The three general breech configurations are *frank*, *complete*, and *footling presentations*. Management of the breech presenting fetus and of those with transverse lie is found in Chapters 28 and 23, respectively.

Fetal Attitude

In the later months of pregnancy, the fetus assumes a characteristic posture described as attitude or habitus. As a rule, the fetus forms an ovoid mass that corresponds roughly to the shape of the uterine cavity (see Fig. 22-1A). The fetus becomes folded upon itself to create a convex back. The head is sharply flexed, the chin nearly contacts with the chest, the thighs are flexed over the abdomen, and the legs bend at the knee. In cephalic presentations, the arms usually lie across the thorax or parallel to the sides. The umbilical cord fills the space between the extremities. This posture results from fetal growth and accommodation to the uterine cavity.

Exceptions form as the fetal head becomes progressively more extended from occiput to face presentations. This results in a progressive change in fetal attitude from a convex (flexed) to a concave (extended) contour of the vertebral column. This progression is seen in Figure 22-1, panels B through D.

Fetal Position

Position refers to the relationship of a defined portion of the fetal presenting part to either the right or left side of the birth canal. The fetal occiput, chin (mentum), and sacrum are the defined landmarks in occiput, face, and breech presentations, respectively. Because the defined presenting part may be on either the mother's left or right side, possible designations are left and right occipital (LO and RO), left and right mental (LM and RM), and left and right sacral (LS and RS). Further, the relationship of the defined landmark to the anterior (A), transverse (T), or posterior (P) portion of the maternal pelvis is considered (Fig. 22-2).

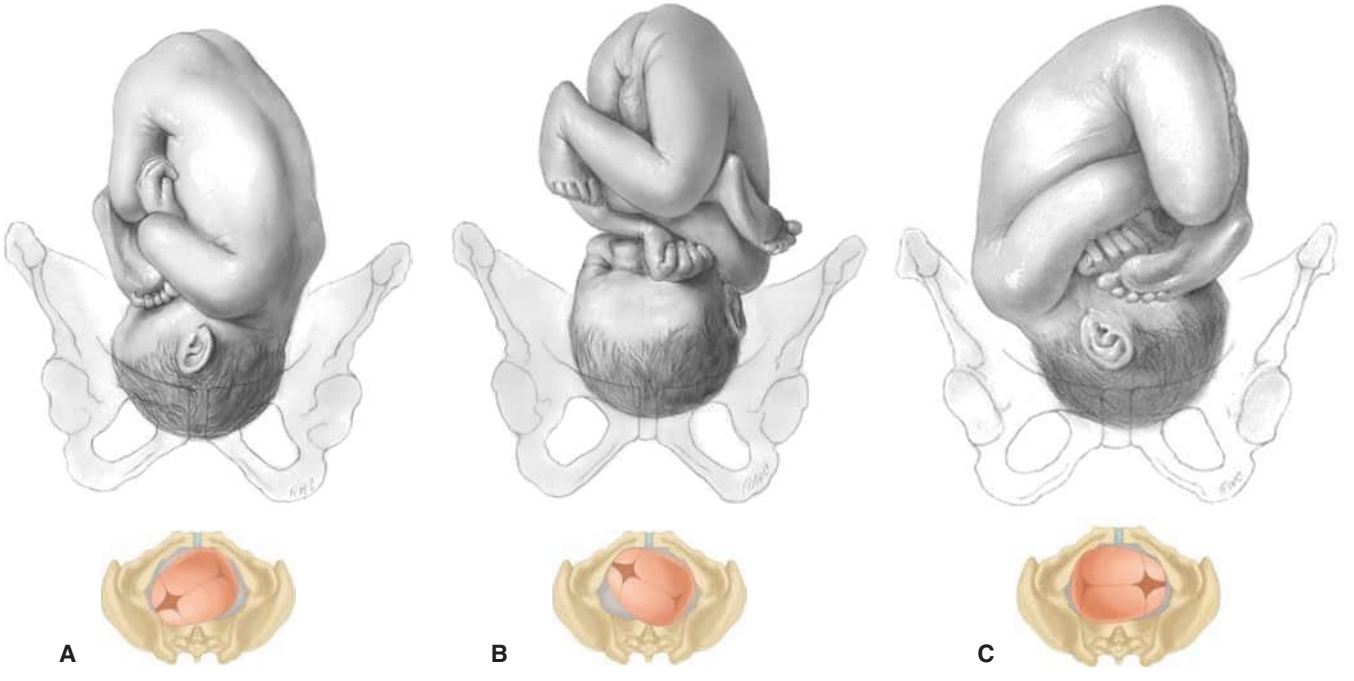
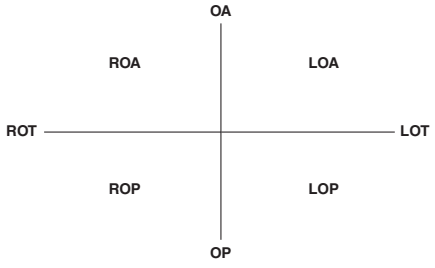


FIGURE 22-2 Longitudinal lie, occiput presentation. **A.** Left occiput anterior (LOA) position. **B.** Left occiput posterior (LOP) position. **C.** Right occiput transverse (ROT) position.

Thus, in an occiput presentation, the presentation and position may be abbreviated in clockwise fashion as shown.



In shoulder presentations, the acromion process of the scapula is the portion of the fetus arbitrarily chosen for its orientation to the mother's right or left side. In addition, the back may be directed anteriorly or posteriorly and also superiorly or inferiorly. Thus, it is customary to further distinguish right or left varieties as dorsoanterior and dorsoposterior (Fig. 23-7, p. 442). Another term used is *transverse lie*, with *back up* or *back down*, which is clinically important when deciding incision type for cesarean delivery.

Diagnosis

To diagnose fetal presentation and position, Leopold maneuvers, vaginal examination, and sonography are primary tools. First, abdominal examination can be conducted systematically employing the four maneuvers described by Leopold in 1894 (Fig. 22-3). The mother lies supine and comfortably positioned with her abdomen bared. Leopold maneuvers can be performed throughout the latter months of pregnancy and during and between the contractions of labor. These may be difficult if not impossible to perform and interpret if the patient is obese, if amnionic fluid volume is excessive, or if the placenta is anteriorly implanted.

The first maneuver assesses the uterine fundus. It permits identification of fetal lie and presentation. The breech feels large and nodular, whereas the head is large, hard, and round.

The second maneuver can help define the presenting part's position. Palms are placed on either side of the maternal abdomen, and gentle but deep pressure is exerted. On one side, a hard, resistant structure is felt—the back. On the other, numerous small, irregular, mobile parts are felt—the fetal extremities. These may move in response to palpation. The back indicates the side on which the occiput lies. In occiput anterior positions, the convex back is felt. In occiput posterior positions, nodular extremity parts are appreciated.

The third maneuver aids confirmation of fetal presentation. The thumb and fingers of one hand grasp the lower portion of the maternal abdomen just above the symphysis pubis. If the presenting part is not engaged, a movable mass will be felt, usually the head. The differentiation between head and breech is made as in the first maneuver.

The fourth maneuver helps determine the degree of descent. The examiner faces the mother's feet, and the fingertips of both hands are positioned on either side of the presenting part. They exert inward pressure and then slide caudad along the axis of the pelvic inlet. In many instances, when the head has descended into the pelvis, the anterior shoulder or the space created by the neck may be differentiated readily from the hard head.

At least in the past, experienced clinicians have accurately identified fetal malpresentation using Leopold maneuvers with a high sensitivity—88 percent, specificity—94 percent, positive predictive value—74 percent, and negative predictive value—97 percent (Lydon-Rochelle, 1993). With experience, it is possible to estimate the size of the fetus with these maneuvers (Field, 1995). However, and especially with an obese woman, estimates by palpation and actual birth weights often correlate poorly (Fox, 2009; Preyer, 2019).

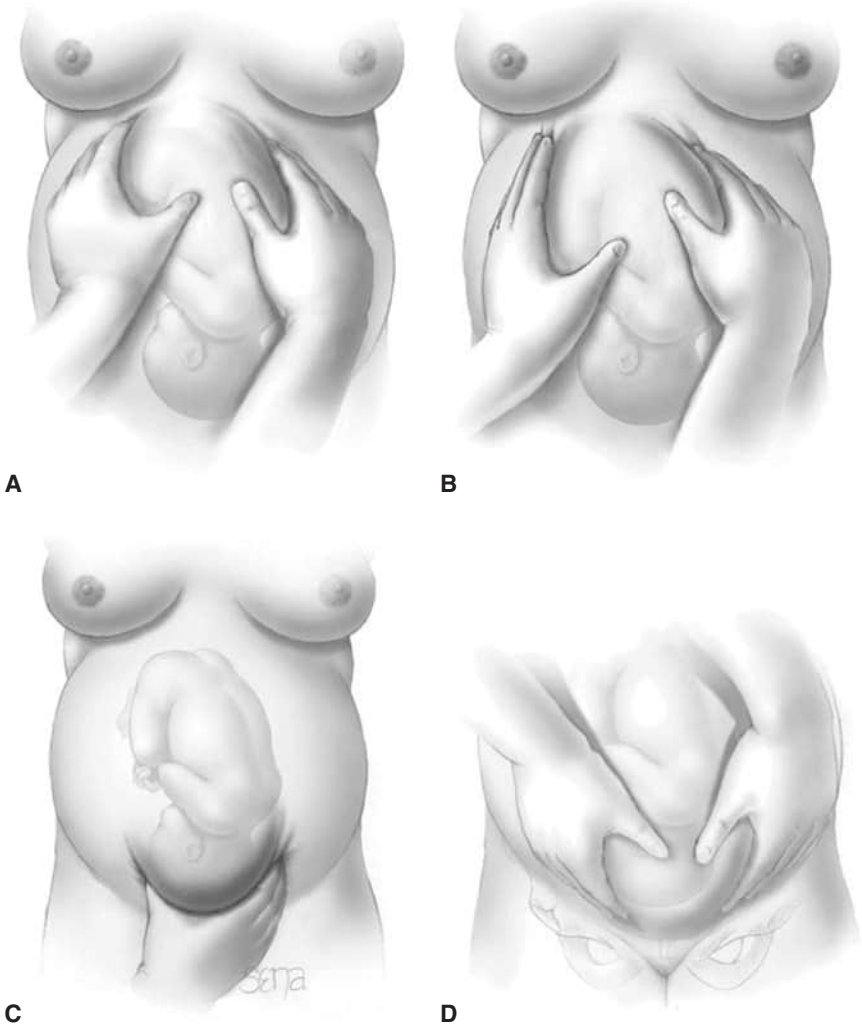


FIGURE 22-3 Leopold maneuvers **(A-D)** performed in fetus with a longitudinal lie and left occiput anterior (LOA) position.

Vaginal examination complements Leopold maneuvers. Before labor, the diagnosis of fetal presentation and position by vaginal examination is challenging because the presenting part must be palpated through a closed cervix and lower uterine segment. However, with labor and cervical dilation, cephalic presentations and their positions are recognized by palpation of the various fetal sutures and fontanels (Fig. 29-1, p. 534). Palpation of facial features signals a face presentation, whereas digital delineation of the fetal sacrum and perineum suggests breech presentation. With a transverse lie, ribs, scapula, or clavicle may be identified. Sonography is used to confirm suspected abnormal fetal presentation or lie.

Sonography can also help clarify fetal position. For the occiput presenting fetus, a transducer is placed transversely on the lower maternal abdomen and moved toward the symphysis. In a fetus positioned occiput anterior, its spine is identified anteriorly and followed to its union with its occiput. The angle between the two is wide and increases as the head flexes and descends into the maternal pelvis. In occiput posterior positions, fetal orbits and nasal bridge lie anteriorly (Bellussi, 2017). Compared with digital interrogation, sonography for fetal head position determination during second-stage labor is more accurate (Ramphul, 2014; Wiafe, 2016).

MECHANISMS OF LABOR

Positional changes of the presenting part are needed for the fetus to navigate through the pelvic canal. Called the mechanisms of labor or *cardinal movements of labor*, these are engagement, descent, flexion, internal rotation, extension, external rotation, and expulsion. During labor, these movements show great temporal overlap. For example, as part of engagement, the head both flexes and descends (Fig. 22-4). Concurrently, uterine contractions effect important modifications in fetal attitude, especially after the head has descended into the pelvis. These changes consist mainly of fetal straightening, loss of dorsal convexity, and closer application of the extremities to the body. As a result, the fetal ovoid is transformed into a cylinder, with the smallest possible cross section typically passing through the birth canal.

Engagement

In an occiput presentation, passage of the biparietal diameter through the pelvic inlet defines *engagement*. The fetal head may engage during the last few weeks of pregnancy or not until after labor commences. In many multiparas and some nulliparas, the fetal head is freely movable above the pelvic inlet at labor onset and is often referred to as "floating." In one study of 5341 nulliparas, lack of fetal head engagement before labor onset did not affect vaginal delivery rates in either spontaneous or induced labor (Segel, 2012).

In most cases, the vertex enters the pelvis with the sagittal suture lying in the transverse pelvic diameter. Left occiput transverse (LOT) position is slightly more common than right occiput transverse (ROT) position (Caldwell, 1934). However, the sagittal suture may not lie exactly midway between the symphysis and the sacral promontory. The sagittal suture frequently is deflected off the midline, either posteriorly toward the promontory or anteriorly toward the symphysis (Fig. 22-5). Such lateral deflection to a more anterior or posterior position in the pelvis is called *asynclitism*. If the sagittal suture approaches the sacral promontory, more of the anterior parietal bone presents itself to the examining fingers, and the condition is called *anterior asynclitism*. If, however, the sagittal suture lies close to the symphysis, more of the posterior parietal bone will present, and the condition is called *posterior asynclitism*. With extreme asynclitism, an ear may be palpable.

Moderate degrees of asynclitism are the rule in normal labor. Successive fetal head shifting from posterior to anterior asynclitism aids descent. However, if severe, the condition is a common reason for cephalopelvic disproportion even with an otherwise normal-sized pelvis.

Descent

This movement is the first requisite for vaginal birth. In nulliparas, engagement may take place before labor onset, and further descent may not follow until second-stage labor. In multiparas, descent usually begins with engagement. Descent stems from one or more of three forces: (1) direct myometrial pressure of the fundus upon the breech with contractions, (2) bearing-down efforts of maternal abdominal muscles, and (3) extension and straightening of the fetal body.

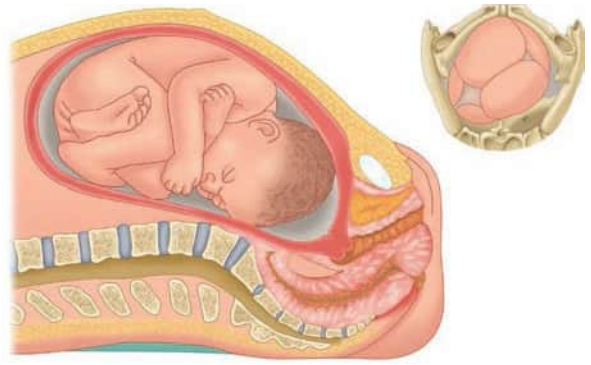
Flexion

As soon as the descending head meets resistance, whether from the cervix, pelvic walls, or pelvic floor, it normally flexes. With this movement, the chin draws closer to the fetal thorax, and the appreciably shorter suboccipitobregmatic diameter replaces the longer occipitofrontal diameter (Fig. 29-1, p. 534). This is an essential requisite for descent because it allows the smallest head diameter to progress.

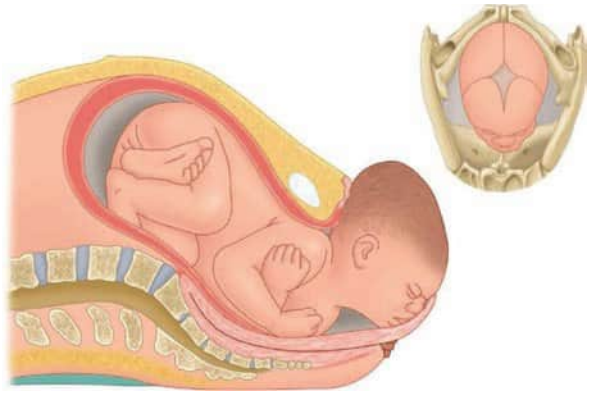
Internal Rotation

This movement turns the occiput gradually away from the transverse axis. Usually the occiput rotates anteriorly toward the symphysis pubis. LOT positions transition to left occiput anterior (LOA) positions (Fig. 22-6). ROT positions rotate to right occiput anterior (ROA) positions. Less commonly, the head may rotate posteriorly toward the hollow of the sacrum to generate occiput posterior positions. Internal rotation is essential for completion of labor, except when the fetus is unusually small.

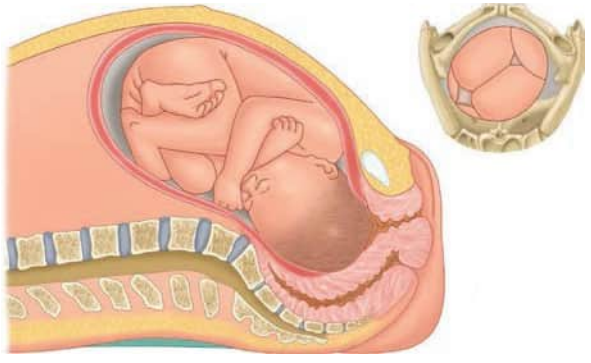
Calkins (1939) studied more than 5000 women in labor to ascertain the time of internal rotation. He concluded that in approximately two thirds, internal rotation is completed by the time the head reaches the pelvic floor; in about another fourth, internal rotation is completed shortly after the head reaches the pelvic floor; and in the remaining 5 percent, rotation does not take place. When the head fails to turn until reaching the pelvic floor, it typically rotates during the next one or two contractions



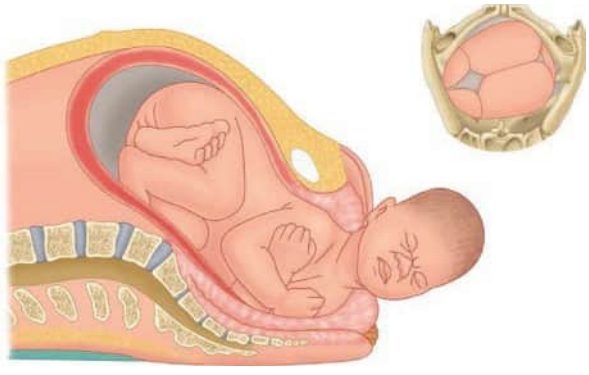
1. Head floating, before engagement



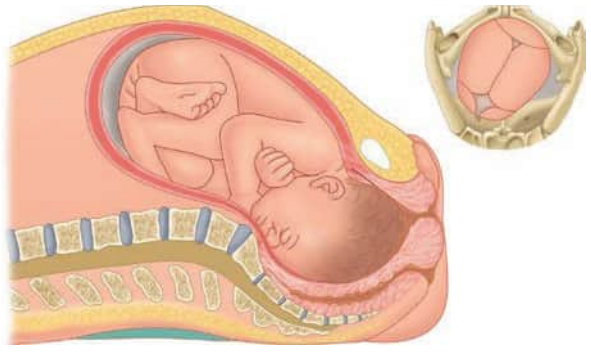
5. Complete extension



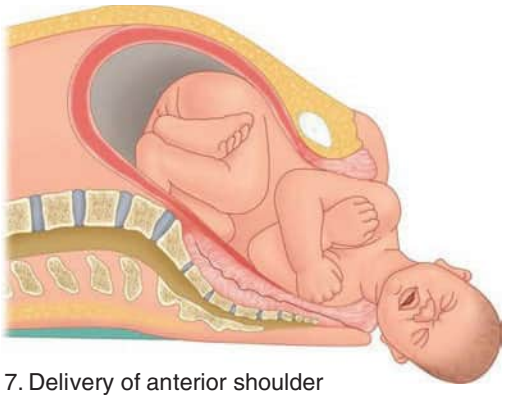
2. Engagement, descent, flexion



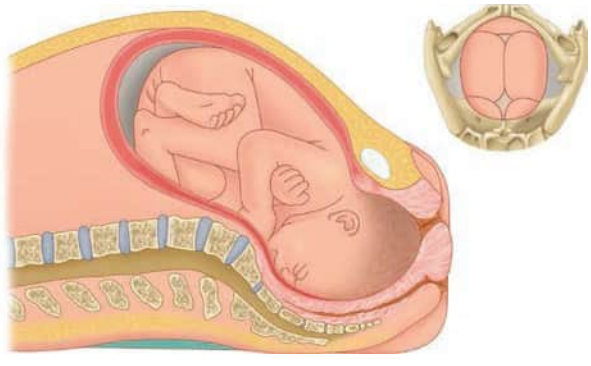
6. Restitution (external rotation)



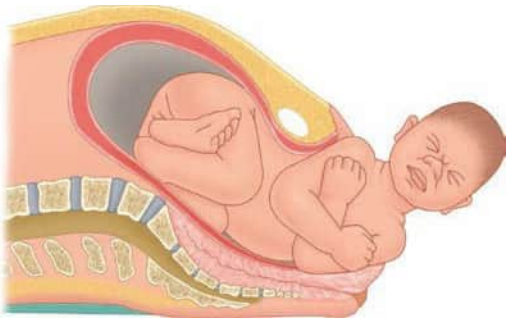
3. Further descent, internal rotation



7. Delivery of anterior shoulder



4. Complete rotation, beginning extension



8. Delivery of posterior shoulder

FIGURE 22-4 Cardinal movements of labor and delivery from a left occiput anterior position.

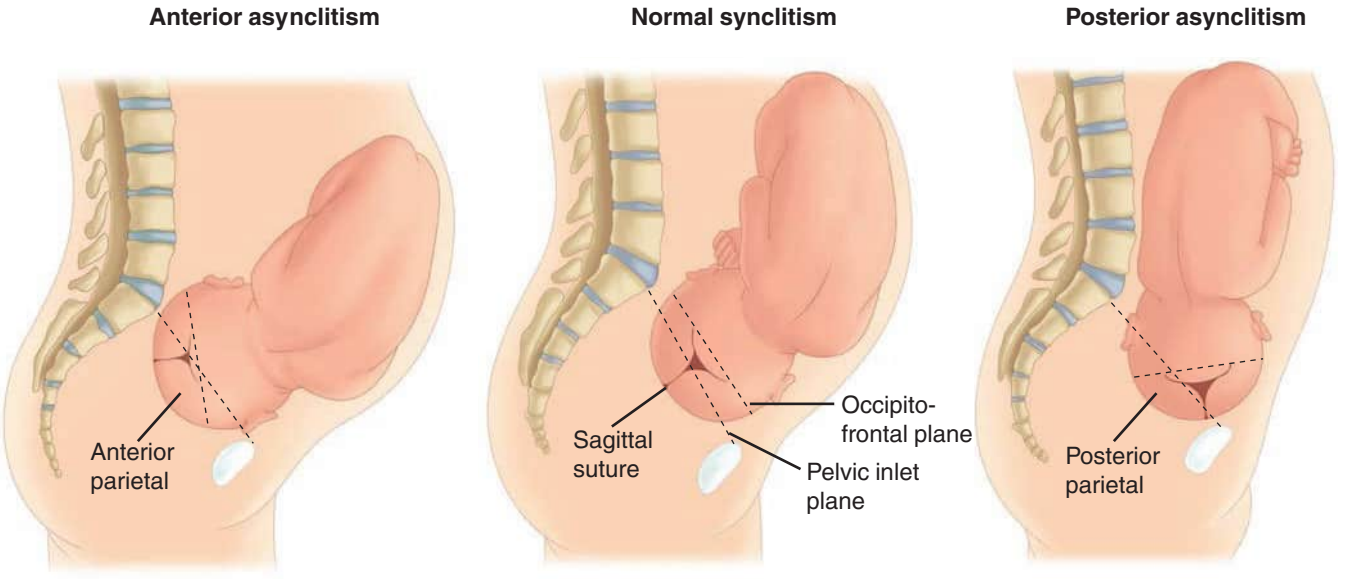


FIGURE 22-5 Synclitism and asynclitism.

in multiparas. In nulliparas, rotation usually occurs during the next three to five contractions.

Extension

After internal rotation, the sharply flexed head reaches the vulva and undergoes extension. If the sharply flexed head, on reaching the pelvic floor, did not extend but was driven farther downward, it would impinge on the posterior portion of the perineum and would eventually be forced through the perineal tissues. When the head presses on the pelvic floor, however, two forces come into play. The first force, exerted by the uterus, acts more posteriorly, and the second, supplied by the resistant pelvic floor and the symphysis, acts more anteriorly. The resultant vector is in the

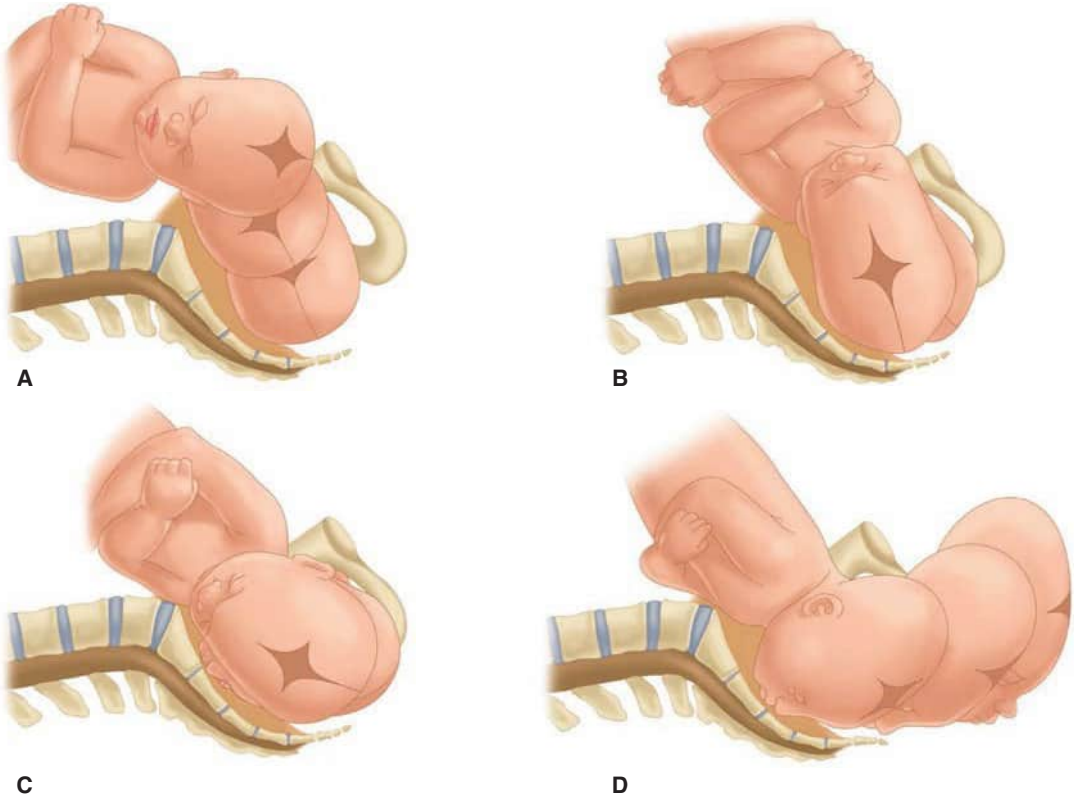


FIGURE 22-6 Mechanisms of labor for the left occiput transverse position, lateral view. **A.** Engagement with posterior asynclitism at the pelvic brim. During descent, the sagittal suture is then deflected toward the sacrum. **B.**This leads to anterior asynclitism. This corrects during additional descent **C.** Internal rotation moves the occiput toward the symphysis. Farther simultaneous descent. **D.** Additional descent with extension of the neck.

direction of the vulvar opening, thereby causing head extension. This brings the base of the occiput into direct contact with the inferior margin of the symphysis pubis (see Fig. 22-6).

With progressive distention of the perineum and vaginal opening, an increasingly large portion of the occiput gradually appears. The head is born as the occiput, anterior fontanel, brow, nose, mouth, and chin pass successively over the perineal body. Immediately after its delivery, the head drops so that the chin lies over the maternal anus.

External Rotation

The delivered head next undergoes *restitution* (see Fig. 22-4). If the occiput was originally directed toward the maternal left, it rotates toward the mother's left ischial tuberosity. If it was originally directed toward the right, the occiput rotates to the right. With restitution, the head reaches a transverse position. The fetal body aligns its bisacromial diameter, which is the distance across the shoulders, with the anteroposterior diameter of the pelvic outlet. Thus, one shoulder is anterior behind the symphysis and the other is posterior.

Expulsion

Almost immediately after external rotation, the anterior shoulder appears under the symphysis pubis, and the perineum soon becomes distended by the posterior shoulder. After delivery of the shoulders, the rest of the body quickly passes. If the anterior shoulder tightly wedges behind the symphysis, *shoulder dystocia* is diagnosed and is described in Chapter 27 (p. 501).

Occiput Posterior Position

In approximately 20 percent of labors, the fetus enters the pelvis in an *occiput posterior (OP)* position (Caldwell, 1934). It appears likely from radiographic evidence that posterior positions are more often associated with a narrow forepelvis (Gardberg, 1994a). Effective contractions, adequate head flexion, and average fetal size together permit most posteriorly positioned occiputs to rotate anteriorly toward the symphysis promptly as soon as they reach the pelvic floor. In perhaps 5 to 10 percent of cases, however, rotation may be incomplete or may not take place at all, especially if the fetus is large (Gardberg, 1994b). Poor contractions, faulty head flexion, or epidural analgesia, which diminishes maternal muscular pushing and relaxes pelvic floor muscles, may predispose to incomplete rotation. If rotation is incomplete, *transverse arrest* may result. If no rotation toward the symphysis proceeds, the occiput may remain in the direct OP position, a condition known as *persistent occiput posterior*. Both can lead to dystocia and cesarean delivery. Risk factors and labor management of a persistent OP position are found in Chapter 27 (p. 500). Techniques to manually rotate from OP to OA positions are illustrated in Chapter 29 (p. 540).

Fetal Head Shape Changes

In occiput presentations, labor forces alter fetal head shape. In prolonged labors before complete cervical dilation, the portion of the fetal scalp immediately over the cervical os becomes edematous. This swelling is called *caput succedaneum*. It usually attains a thickness of only a few millimeters, but in prolonged labors it may be sufficiently extensive to prevent differentiation of the various sutures and fontanels. More commonly, the caput is formed when the head is in the lower portion of the birth canal and frequently only after the resistance of a rigid vaginal outlet is encountered. Because it develops over the most dependent area of the head, one may deduce the original fetal head position. In cases of marked asynclitism and dystocia, the caput succedaneum may form far from the sagittal midline (Fig. 22-7).

Molding refers to changes in the bony fetal head shape as a result of external compressive forces (see Fig. 22-7B). Possibly related to Braxton Hicks contractions, some molding develops before labor. Despite these shape changes, most studies indicate that the parietal bones seldom overlap. A "locking" mechanism

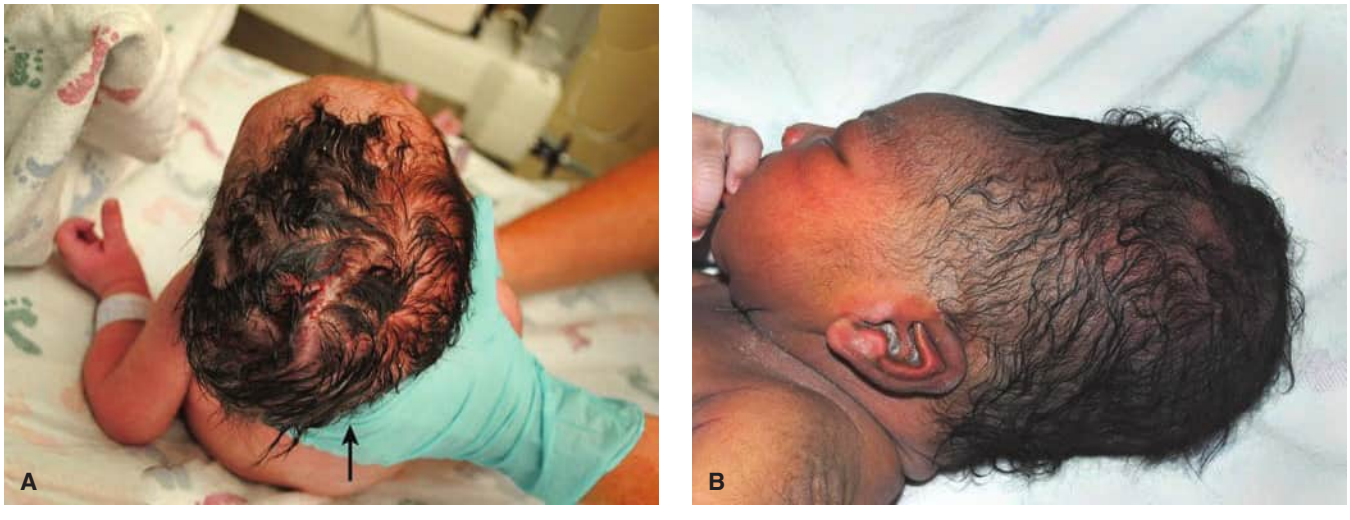


FIGURE 22-7 Fetal head molding and caput succedaneum formation. **A.** This newborn was delivered by cesarean for failure to progress and active labor arrest. The obvious caput succedaneum, which developed far from and to the left of the sagittal midline (*arrow*), reflects marked asynclitism during labor. **B.** This neonate after vaginal birth shows significant caput succedaneum and elongated molding.

at the coronal and lambdoidal sutures actually prevents such overlapping (Carlan, 1991).

Molding yields a shortened suboccipitobregmatic diameter. Of greatest importance in women with contracted pelves or asynclitism, the degree to which the head can mold may determine the difference between vaginal and cesarean birth.

Some older literature implicated severe head molding as a cause for possible cerebral trauma. Because of the many associated factors, for example, prolonged labor with fetal sepsis and acidosis, it is impossible to link molding to any alleged fetal or neonatal neurological sequelae. Most molding resolves within the week following delivery, although persistent cases have been described (Graham, 2006). Differentiation of molding, caput succedaneum, and cephalohematoma is discussed in Chapter 33 (p. 608).

NORMAL LABOR CHARACTERISTICS

The greatest impediment to understanding normal labor is recognizing its start. The strict definition describes uterine contractions that bring about demonstrable cervical effacement and dilation. Pinpointing when labor actually begins, however, is challenging because determination is retrospective. Several methods are used to mark its start. Despite these, a recent systematic review of labor definitions emphasizes the lack of consensus regarding definitions of labor onset (Hanley, 2016).

One method defines onset as the clock time when painful contractions become regular. However, uterine activity that causes discomfort but that does not represent true labor may develop at any time during pregnancy. False labor eventually wanes spontaneously, whereas the contractions of true labor typically progress to an effective, regular pattern.

A second method defines the onset of labor as beginning at the time of admission to a labor unit. In the United States, admission for labor is frequently based on the extent of cervical dilation accompanied by painful contractions. If a woman has intact membranes, a cervical dilation of 3 to 4 cm or greater and frequent painful contractions are reasonably reliable diagnostic criteria.

First Stage of Labor

For labor progression, Friedman (1954) described a characteristic sigmoid pattern by graphing cervical dilation against time. With Friedman's concept, the first stage of labor contains three functional labor divisions, each with its own physiological characteristics (Fig. 22-8). First, during the *preparatory division*, although the cervix dilates little, its connective tissue components change considerably (Chap. 21, p. 406). Sedation and conduction analgesia are capable of arresting this labor division. The *dilatational division*, during which dilation proceeds at its most rapid rate, is unaffected by sedation. Last, the *pelvic division* commences with the deceleration phase of cervical dilation. The cardinal movements of labor take place principally during this pelvic division. In actual practice, however, the onset of the pelvic division is seldom clearly identifiable.

Two phases of cervical dilation are defined. The *latent phase* corresponds to the preparatory division, and the *active phase* to the dilational division. Friedman further subdivided the active phase into the *acceleration phase*, the *phase of maximum slope*, and the *deceleration phase* (Fig. 22-9).

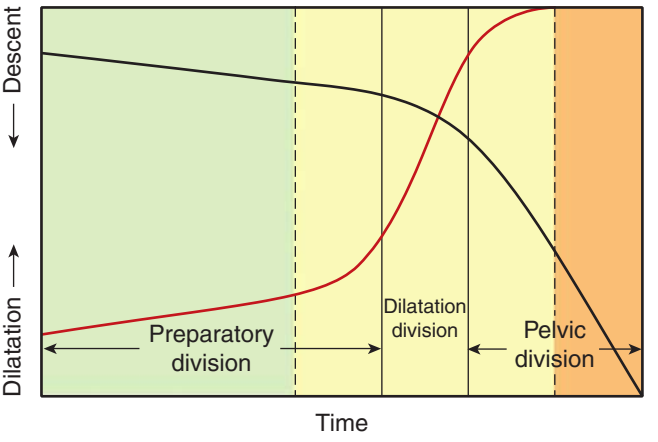


FIGURE 22-8 Labor progress is described by dilatation and descent curves and is partitioned into: (1) a preparatory division, including latent and acceleration phases; (2) a dilatational division, which contains the phase of maximum slope; and (3) a pelvic division, which encompasses both the deceleration phase and second-stage labor as well as the phase of maximum slope of descent.

Latent Phase

The onset of latent labor, as defined by Friedman (1972), is the point at which the mother perceives regular contractions. For most women, this phase ends once cervical dilation of 4 cm is achieved. This threshold may be clinically useful, for it defines dilation limits beyond which active labor can be expected. More recently, the American College of Obstetricians and Gynecologists and Society for Maternal-Fetal Medicine (2019c) has redefined active labor to begin at 6 cm. A fuller discussion of these labor changes is found in Chapter 23 (p. 436).

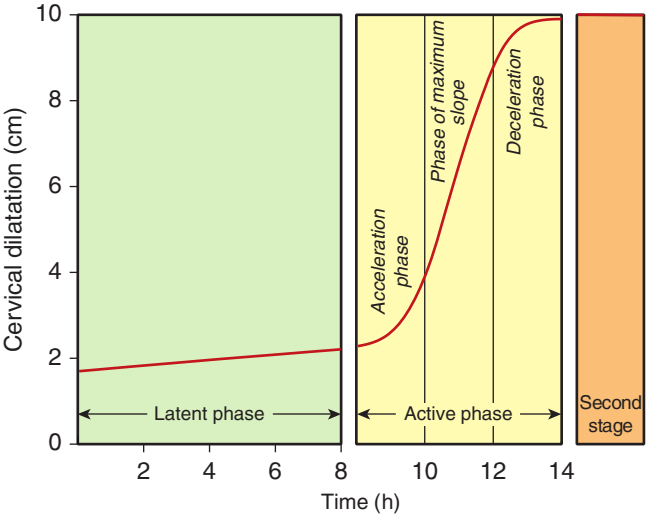


FIGURE 22-9 Composite of the average dilatation curve for nulliparous labor. The first stage is divided into a relatively flat latent phase and a rapidly progressive active phase. The active phase contains an acceleration phase, a phase of maximum slope, and a deceleration phase.

A *prolonged latent phase* was defined as one exceeding 20 hours in the nullipara and 14 hours in the multipara by Friedman and Sachtleben (1963). These times corresponded to the 95th percentiles. Factors that affected latent phase duration include excessive sedation or epidural analgesia; unfavorable cervical condition, that is, thick, uneffaced, or undilated; and false labor. Of women in latent labor who had been administered heavy sedation, 85 percent eventually entered active labor. In another 10 percent, uterine contractions ceased, which suggests false labor. In the remaining 5 percent, an abnormal latent phase persisted and required oxytocin stimulation. Amniotomy was discouraged because of the 10-percent incidence of false labor.

Friedman (1972) later reported that latent phase prolongation did not adversely influence fetal or maternal morbidity or mortality rates. However, prolongation of the latent phase appears associated with longer active labor duration and greater likelihood of obstetrical interventions (Ängeby, 2018; Chelmow, 1993; Tilden, 2020).

Active Phase

The progress of labor in nulliparas has particular significance because these curves all reveal a rapid change in the slope of cervical dilation rates between 3 and 5 cm (see Fig. 22-9). *Thus, cervical dilation of 3 to 6 cm or more, in the presence of uterine contractions, can be taken to reliably represent the threshold for active labor*. Similarly, these curves provide useful guideposts for labor management.

Turning again to Friedman (1955), the mean duration of active-phase labor in nulliparas was 4.9 hours. But, the standard deviation of 3.4 hours is large, hence, the active phase was reported to have a statistical maximum of 11.7 hours. Indeed, rates of cervical dilation ranged from a minimum of 1.2 up to 6.8 cm/hr. Friedman (1972) also found that multiparas progress somewhat faster in active-phase labor, with a *minimum* normal rate of 1.5 cm/hr. His analysis of active-phase labor concomitantly describes rates of fetal descent and cervical dilation (see Fig. 22-8). Descent begins in the later stage of active dilation, commencing at 7 to 8 cm in nulliparas and becoming most rapid after 8 cm.

Others have reassessed the Friedman labor curves. Zhang and associates (2010) studied electronic labor records from 62,415 parturients with spontaneous labor at term and vaginal birth. For primiparas, the median time to progress from 4 to 5 cm was 1.3 hours, from 5 to 6 cm 0.8 hours, and thereafter, additional centimeters were gained approximately each 0.5 hours. They found that normal labor may take >6 hours to progress from 4 to 5 cm and >3 hours to progress from 5 to 6 cm dilation. Rates for multiparas were similar to nulliparas from 4 to 6 cm, but then, labor accelerated much faster in multiparas. Data from this study form the foundation for new guidelines regarding cesarean delivery indications for labor arrest put forth in the American College of Obstetricians and Gynecologists' Obstetric Care Consensus (2019c). These are described in Chapter 23 (p. 436).

Second Stage of Labor

This stage begins with complete cervical dilation and ends with fetal delivery. The median duration is approximately 50 minutes for nulliparas and about 20 minutes for multiparas, but it is highly variable (Kilpatrick, 1989). In a woman of higher parity with a previously dilated vagina and perineum, two or three expulsive efforts after full cervical dilation may suffice to complete delivery. Conversely, in a woman with a contracted pelvis, with a large fetus, or with impaired expulsive efforts from conduction analgesia or sedation, the second stage may become abnormally long. Nulliparas with high starting fetal station may experience a longer second stage (Ashwal, 2021). Greater maternal body mass index does not interfere with second-stage labor (Carlhäll, 2013; Robinson, 2011).

Labor Duration

The normal duration of labor may be clouded by the many clinical variables that affect the conduct of labor in modern obstetrical units. Kilpatrick and Laros (1989) reported that the mean length of first- and second-stage labors approximates 9 hours in nulliparas without regional analgesia and that the 95th percentile upper limit was 18.5 hours. Corresponding times for multiparas were a mean of 6 hours and a 95th percentile maximum of 13.5 hours. These authors defined labor onset as the time when a woman recalled regular, painful contractions every 3 to 5 minutes that led to cervical change.

Spontaneous labor was analyzed in nearly 25,000 women delivered at term at Parkland Hospital in the early 1990s. Almost 80 percent of women were admitted with a cervical dilation of ≤5 cm. Parity—nulliparous versus multiparous—and cervical dilation at admission were significant determinants of spontaneous labor length. The median time from admission to spontaneous delivery for all parturients was 3.5 hours, and 95 percent of all women delivered within 10.1 hours. These results suggest that normal human active labor is relatively short.

MANAGEMENT OF NORMAL LABOR

Birthing is a normal physiological process that most women experience without complications. However, unexpected intrapartum complications can arise quickly. Thus, every woman and her supporters should feel welcomed and comfortable, yet safety measures must be in place for the mother and her newborn if complications suddenly develop. The American Academy of Pediatrics and the American College of Obstetricians and Gynecologists (2017) have collaborated in the development of *Guidelines for Perinatal Care*. These provide detailed information on the appropriate content of intrapartum care, including both personnel and facility requirements. Labor and delivery outside the hospital is elected by some parturients. This option is discussed in Chapter 27 (p. 504).

Emergency Medical Treatment and Labor Act—EMTALA

By law, all Medicare-participating hospitals with emergency services must provide an appropriate screening examination for any pregnant woman experiencing contractions and presenting to the emergency department for evaluation. The definition of an emergency condition makes specific reference to a pregnant

woman who is having contractions. Labor is defined as "the process of childbirth beginning with the latent phase of labor continuing through delivery of the placenta. A woman experiencing contractions is in true labor unless a physician certifies that after a reasonable time of observation the woman is in false labor." A woman in true labor is considered "unstable" for interhospital transfer purposes until the newborn and placenta are delivered. A stable woman may, however, be transferred at the direction of the patient or by a physician who certifies that the benefits of treatment at another facility outweigh the transfer risks.

Identification of Labor

Pregnant women are urged to report early in labor rather than to procrastinate until delivery is imminent. Early admittance is important if during antepartum care, the woman, her fetus, or both are found to carry risks for intrapartum complications.

Although the differentiation between false and true labor is difficult at times, the diagnosis usually can be clarified by cervical dilation and by contraction frequency and intensity. Pates and associates (2007) studied one commonly used recommendation given to pregnant women. Namely, in the absence of ruptured membranes or bleeding, uterine contractions 5 minutes apart for 1 hour—that is, ≥12 contractions in 1 hour—may signify labor onset. Among 768 women in this study at Parkland Hospital, active labor defined as cervical dilation ≥4 cm was diagnosed within 24 hours in three fourths of women with ≥12 contractions per hour.

In those instances when a diagnosis of labor cannot be established with certainty, observation for a longer period is reasonable. Women who present to Parkland Hospital for labor symptoms at $\geq 24^{0/7}$ weeks gestation are routinely evaluated in a labor triage unit, which is contiguous to our labor and delivery unit. All women in the triage unit are evaluated by nurse practitioners and certified nurse midwives using written protocols. For those with uncomplicated pregnancies, women with intact membranes and cervical dilation <4 cm receive continuous external fetal monitoring for up to 2 hours. Women diagnosed with labor by either cervical change or persistent uterine contractions are admitted. After review by a physician, women without cervical change or with abatement of contractions return home with a diagnosis of false labor. In a recent study, a total of 3949 women with uncomplicated pregnancies between $37^{0/7}$ and $41^{6/7}$ weeks' gestation were diagnosed with false labor. The mean interval from hospital discharge to when they again presented was 4.9 days (Nelson, 2017). Within this protocol, hospital discharge with false labor at term was not associated with higher rates of adverse neonatal outcomes or cesarean delivery. The American College of Obstetricians and Gynecologists (2020a) has endorsed hospital-based obstetrical triage units.

Instead of false labor, labor in the latent phase may be diagnosed. In this phase, some women may require admission for pain management. However, for women without antepartum risks and with reassuring maternofetal status, expectant care during latent labor is reasonable (American College of Obstetricians and Gynecologists, 2019a). Studies support the value of this approach to potentially lower rates of interventions that include oxytocin, antibiotics for intrapartum fever, and cesarean delivery (Bailiet, 2005; Wood, 2016). Instructions on coping and self-care during this time have value (Hosek, 2014). Moreover, a mutually agreed upon time is set for reevaluation.

Initial Evaluation

For the gravida presenting with symptoms of labor, blood pressure, temperature, pulse, and respiratory rate are recorded. Fetal heart rate is evaluated using a portable Doppler device, sonography, or fetoscope. Our practice uses extended electronic fetal monitoring to assess initial fetal status. The pregnancy record is promptly reviewed to identify complications. A vaginal examination is performed unless there is a known placenta previa or vasa previa. The gloved index and second fingers are introduced into the vagina while avoiding the anal region.

Ruptured Membranes

During prenatal care, the woman is instructed to be aware of fluid leakage from the vagina and to report this event promptly. Rupture of the membranes is significant for three reasons. First, if the presenting part is not fixed in the pelvis, the umbilical cord can prolapse and be compressed. Second, labor is likely to begin soon if the pregnancy is at or near term. Third, if delivery is delayed after membrane rupture, intrauterine and neonatal infection is more likely as the time interval lengthens (Herbst, 2007).

During sterile speculum examination, ruptured membranes are diagnosed if amnionic fluid pools in the posterior fornix or clear fluid flows from the cervical canal. If the diagnosis remains uncertain, one method involves pH determination of vaginal fluid. The pH of vaginal secretions normally ranges from 4.5 to 5.5, whereas the pH of amnionic fluid is usually >7.0. The use of the indicator *nitrazine* to identify ruptured membranes is a simple and fairly reliable method. Test papers are impregnated with the dye, and the color of the reaction between these paper strips and vaginal fluids is interpreted by comparison with a standard color chart posted on the strip's container. A pH above 6.5 is consistent with ruptured membranes. False-positive test results may stem from blood, semen, or bacterial vaginosis, which raise pH. Scant fluid can yield a false-negative test result.

Another test to identify amnionic fluid microscopically evaluates vaginal fluid that is dried on a slide. Arborization or a fern pattern suggests amnionic rather than cervical fluid. Amnionic fluid crystallizes and ferns due to its concentrations of sodium chloride, proteins, and carbohydrates.

Of other methods, detection of alpha-fetoprotein in the vaginal vault has been used to identify amnionic fluid (Yamada, 1998). Rarely required, identification may also follow injection of 1 to 4 mL of a 5-percent sodium fluorescein solution into the amnionic sac via abdominal amniocentesis (Ireland, 2017).

Last, specific amnionic fluid proteins can be sought using point-of-care assays. These include *AmniSure*, which binds placental alpha microglobulin-1; *Actim PROM*, with binds insulin growth factor binding protein-1 (IGFBP-1); and *ROM Plus*, which detects IGFBP-1 plus alpha-fetoprotein (Eleje, 2017; Palacio, 2014). False-positive and false-negative results are not uncommon. The Food and Drug Administration (2018)

emphasizes the need to incorporate clinical findings if these methods are used.

Cervical Assessment

Progress during labor produces specific cervical changes. *Cervical dilation* is assessed by sweeping the examining finger from the inner cervical rim on one side of the opening to the opposite inner rim. The diameter traversed is estimated in centimeters. Effective labor will dilate the cervix, which is considered fully dilated when the diameter measures 10 cm. The presenting part of a term-size newborn usually can pass through a cervix this widely dilated.

Cervical effacement is the length of the cervical canal compared with that of an unlabored cervix. When the length of the cervix is reduced by one half, it is 50-percent effaced. When the cervix becomes as thin as the adjacent lower uterine segment, it is completely, or 100-percent, effaced.

Cervical position reflects the relationship of the cervical os to the center point of the presenting part. It is categorized as posterior, midposition, or anterior. Fetal descent will gradually move the cervix anteriorly. Along with position, the *consistency* of the cervix is determined to be soft, firm, or intermediate between these two. Cervical softening aids dilation and effacement.

Fetal station describes the presenting fetal part's leading edge in the birth canal in relationship to the ischial spines. These spines lie halfway between the pelvic inlet and the pelvic outlet and lie at the level of the midpelvis. When the lowermost portion of the presenting fetal part reaches the spines, it is designated as being at zero (0) station.

In the past, the long axis of the birth canal above and below the ischial spines was arbitrarily divided into thirds by some and into fifths (approximately 1 cm) by other groups. In 1989, the American College of Obstetricians and Gynecologists adopted the classification of station that divides the pelvis above and below the spines into fifths. Each fifth represents 1 cm above or below the spines. Thus, as the presenting fetal part descends from the inlet *toward* the ischial spines, the designation is –5, –4, –3, –2, –1, and then 0 station. Below the spines, as the presenting fetal part descends, it passes +1, +2, +3, +4, and +5 stations to delivery. Station +5 cm corresponds to the fetal head being visible at the introitus.

If the leading part of the fetal head is at 0 station or below, most often the fetal head has engaged—thus, the biparietal plane has passed through the pelvic inlet. If the head is unusually molded or if caput succedaneum formation is extensive, or both, engagement might not have taken place although the *scalp* is at 0 station.

In addition to charting the progress of labor, these five characteristics—cervical dilation, effacement, consistency, position, and fetal station—are assessed when tabulating the Bishop score. This score is commonly used to predict labor induction outcome and is discussed in Chapter 26 (p. 488). Taken together, these factors suggest the subjective "favorability" of the cervix for induction success.

Laboratory Studies

When a woman is admitted in labor, most often the hematocrit or hemoglobin concentration is rechecked. The hematocrit can be measured easily and quickly. At Parkland Hospital, blood is collected in a standard collection tube with anticoagulant. From this, a heparinized capillary tube is filled to spin in a microhematocrit centrifuge in the labor and delivery unit. This provides a hematocrit value within 3 minutes. The initial collection tube is also sent to the hematology laboratory for evaluation if the point-of-care hematocrit is <30 volume percent. Another labeled tube of blood is allowed to clot and sent to the blood bank for blood type and antibody screen. Some states, for example, Texas, require routine testing for syphilis, hepatitis B, and HIV in all women admitted to labor and delivery units, even if these were done during prenatal care. In some labor units, a clean-catch voided specimen is examined in all women for protein and glucose. At Parkland Hospital, we obtain a urine specimen for protein determination in hypertensive women only (Chap. 40, p. 689).

■ Management of First-stage Labor

As soon as possible after admittance, the remainder of a general examination is completed. Whether a pregnancy is normal can best be determined when all examinations, including record and laboratory review, are completed. A rational plan for monitoring labor can then be established based on the needs of the fetus and the mother. Because labor lengths vary markedly among individuals, precise statements to the patient regarding anticipated labor duration are unwise.

Intrapartum Fetal Monitoring

This is discussed in detail in Chapter 24. Briefly, the American Academy of Pediatrics and American College of Obstetricians and Gynecologists (2017) recommend that during first-stage labor, in the absence of any abnormalities, the fetal heart rate should be checked immediately after a contraction at least every 30 minutes and then every 15 minutes during second-stage labor. If continuous electronic monitoring is used, the tracing is evaluated at least every 30 minutes during the first stage and at least every 15 minutes during the second stage. For women with pregnancies at risk, fetal heart auscultation is performed at least every 15 minutes during first-stage labor and every 5 minutes during the second stage. Continuous electronic monitoring may be used with evaluation of the tracing every 15 minutes during the first stage of labor, and every 5 minutes during the second stage.

Maternal Monitoring

Temperature, pulse, and blood pressure are evaluated at least every 4 hours. If membranes have been ruptured for many hours or if there is a borderline temperature elevation, the temperature is checked hourly.

Although uterine contractions are usually assessed with electronic monitoring, they can be quantitatively and qualitatively evaluated manually. With the palm of the hand resting lightly on the uterus, the time of contraction onset is determined. Its intensity is gauged from the degree of muscle tone the uterus achieves. At the acme of effective contractions, the finger or thumb cannot readily indent the uterus during a "firm" contraction. The time at which the contraction disappears is noted next. This sequence is repeated to evaluate the frequency, duration, and intensity of contractions.

During the first stage of labor, the need for subsequent vaginal examinations to monitor cervical change and presenting part position will vary considerably. When the membranes rupture, an examination to exclude cord prolapse is performed expeditiously if the fetal head was not definitely engaged at the previous examination. The fetal heart rate is also checked immediately and during the next uterine contraction to help detect occult umbilical cord compression. At Parkland Hospital, periodic pelvic examinations are typically performed at 2- to 3-hour intervals for gravidas in active labor to evaluate labor progress. Evidence implicating the number of vaginal examinations in infection-related morbidity is conflicting (Cahill, 2012; Soper, 1989).

Maternal Position

In bed, the laboring woman may assume the position she finds most comfortable, and often this will be lateral recumbency. Lying supine is typically avoided to avert aortocaval compression and its potential to lower uterine perfusion (Chap. 4, p. 64). However, the normal laboring woman need not be confined to bed early in labor. A comfortable chair may be beneficial psychologically and perhaps physiologically. Others encourage ambulation.

Proponents of walking report that it shortens labor, lowers rates of oxytocin augmentation, diminishes the need for analgesia, and decreases the frequency of operative vaginal delivery (Flynn, 1978; Read, 1981). In their Cochrane review, Lawrence and associates (2013) reported that labor in ambulant or upright positions shortened first-stage labor by approximately 1 hour and lowered cesarean delivery and epidural analgesia rates. However, they cautioned interpretation given variable study quality. Lupe and Gross (1986) concluded, however, that no conclusive evidence supports assertions that upright maternal posture or ambulation improves labor. They reported that women preferred to lie on their side or sit in bed. Few chose to walk, fewer to squat, and none wanted the knee-chest position. Parturients tended to assume fetal positions in later labor. Most women enthusiastic about ambulation returned to bed when active labor began (Carlson, 1986; Williams, 1980).

Bloom and colleagues (1998) conducted a randomized trial to study the effects of walking during first-stage labor. In 1067 women with uncomplicated term pregnancies delivered at Parkland Hospital, these investigators reported that ambulation did not affect labor duration. Ambulation did not reduce the need for analgesia nor was it harmful to the newborn. Because of these observations, we give women without complications the option to select either recumbency or supervised ambulation during labor.

Pain Management

In general, the needs and desires for pain relief are directed by the parturient. Relaxation techniques may have a role for pain relief and patient satisfaction, although evidence-based data are not robust (Smith, 2018). Discussed in the last section, ambulation is another option. Some women choose to spend part of first-stage labor in a large water tub, if available, for pain relief. With this practice, one Cochrane review found lower rates of regional analgesia use and no greater adverse neonatal or maternal effects compared with traditional labor (Cluett, 2018).

Pharmacologic options include epidural analgesia; intermittent intravenous (IV) or intramuscular (IM) opioids or meperidine (Table 25-2, p. 469), and less often, nitrous oxide. These are discussed in detail in Chapter 25.

Oral Intake

Food and liquids with particulate matter should be withheld during active labor and delivery. Gastric emptying time is remarkably prolonged once labor is established and analgesics are administered. As a consequence, ingested food and most medications remain in the stomach and are poorly absorbed. They may be vomited and aspirated (Chap. 25, p. 482). However, oral intake of moderate amounts of clear liquids is reasonable for women with uncomplicated labor (American Academy of Pediatrics, 2017; American Society of Anesthesiologists, 2016). Water, clear tea, black coffee, carbonated beverages, Popsicles, and pulp-free juices are options. In those with appreciable risks for aspiration or those with significant risks for cesarean delivery, further restriction may be instituted. For example, for those with planned cesarean delivery, liquids are halted 2 hours before and solids are stopped 6 to 8 hours prior to surgery (American College of Obstetricians and Gynecologists, 2019b).

Intravenous Fluids

Although an IV infusion system is often routinely established early in labor, real need for this in the normal pregnant woman is limited. Access allows parenteral analgesia or IV fluid infusion prior to regional analgesia. In the immediate puerperium, a dilute oxytocin solution can be given prophylactically to prevent uterine atony and at times therapeutically to treat it. Moreover, with longer labors, the administration of glucose, sodium, and water to the otherwise fasting woman at the rate of 60 to 120 mL/hr prevents dehydration and acidosis.

Although not mandatory, IV hydration may shorten labor length, and most studies of fluid selection use first-stage labor length as a primary outcome. From these investigations, data support use of fluids containing dextrose compared with fluid without it (Riegel, 2018; Shrivastava, 2009). For administration, rates of 125 or 250 mL/hr are suitable (Dawood, 2013; Ehsanipoor, 2017; Fong, 2017). In our practice, saline with 5-percent dextrose is infused at a rate of 150 mL/hr.

Rupture of Membranes

If the membranes are intact, temptation is great, even during normal labor, to perform amniotomy. Benefits are earlier detection of meconium-stained amnionic fluid and the opportunity to apply an electrode to the fetus or insert a pressure catheter into the uterine cavity for monitoring. In one metaanalysis of 15 studies, normal spontaneous labor was not shortened by amniotomy (Smyth, 2013). Risks include potential uterine infection if performed early and possible cord prolapse. To help prevent prolapse, the fetal head must be well applied to the cervix and not dislodged from the pelvis during amniotomy. The use of amniotomy in the setting of abnormal labor is discussed in Chapter 23 (p. 434).

With prolonged membrane rupture and unknown group B streptococcal (GBS) status, antimicrobial administration for prevention of GBS infections is recommended for intrapartum

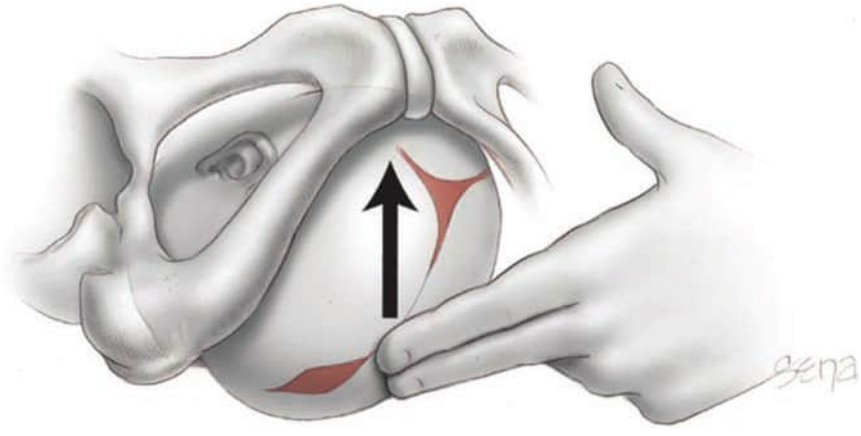


FIGURE 22-10 Locating the sagittal suture by vaginal examination.

risk factors (American College of Obstetricians and Gynecologists, 2020b). These include rupture of membranes greater than 18 hours or intrapartum temperature >38.0°C or >100.4°F (Chap. 67, p. 1194). This practice similarly lowers rates of chorioamnionitis and endometritis (Saccone, 2015).

Urinary Bladder Function

Distention of the bladder can hinder descent of the fetal presenting part and lead to subsequent bladder hypotonia and infection. Periodically, the suprapubic region is palpated to detect distention. If the bladder is readily seen or palpated above the symphysis, the woman should be encouraged to void. Those unable to do so on a bedpan may be able to ambulate with assistance to a toilet. Catheterization is indicated if the bladder is distended and voiding is not possible. Regional analgesia is a common reason. In these cases, continuous or intermittent catheterization is suitable, and both have comparable rates of puerperal urinary tract infection and urinary retention (Li, 2019). Postpartum retention is discussed in Chapter 36 (p. 643).

■ Management of Second-stage Labor

In later first-stage or early second-stage labor, attempts are made to determine head position. The fingers are directed posteriorly and then swept forward over the fetal head toward the maternal symphysis (Fig. 22-10). During this movement, the fingers necessarily cross the sagittal suture, and its lie is delineated. Next, the positions of the two fontanels are ascertained. For this, fingers are passed to the most anterior extension of the sagittal suture, and the fontanel encountered there is examined and identified. The fingers then pass along the sagittal suture to the other end of the head until the other fontanel is felt and differentiated (Fig. 22-11). Last, the station, or extent to which the presenting part has descended into the pelvis, also can be established. Using these maneuvers, the various sutures and fontanels are determined. In unclear cases, sonography can be used as described earlier (p. 420).

With full cervical dilation, which signifies the onset of the second stage, a woman typically begins to bear down. With descent of the presenting part, she develops the urge to defecate. Uterine contractions and the accompanying expulsive forces may now last 1 minute and recur at intervals less than 90 seconds. As discussed earlier, the median duration of the second stage is 50 minutes in nulliparas and 20 minutes in multiparas, although this length can vary. Monitoring intervals of the fetal heart rate were discussed earlier (p. 427), and interpretation of second-stage electronic fetal heart rate patterns is discussed in Chapter 24 (p. 447).

In most cases, bearing down is reflexive and spontaneous during second-stage labor. In those with neuraxial analgesia, this urge may be blunted. To improve spontaneous birth rates, delayed pushing for 60 minutes once the second stage is reached has been suggested to permit passive fetal descent to increase pushing efficiency and minimize maternal exhaustion. One large randomized trial compared immediate and delayed pushing in nulliparas at term with neuraxial analgesia. Routes of delivery were similar. The immediate group actively pushed longer, a mean difference of 9 minutes, but had lower rates of chorioamnionitis (Cahill, 2018). A subsequent metaanalysis noted similar findings (Di Mascio, 2020).

During pushing, a woman may not employ her expulsive forces to good advantage and coaching is desirable. When the next uterine contraction begins, she is instructed to exert downward pressure as though she were straining at stool. A woman is not encouraged to push beyond the completion of each contraction. Instead, she and her fetus are allowed to rest and recover. During this period of active pushing, the fetal heart rate auscultated during the contraction is likely to be slow but should recover to normal range before the next expulsive effort. Fetal and obstetrical outcomes appear to be unaffected whether pushing

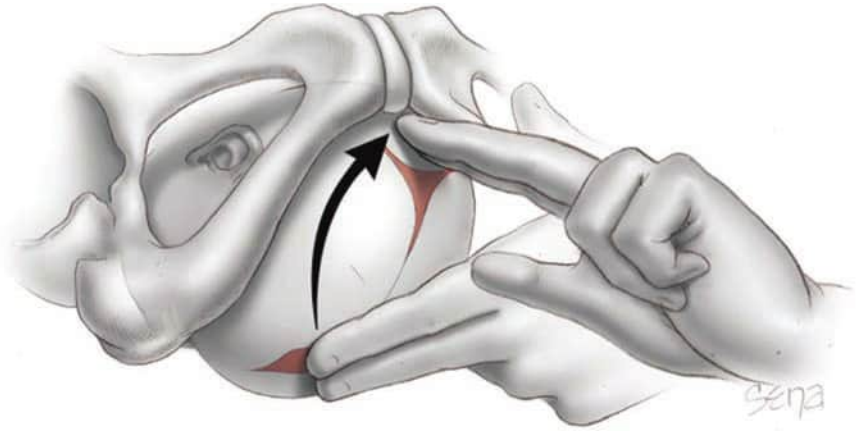


FIGURE 22-11 Differentiating the fontanels by vaginal examination.

is coached or uncoached during second-stage labor (Bloom, 2006; Tuuli, 2012).

Several positions during the second stage have been recommended to augment pushing efforts. The Birth in the Upright Maternal Position with Epidural in Second Stage (BUMPES) trial compared a lateral recumbent position and a supported upright one for nulliparas. Upright positions include standing, sitting out of bed, kneeling, or squatting. The lateral recumbent position required the head of the bed to have an incline ≤30 degrees. When compared, the recumbent group had a spontaneous birth rate of 41 percent, which was significantly higher than the 35-percent spontaneous birth rate experienced by the upright group. Otherwise, rates of operative vaginal delivery (OVD), anal sphincter tear, and neonatal outcome measures were similar (Epidural and Position Trial Collaborative Group, 2017). In a subsequent Cochrane review of studies that included nulliparas and multiparas, upright or recumbent position had little or no affect on rates of "operative birth," which combined OVD and cesarean delivery (Walker, 2018). In those without epidural analgesia, Gupta and coworkers (2017) in their Cochrane review compared upright positions with supine or lithotomy positions during second-stage labor in multiparas and nulliparas. Upright positions offered a marginally shorter interval to delivery and fewer episiotomies and OVDs. However, rates of blood loss >500 mL and perhaps of second-degree lacerations were increased. In sum, no one position is mandated for labor. Repositioning with the goal of maternal comfort and optimal fetal trajectory is suitable as long as appropriate maternal and fetal monitoring can be achieved (American College of Obstetricians and Gynecologists, 2019a). To help avoid femoral or lumbosacral nerve injury from lithotomy positions, hips are not overly flexed, abducted, or externally rotated for extended periods (Chap. 36, p. 644). From early data, transperineal ultrasound assessment of the fetal head's *angle of progression* relative to the symphysis during the second stage may be a tool to predict vaginal birth (Nassr, 2021).

As the head descends through the pelvis, the perineum begins to bulge and the overlying skin becomes stretched. Now the scalp of the fetus may be visible through the vulvar opening. At this time, the woman and her fetus are prepared for delivery, which is described in Chapter 27 (p. 498).

LABOR MANAGEMENT PROTOCOLS

An orderly and systematic approach to labor management results in reproducible beneficial maternal and perinatal outcomes (Althabe, 2008). In Dublin more than 30 years ago, O'Driscoll and associates (1984) pioneered the concept that a disciplined, standardized labor management protocol reduced the number of cesarean deliveries for dystocia. Their overall cesarean delivery rate was 5 percent in the 1970s and 1980s with such management. The approach is now referred to as *active management of labor*. Two of its components—amniotomy and oxytocin—have been widely used, especially in English-speaking countries outside the United States. With this protocol, labor is diagnosed when painful contractions are accompanied by complete cervical effacement, bloody "show," or ruptured membranes. Women with such findings are committed to delivery within 12 hours. Pelvic examination is performed each hour for the next 3 hours, and thereafter at 2-hour intervals. When dilation has not increased by at least 1 cm/hr, amniotomy is performed. Progress is again assessed at 2 hours, and high-dose oxytocin infusion, described in Chapter 26 (p. 493), is started unless dilation of at least 1 cm/hr is attained. Women are constantly attended by midwives. If membranes rupture before admission, oxytocin is begun for no progress at the 1-hour mark.

López-Zeno and colleagues (1992) prospectively compared such active management with their "traditional" approach to labor management at Northwestern Memorial Hospital in Chicago. They randomly assigned 705 nulliparas with uncomplicated pregnancies in spontaneous labor at term. The cesarean delivery rate was significantly lower with active versus traditional management—10.5 versus 14.1 percent, respectively. Subsequent studies did not show this. Wei and associates (2013) in a Cochrane database review found a modest reduction in cesarean delivery rates when active management of labor was compared with standard care. Frigoletto and coworkers (1995) reported another randomized trial with 1934 nulliparous women at Brigham and Women's Hospital in Boston. Although they found that such management somewhat shortened labor, it did not affect the cesarean delivery rate. These observations have since been reported by others (Brown, 2008).

At Parkland Hospital, women are admitted if active labor is diagnosed or if ruptured membranes are confirmed. Labor is defined as cervical dilation of ≥4 cm in the presence of regular uterine contractions. Management guidelines direct that a pelvic examination subsequently be performed approximately every 2 hours. Ineffective labor is suspected when the cervix does not dilate within approximately 2 hours of admission. Amniotomy is then performed, and labor progress determined at the next 2-hour evaluation. In women whose labors do not progress, an intrauterine pressure catheter is placed to assess uterine function. Hypotonic contractions and no cervical dilation after an additional 2 to 3 hours result in stimulation of labor using the high-dose oxytocin regimen described in Chapter 26 (p. 493). The goal is uterine activity of 200 to 250 Montevideo units for 4 hours before dystocia is diagnosed.

In cases in which hypotonic contractions are strongly suspected, internal monitors may be placed with amniotomy and again cervical change and contraction pattern are assessed in 2 hours. Confirmation of deficient Montevideo units at that time may prompt oxytocin augmentation for maternal or fetal indications.

Dilation rates of 1 to 2 cm/hr are accepted as evidence of progress after satisfactory uterine activity has been established with oxytocin. This can require up to 8 hours or more before cesarean delivery is performed for dystocia. The cumulative time required to effect this stepwise management approach permits many women to establish effective labor. This management protocol has been evaluated in >20,000 women with uncomplicated pregnancies. Importantly, these labor interventions and the relatively infrequent use of cesarean delivery did not jeopardize the fetus-newborn.

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CHAPTER 23

Abnormal Labor

Labor arrest, abnormal fetal presentation, or fetal jeopardy are indications for a large percentage of primary cesarean deliveries in the United States (Boyle, 2013). Lowering dystocia rates offers the potential to decrease rates of this surgery and associated maternal morbidity.

DYSTOCIA

Dystocia literally means *difficult labor* and is characterized by abnormally slow labor progress. Causes are grouped into three distinct categories. Mechanistically, these simplify into abnormalities of the *powers*—poor uterine contractility and maternal expulsive effort; of the *passenger*—the fetus; and of the *passage*—the pelvis and lower reproductive tract.

These three groups act singly or in combination to produce dysfunctional labor (Table 23-1). For the powers, uterine contractions may be insufficiently strong or inappropriately coordinated to efface and dilate the cervix. This is termed *uterine dysfunction*. Moreover, during second-stage labor, voluntary maternal pushing may be inadequate. For the passenger, fetal

TABLE 23-1. Some Causes of Dystocia in Term Vertex Singletons

Fetal characteristics
Presentation: face, brow, sinciput
Position: OT, OP, asynclitism
Macrosomia
Anomaly: sacrococcygeal teratoma, hydrocephalus, craniofacial tumor, anencephaly
Intrapartum findings
Hydramnios
Chorioamnionitis
Neuraxial analgesia
Higher station at labor onset
Poor maternal pushing: sedation, severe pain, dense regional block, neurologic disease
Maternal characteristics
Nulliparity
Increasing age
Obesity
Large leiomyoma
Uterine müllerian anomaly
Anthropoid, android, or platypelloid pelvis types
Narrow pelvic diameters
Short stature
Pelvic tumor
Prior pelvic fracture

OP = occiput posterior; OT = occiput transverse.

abnormalities of presentation, position, or anatomy may slow progress. Last, for the passage, structural changes can contract the maternal bony pelvis. Or, soft tissue abnormalities of the reproductive tract may block fetal descent.

To describe ineffective labors, two commonly used terms are *cephalopelvic disproportion (CPD)* and *failure to progress*. CPD describes obstructed labor resulting from disparity between the fetal head size and maternal pelvis. The term CPD originated at a time when the main indication for cesarean delivery was overt pelvic contracture from rickets (Olah, 1994). Such absolute disproportion is now rare, and most cases result from malposition of the fetal head within the pelvis (asynclitism). True disproportion is a tenuous diagnosis because 50 to 75 percent of women undergoing cesarean delivery for this reason subsequently deliver even larger newborns vaginally (Lewkowitz, 2015; Place, 2019).

A second phrase, *failure to progress* in either spontaneous or stimulated labor, has become an increasingly popular description of ineffectual labor. This term reflects lack of progressive cervical dilation or halted fetal descent.

ABNORMALITIES OF THE EXPULSIVE FORCES

Types of Uterine Dysfunction

Uterine contractions are needed to dilate the cervix and to expel the fetus. A contraction is initiated by spontaneous action potentials in the membrane of smooth muscle cells. Unlike the heart, a single pacemaker or its site remain unresolved (Young, 2018). Resulting uterine contractions in normal labor show a rising and falling gradient of myometrial activity (Reynolds, 1951). Normal spontaneous contractions can exert pressures approximating 60 mm Hg (Hendricks, 1959). Even so, the lower limit of contraction pressure required to dilate the cervix is 15 mm Hg (Caldeyro-Barcia, 1950).

In abnormal labor, two physiological types of uterine dysfunction may develop. In the more common *hypotonic uterine dysfunction*, basal tone is normal and uterine contractions have a normal gradient pattern (synchronous). However, pressure during a contraction is insufficient to dilate the cervix. In the second type, *hypertonic uterine dysfunction* or *incoordinate uterine dysfunction*, either basal tone is elevated appreciably or the pressure gradient is distorted.

Risk Factors for Uterine Dysfunction

Various factors are implicated in uterine dysfunction. First, neuraxial analgesia can slow labor and has been associated with longer first and second stages of labor (Sharma, 2004). With current anesthesia methods, however, its effect on labor length is blunted (Anim-Somuah, 2018; Myers, 2020). Moreover, cesarean delivery rates are not higher, and supporting studies are presented in Chapter 25 (p. 477).

Chorioamnionitis is associated with prolonged labor. Uterine infection may directly contribute to uterine dysfunction or instead may simply be an associated consequence of prolonged, dysfunctional labor (Mark, 2000; Satin, 1992). Affected gravidas are monitored for labor progress, and augmentation of protracted labor is prudent (American College of Obstetricians and Gynecologists, 2019a).

A higher station at the onset of labor is significantly linked with subsequent dystocia (Friedman, 1965, 1976; Roshanfekr, 1999). Although a risk factor, most nulliparas without fetal head engagement at diagnosis of active labor still deliver vaginally. These observations apply especially for parous women because the head typically descends later in labor.

Dystocia rate rises proportionally with maternal age even after adjusting for maternal and fetal weight and parity (Timofeev, 2013; Waldenström, 2017). Maternal obesity lengthens the first stages of labor by 30 to 60 minutes in nulliparas, even after adjusting for associated diabetes, fetal weight, and parity (Carlhäll, 2013; Kominiarek, 2011). Dystocia-associated cesarean delivery rates are higher in this group (Fyfe, 2011; Kawakita, 2016). Growing evidence suggests a pathologic biological effect of obesity on normal parturition (Azais, 2017; Carlson, 2015).

Labor Disorders

Latent-phase Prolongation

Uterine dysfunction can in turn lead to labor abnormalities (Table 23-2). First, the latent phase may be prolonged, which is defined as >20 hours in the nullipara and >14 hours in the multipara (Friedman, 1961, 1963b). In some, uterine contractions cease, suggesting false labor. In the remainder, an abnormally long latent phase persists and is often treated with amniotomy and oxytocin stimulation (Friedman, 1963a). The diagnosis of uterine dysfunction in the latent phase is difficult and commonly is made retrospectively. Women who are not yet in active labor often are erroneously treated for perceived uterine dysfunction.

Active-phase Disorders

In active labor, disorders are divided into those with slow progress—a *protraction disorder* or those with halted progress—an *arrest disorder*. Terms presented in Table 23-2 and their diagnostic criteria describe abnormal labor. To be diagnosed with either of these, a woman must be in the active phase of labor.

The criteria and management of abnormal labor have undergone modification, and the American College of Obstetricians and Gynecologists and the Society for Maternal–Fetal Medicine (2019b) describe these in their Obstetric Care Consensus titled *Safe Prevention of the Primary Cesarean Delivery*. The Obstetric Care Consensus was a response to the rising cesarean delivery rate because nearly one third of women who give birth each year in the United States undergoes this surgery (Martin, 2019). New recommendations stem from data of normal labor progress in a more contemporary cohort. The World Health Organization (2018) has also revised its recommendations on labor progress. These guidelines have prompted controversy by their significant revision of the preexisting understanding of abnormal labor.

Active-phase Protraction. Of active-phase disorders, protraction disorders are less well described. Previously, protraction has been defined as <1 cm/hr cervical dilation for a minimum of 4 hours. These criteria were adapted from those of Cohen and Friedman (1983) and shown in Table 23-2. For this disorder, observation for further progress is appropriate treatment. In monitoring active labor, if hypotonic contractions are strongly suspected, internal monitors may be placed with amniotomy and again cervical change and contraction pattern are reassessed.

TABLE 23-2. Abnormal Labor Patterns, Diagnostic Criteria, and Methods of Treatment

LABOR PHASE: Labor Disorder	Traditional Criteria and Treatment: Nulliparas		Traditional Criteria and Treatment: Multiparas	Obstetrical Care Consensus Criteria
LATENT PHASE				
Prolongation Disorder				
Prolonged latent phase	>20 hr	>14 hr	Supportive care Oxytocin or amniotomy CD not indicated	Supportive care Oxytocin or amniotomy CD not indicated
ACTIVE PHASE				
Protraction Disorders				
Protracted active-phase dilation	<1.2 cm/hr	1.5 cm/hr	Expectant care CD for CPD	CD not indicated
Protracted descent	<1 cm/hr	<2 cm/hr		
Arrest Disorders				
Prolonged deceleration phase	>3 hr	>1 hr	CD for CPD No CPD: oxytocin	CD indications: Ruptured membranes ***and*** No progress after 4 hr of adequate contractions ***or*** No progress after 6 hr of inadequate contractions despite oxytocin stimulation
Secondary arrest of dilation	>2 hr	>2 hr		
Arrest of descent	>1 hr	>1 hr		
Failure of descent	No descent in deceleration phase or second stage			

CD = cesarean delivery; CPD = cephalopelvic disproportion.
American College of Obstetricians and Gynecologists, 2019b; Cohen, 1983.

Deficient Montevideo units and poor active labor progress typically prompts oxytocin augmentation. In accord with the Consensus Committee (2019b), slow but progressive first-stage labor should not be an indication for cesarean delivery.

Active-phase Arrest. Handa and Laros (1993) diagnosed active-phase arrest, defined as no dilation for ≥2 hours, in 5 percent of term nulliparas. This incidence has not changed since the 1950s (Friedman, 1978). Inadequate uterine contractions, defined as <180 Montevideo units, calculated as shown in Figure 23-1, were diagnosed in 80 percent of women with active-phase arrest. Hauth and coworkers (1986, 1991) reported that when labor is effectively induced or augmented with oxytocin, 90 percent of women achieve 200 to 225 Montevideo

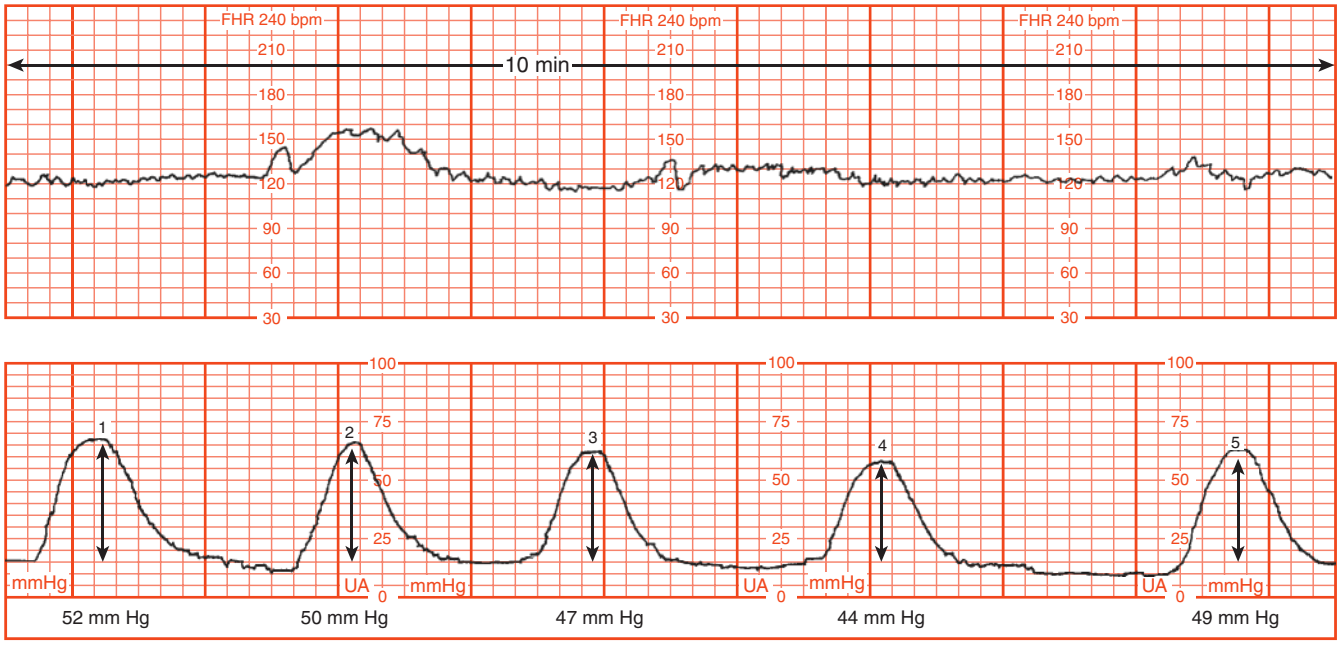

FIGURE 23-1 Montevideo units are calculated by subtracting the baseline uterine pressure from the peak contraction pressure for each contraction in a 10-minute window and adding the pressures generated by each contraction. In the example shown, there were five contractions producing pressure changes of 52, 50, 47, 44, and 49 mm Hg, respectively. The sum of these five contractions is 242 Montevideo units.

units, and 40 percent achieve at least 300 Montevideo units. These results suggest that certain minimums of uterine activity should be achieved before performing cesarean delivery for dystocia. Oxytocin regimens suitable to augment labor mirror those to induce labor. These regimens are outlined in detail in Chapter 26 (p. 493).

Other criteria should also be met. First, the latent phase should be completed, and the cervix is dilated ≥4 cm. Also, a uterine contraction pattern of ≥200 Montevideo units in a 10-minute period has been present for ≥4 hours without cervical change (Rouse, 1999). The Consensus Committee has extended this further, as described next.

Obstetric Care Consensus Committee. Four recommendations of the Consensus Committee apply to management of first-stage labor. The first admonishes against cesarean delivery in the latent phase. Specifically, a prolonged latent phase should not be the sole indication for cesarean delivery. This guideline is not new and is traceable to Friedman's work.

The second directive, too, is conventional practice. It recommends against cesarean delivery if labor is progressive but slow—a *protraction disorder*. This instance is typically managed with observation, assessment of uterine activity, and stimulation of contractions as needed.

A third instruction addresses the cervical dilation threshold that serves to herald active labor. Namely, a cervical dilation of 6 cm—not 4 cm—is now the recommended threshold. Moreover, before this threshold, standards for active-phase progress should not be applied. Of note, the WHO (2018) recognizes 5 cm as the active-labor threshold. Other large studies noted labor acceleration after 5 cm (Ashwal, 2020; Oladapo, 2018).

A fourth stipulation notes that cesarean delivery for active-phase arrest is best reserved for women with cervical dilation ≥6 cm and ruptured membranes who fail to progress despite 4 hours of adequate uterine activity or despite at least 6 hours of oxytocin administration but inadequate contractions.

Of these, the change of thresholds from 4 to 6 cm has prompted the most scrutiny. Described in Chapter 22 (p. 424), original labor curves have been used since first proposed approximately 40 years ago by Friedman (1978). Instead, Zhang and coworkers (2002) proposed a new labor curve derived from a more contemporaneous cohort delivered between 1992 and 1996. The Friedman labor curves reflected women in spontaneous labor with infrequent use of neuraxial labor analgesia or oxytocin augmentation. In contrast, in the later cohort, approximately 50 percent of women had neuraxial analgesia or augmentation. In the later group, the rate of cervical change is slow between 4 and 6 cm but accelerates thereafter. This could reasonably be interpreted as the active phase beginning at 6 cm. In comparing both labor curves, the active phase curve in the Zhang cohort flattens beginning at 3 to 4 cm (Fig. 23-2). Namely, the 6-cm rule for active labor derives from a slowing of the rate or flattening of the slope of cervical change in first-stage labor.

These findings by Zhang and coworkers (2002) are consistent with the labor results obtained in the subsequent Safe Labor Consortium study (Zhang, 2010). However, this study derived its numbers from a retrospective observational dataset built from abstracted labor and delivery information from 19

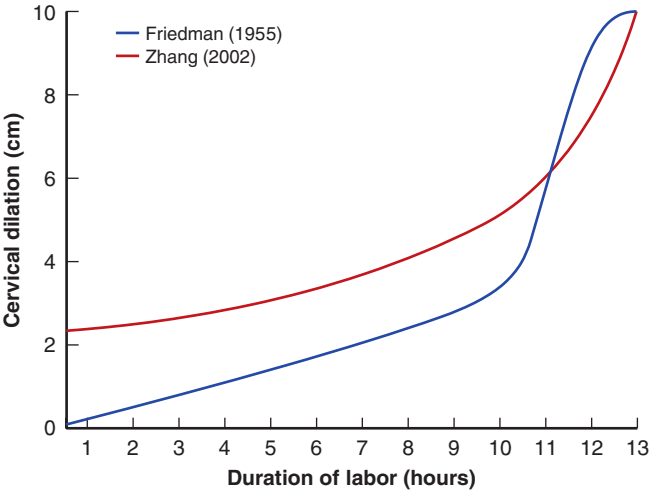

FIGURE 23-2 Cervical dilation curves from Friedman (1955) and Zhang (2002).

hospitals across the United States. Various statistical methods and heavy manipulations of these numbers were used (Cohen, 2015b). Moreover, women were analyzed after excluding all women with cesarean deliveries or asphyxiated newborns. The Consensus Committee (2019b) was explicit that "the Consortium on Safe Labor data, rather than the standards proposed by Friedman, should inform evidence-based labor management."

Critics of the Consensus Committee recommendations note that the Consortium on Safe Labor data were derived from clinical settings with a net cesarean rate of 30 percent. Thus, adherence to the new recommendations may fail to achieve desired cesarean rate reductions. Also, the study lacked a focus on neonatal safety, given that all the asphyxiated neonates were excluded. Supporters note that the study of prolonged first-stage labors by Cheng and coworkers (2010) found higher rates of cesarean delivery and chorioamnionitis but not higher rates of neonatal morbidity. However, Harper and associates (2014) analyzed maternal and neonatal adverse outcomes related to first-stage labor lengths. In 5030 women, first-stage labor durations were divided into those <90th percentile or those ≥90th percentile, with incremental increases thereafter. These authors and those of other large studies similarly found maternal and neonatal composite morbidity scores that were higher in cohorts after adoption of Consensus Committee guidelines compared with groups prior to implementation (Blankenship, 2020; Rosenbloom, 2017). This concern for adverse fetal and maternal effects resulting from the new Consensus Committee guidelines was echoed by Cohen and Friedman (2015a,b).

Another caveat notes that the efficacy of these recommendations to achieve their primary goal is limited. One retrospective cohort study compared 3200 women with uncomplicated term pregnancy undergoing spontaneous or induced labor before guideline changes and 3000 similar gravidas after these changes. The cesarean delivery rate for first-stage labor arrest dropped from 1.8 to 0.9 percent in nulliparas during this time (Thuillier, 2018). Percent changes were not significant in multiparas. Adverse maternal and neonatal outcomes did not significantly differ between epoch groups. In another evaluation of outcomes before and after guideline implementation, cesarean delivery rates were unchanged (Rosenbloom, 2017).

The Consensus Committee suggests that cesarean deliveries for dystocia are being done before 6 cm cervical dilation. However, evidence suggests that all of the Committee's first-stage recommendations are actually already empirically in use but are concurrent with an overall cesarean delivery rate >30 percent. For example, Nelson and associates (2020) analyzed data from nearly 9000 women with primary cesarean deliveries for dystocia at 13 university hospitals between 1999 and 2000. Notably, the median cervical dilation at the time of cesarean for dystocia was 6 cm. As another example, primary cesarean delivery rates for dystocia at Parkland Hospital between 1988 and 2017 did not change significantly. Thus, Consensus Committee guidelines may fail to prevent additional cesareans for dystocia. Logically, further study is needed.

Second-stage Descent Disorders

As discussed in Chapter 22 (p. 425), fetal descent largely follows complete dilation. Moreover, the second stage incorporates many of the cardinal movements necessary for the fetus to negotiate the birth canal. Thus, disproportion of the fetus and pelvis frequently becomes apparent during second-stage labor.

Similar to first-stage labor, time boundaries have been supported to limit second-stage duration to minimize adverse maternal and fetal outcomes. The second stage in nulliparas has been limited to 2 hours and extended to 3 hours when regional analgesia is used. For multiparas, 1 hour has been the limit, extended to 2 hours with regional analgesia. Several studies supported this extension (Cohen, 1977; Menticoglou, 1995a,b; Saunders, 1992). However, of maternal outcomes, higher rates of chorioamnionitis, anal sphincter injury, operative vaginal birth, and postpartum hemorrhage accrue as the second stage lengthens (Allen, 2009; Rouse, 2009).

Newer guidelines have been promoted by the Consensus Committee (2019b) for second-stage labor. These recommend that a nullipara push for at least 3 hours and a multipara push for at least 2 hours before second-stage labor arrest is diagnosed. Importantly, one caveat is that maternal and fetal status should be reassuring. These authors provide options to these times before cesarean delivery is performed. Namely, longer durations may be appropriate as long as progress is documented. Also, a specific maximal length of time spent in second-stage labor beyond which all women should undergo operative delivery has not been identified.

Intuitively, the goal to lower cesarean delivery rates is best balanced with one to ensure neonatal safety. It is problematic that no robust data on neonatal outcomes support the safety of allowing prolonged second-stage labor. Data from many evaluations reveal that serious newborn consequences attend second-stage labors longer than 3 hours (Bleich, 2012; Cahill, 2018; Nelson, 2020; Rosenbloom, 2017). Other data, when adjusted for labor variables, show no difference in adverse neonatal complications for these longer second stages (Cheng, 2004; Le Ray, 2009; Rouse, 2009). Some investigators have argued that the absolute number of such outcomes is small and overall outcomes remain good (Grantz, 2018; Grobman, 2016; Laughon, 2014). That said, some of the adverse outcomes are severe. To fully ascertain specific effect of these guidelines on morbidity rates, randomized controlled trials are needed.

It is possible that prolonged first-stage labor presages that with the second stage. Nelson and coworkers (2013) studied the relationships between the lengths of the first and second stages of labor in 12,523 nulliparas at term delivered at Parkland Hospital. The second stage significantly lengthened concomitantly with increasing first-stage duration. The 95th percentile was 15.6 and 2.9 hours for the first and second stages, respectively. Women with first stages lasting longer than 15.6 hours (>95th percentile) had a 16-percent rate of second-stage labor lasting 3 hours (95th percentile). This compared with a 4.5-percent rate of prolonged second stages in women with first-stage labors lasting <95th percentile.

Maternal Pushing Efforts

With full cervical dilation, most women cannot resist the urge to push with uterine contractions. The combined force created by contractions of the uterus and abdominal musculature propels the fetus downward. However, at times, force created by abdominal musculature is compromised sufficiently to slow or even prevent spontaneous vaginal delivery. Heavy sedation or regional analgesia may reduce the reflex urge to push and may impair the ability to contract abdominal muscles sufficiently. Allowing time for these to abate is reasonable. In other instances, the urge to push is overridden by the intense pain created by bearing down. Depending on fetal station and anticipated second stage, options include emotional support and encouragement, parenteral analgesia, pudendal blockade, or neuraxial analgesia.

PREMATURELY RUPTURED MEMBRANES AT TERM

Membrane rupture at term without spontaneous uterine contractions complicates approximately 8 percent of pregnancies. In the past, labor stimulation was initiated if contractions did not begin after 6 to 12 hours. Practice-changing research included that of Hannah (1996) and Peleg (1999) and their associates, who enrolled a total of 5042 pregnancies with ruptured membranes in a randomized investigation. They measured the effects of induction versus expectant management and also compared induction using intravenous oxytocin with that using prostaglandin E_2 gel. There were approximately 1200 pregnancies in each of the four study arms. They concluded that labor induction with intravenous oxytocin was preferred management. This was based on significantly fewer intrapartum and postpartum infections in women whose labor was induced. There were no significant differences in cesarean delivery rates. Subsequent analysis by Hannah and coworkers (2000) indicated higher rates of adverse outcomes when expectant management at home was compared with in-hospital observation. Mozurkewich and associates (2009) reported lower rates of chorioamnionitis, metritis, and neonatal intensive care unit admissions for women with term ruptured membranes whose labors were induced compared with those managed expectantly. At Parkland Hospital, labor is induced soon after admission when ruptured membranes are confirmed at term. In those with hypotonic contractions or with advanced cervical dilation, oxytocin is selected to lower potential hyperstimulation risk. In those with an unfavorable cervix, no or few contraction, and no significant fetal heart rate decelerations, prostaglandin E_1 (misoprostol) is chosen to promote cervical

ripening and contractions. The benefit of prophylactic antibiotics in women with ruptured membranes before labor at term is unclear (Passos, 2012). However, in those with membranes ruptured longer than 18 hours, antibiotics are instituted for group B streptococcal infection prophylaxis (Chap. 67, p. 1194).

PRECIPITOUS LABOR AND DELIVERY

Labor can be too slow, but it also can be abnormally rapid. *Precipitous labor and delivery* is extremely rapid labor and delivery. It may result from an abnormally low resistance of the soft parts of the birth canal, from abnormally strong uterine and abdominal contractions, or rarely from a lack of pain with contractions to cue advanced labor.

Precipitous labor terminates in expulsion of the fetus in <3 hours. Using this definition, 25,260 live births—3 percent—were complicated by precipitous labor in the United States in 2013 (Martin, 2015). Despite this incidence, little information is published on maternal and perinatal outcomes.

For the mother, complications are few if the cervix is effaced appreciably and compliant, if the vagina has been stretched previously, and if the perineum is relaxed. Conversely, vigorous uterine contractions combined with a long, firm cervix and a noncompliant birth canal may lead to uterine rupture or extensive lacerations of the cervix, vagina, vulva, or perineum (Sheiner, 2004). It is in these latter circumstances that *amniotic-fluid embolism* most likely develops (Chap. 42, p. 743). Precipitous labor is frequently followed by uterine atony. In one report of 99 term pregnancies, short labors were more common in multiparas who typically had contractions at intervals less than 2 minutes. Precipitous labors have been linked to cocaine abuse and associated with placental abruption, meconium, postpartum hemorrhage, and low Apgar scores (Mahon, 1994).

For the neonate, adverse perinatal outcomes from rapid labor may be increased considerably for several reasons. The uterine contractions, often with negligible intervals of relaxation, prevent appropriate uterine blood flow and fetal oxygenation. Related to trauma, resistance of the birth canal rarely may cause intracranial injury. In one review of 22 cases of Erb or Duchenne palsy, precipitous second-stage labor was associated in a third of the cases (Acker, 1988). During unattended birth, the newborn may fall to the floor and be injured. Last, needed resuscitation may not be immediately available due to delivery speed.

As treatment, analgesia is unlikely to modify these forceful contractions significantly. The use of tocolytic agents such as magnesium sulfate or terbutaline is unproven in these circumstances. A single, intramuscular 250-ug terbutaline dose may be reasonable in an attempt to resolve a nonreassuring fetal heart rate pattern. This is balanced against the risk of associated uterine atony if delivery is imminent. Certainly, oxytocin administration should be stopped.

FETOPELVIC DISPROPORTION

Pelvic Capacity

Fetopelvic disproportion arises from diminished pelvic capacity or from abnormal fetal size, structure, presentation, or position. Commonly, both are present. The pelvic inlet, midpelvis, or pelvic outlet may be contracted solely or in combination. Any contraction of the pelvic diameters that diminishes pelvic capacity can create dystocia. Normal pelvic anatomy is also discussed in Chapter 2 (p. 28).

Contracted Inlet

Before labor, the fetal biparietal diameter averages from 9.5 to 9.8 cm. Thus, it might prove difficult or even impossible for some fetuses to pass through a pelvic inlet that has an anteroposterior diameter <10 cm. Mengert (1948) and Kaltreider (1952), employing x-ray pelvimetry, demonstrated that the incidence of difficult deliveries rises when either the anteroposterior diameter of the inlet is <10 cm or the transverse diameter is <12 cm. Either threshold can be used to consider a pelvis contracted. As expected, when both diameters are shortened, dystocia rates are much greater than when only one is diminished.

The anteroposterior diameter of the inlet is also called the *obstetrical conjugate.* It is commonly approximated by manually measuring the *diagonal conjugate*, which is approximately 1.5 cm greater. To measure the diagonal conjugate, a hand with the palm oriented laterally extends its index finger to the promontory. The distance from the fingertip to the point at which the lowest margin of the symphysis strikes the same finger's base is the diagonal conjugate. Inlet contraction usually is defined as a diagonal conjugate <11.5 cm.

A diminutive woman is likely to have a small pelvis, but she is also likely to have a small neonate. Thoms (1937) studied 362 nulliparas and found that the mean birthweight of their offspring was significantly lower—280 g—in women with a small pelvis than in those with a medium or large pelvis.

Normally, cervical dilation is aided by hydrostatic action of the unruptured membranes or by direct application of the presenting part against the cervix after membrane rupture. In contracted pelves, however, because the head is arrested in the pelvic inlet, the entire force exerted by contractions acts directly on the portion of membranes that contact the dilating cervix. Consequently, early spontaneous rupture of the membranes is more likely.

After membrane rupture, absent pressure by the head against the cervix and lower uterine segment predisposes to less effective contractions. Hence, further dilation may proceed very slowly or not at all. Cibils and Hendricks (1965) reported that the mechanical adaptation of the fetal passenger to the bony passage plays an important part in determining the efficiency of contractions. Better adaptation begets more efficient contractions.

A contracted inlet also plays an important part in the production of abnormal presentations. In nulliparas with normal pelvic capacity, the presenting part at term commonly descends into the pelvic cavity before labor onset. If the inlet is contracted considerably or if asynclitism is marked, descent usually does not take place until after labor onset, if at all. Cephalic presentations still predominate, but the head floats over the pelvic inlet or rests more laterally in one of the iliac fossae. Accordingly, very slight influences may cause the fetus to assume other presentations. In women with contracted pelves, face and

shoulder presentations are encountered more frequently, and the cord prolapses more often.

Contracted Midpelvis

This finding is more common than inlet contraction. It frequently causes transverse arrest of the fetal head, which potentially can lead to a difficult midforceps operation or to cesarean delivery.

The obstetrical plane of the midpelvis extends from the inferior margin of the symphysis pubis through the ischial spines and touches the sacrum near the junction of the fourth and fifth vertebrae. A transverse line theoretically connecting the ischial spines divides the midpelvis into anterior and posterior portions (Fig. 2-16, p. 29). The former is bounded anteriorly by the lower border of the symphysis pubis and laterally by the ischiopubic rami. The posterior portion is bounded dorsally by the sacrum and laterally by the sacrospinous ligaments, forming the lower limits of the sacrosciatic notch.

Average midpelvis measurements are as follows: *transverse*, or interischial spinous, 10.5 cm; *anteroposterior*, from the lower border of the symphysis pubis to the junction of S_4 and S_5, 11.5 cm; and *posterior sagittal*, from the midpoint of the interspinous line to the same point on the sacrum, 5 cm. The definition of midpelvic contractions has not been established with the same precision possible for inlet contractions. Even so, the midpelvis is likely contracted when the sum of the interspinous and posterior sagittal diameters of the midpelvis—normally, 10.5 plus 5 cm, or 15.5 cm—falls to 13.5 cm or less. This concept was emphasized by Chen and Huang (1982) in evaluating possible midpelvic contraction. Midpelvic contraction is suspected whenever the interspinous diameter is <10 cm. When it measures <8 cm, the midpelvis is contracted.

Although no precise manual method permits measure of midpelvic dimensions, a suggestion of contraction sometimes can be inferred if the spines are prominent, the pelvic sidewalls converge, or the sacrosciatic notch is narrow. Moreover, Eller and Mengert (1947) noted that the relationship between the intertuberous and interspinous diameters of the ischium is sufficiently constant that narrowing of the interspinous diameter can be anticipated when the intertuberous diameter is narrow. A normal intertuberous diameter, however, does not always exclude a narrow interspinous diameter.

Contracted Outlet

This finding usually is defined as an interischial tuberous diameter of 8 cm or less. The pelvic outlet may be roughly likened to two triangles, with the interischial tuberous diameter constituting the base of both. The sides of the anterior triangle are the pubic rami, and its apex is the inferoposterior surface of the symphysis pubis. The posterior triangle has no bony sides but is limited at its apex by the tip of the last sacral vertebra—not the tip of the coccyx. Diminution of the intertuberous diameter with consequent narrowing of the anterior triangle must inevitably force the fetal head posteriorly. Floberg and associates (1987) reported that outlet contractions were found in almost 1 percent of more than 1400 unselected nulliparas with term pregnancies. A contracted outlet may cause dystocia not so much by itself but by an often-associated midpelvic contraction. *Outlet contraction without concomitant midplane contraction is rare.*

Although the disproportion between the fetal head and the pelvic outlet is not sufficiently great to give rise to severe dystocia, it may play an important part in perineal tears. With increased narrowing of the pubic arch, the occiput cannot emerge directly beneath the symphysis pubis but is forced farther down upon the ischiopubic rami. The perineum, consequently, becomes increasingly distended and thus exposed to risk of laceration.

Pelvic Fractures

Vallier (2012) and Riehl (2014) reviewed experiences with pelvic fractures and pregnancy. Trauma from automobile collisions was the most common cause. Moreover, they note that fracture pattern, minor malalignment, and retained hardware are not absolute indications for cesarean delivery. In determining vaginal delivery candidates, fracture healing requires 8 to 12 weeks and thus recent fracture merits cesarean delivery (Amorosa, 2013). With a healed fracture, care includes review of pelvic radiographs and possible pelvimetry later in pregnancy.

Radiologic Assessment

Current evaluation of pelvic capacity typically uses only digital interrogation of the bony pelvis. Of radiological methods, x-ray pelvimetry with cephalic presentations provides poor predictive value to diagnose CPD (Mengert, 1948; Pattinson, 2017). Similarly, magnetic resonance pelvimetry fails to provide suitable accuracy in predicting cesarean delivery for dystocia (Sporri, 2002; Zaretsky, 2005).

Fetal size alone is seldom the reason for failed labor. Indeed, most cases of CPD arise in fetuses whose weight is well within the range of the general obstetrical population. Figure 23-3 depicts Parkland Hospital data, in which two thirds of neonates who

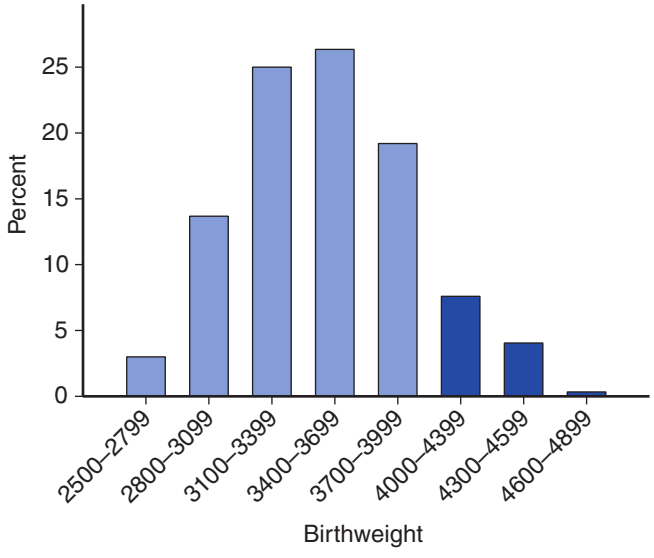

FIGURE 23-3 Birthweight distribution of 362 newborns born by cesarean delivery after a failed forceps attempt at Parkland Hospital from 1989–1999. Only 12 percent (n = 44) of the newborns weighed >4000 g (*dark bars*).

required cesarean delivery after failed forceps delivery weighed <3700 g. Thus, head malposition more likely obstructs fetal passage through the birth canal. These include asynclitism, occiput posterior position, and face, brow, or sinciput presentation.

For fetal head size estimation, clinical and radiographical methods to predict CPD also have proved disappointing. First, Mueller (1885) and Hillis (1930) described a clinical maneuver in which the fetal head is grasped through the abdominal wall, and firm pressure is directed downward along the axis of the inlet. If no disproportion exists, the head readily enters the pelvis, and vaginal delivery can be predicted. However, a prospective evaluation of this *Mueller-Hillis maneuver* found it poorly predicted subsequent labor dystocia (Thorp, 1993).

Measurements of fetal head diameters using plain radiographical techniques are hindered by parallax distortions. The biparietal diameter and head circumference can be measured sonographically, and Thurnau and colleagues (1991) used the *fetal-pelvic index* to identify labor complications. However, the sensitivity of such measurements to predict CPD is poor (Ferguson, 1998; Korhonen, 2015).

Face Presentation

Etiology and Diagnosis

With this presentation, the neck is hyperextended so that the occiput is in contact with the fetal back, and the chin (mentum) is presenting (Fig. 23-4). The rate is approximately 0.1 percent of births (Arsène, 2019; Gardberg, 2011).

Causes of face presentations are numerous and include conditions that favor neck extension or prevent flexion. Preterm fetuses, with their smaller head dimensions, can engage before conversion to occiput presentation, and multifetal gestations carry increased risk (Arsène, 2019; Shaffer, 2006). High parity is another predisposing factor (Fuchs, 1985). In these cases, a pendulous maternal abdomen permits the fetal back to sag forward, which promotes extension of the cervical spine. Fetal malformations and hydramnios are other risk factors for face or brow presentations, and anencephalic fetuses naturally present by the face (Bashiri, 2008). Last, extended neck positions develop more frequently when the pelvis is contracted or the fetus is very large. In a series of 141 face presentations studied by Hellman and coworkers (1950), the incidence of inlet contraction was 40 percent. This high incidence of pelvic contraction should be kept in mind when considering management.

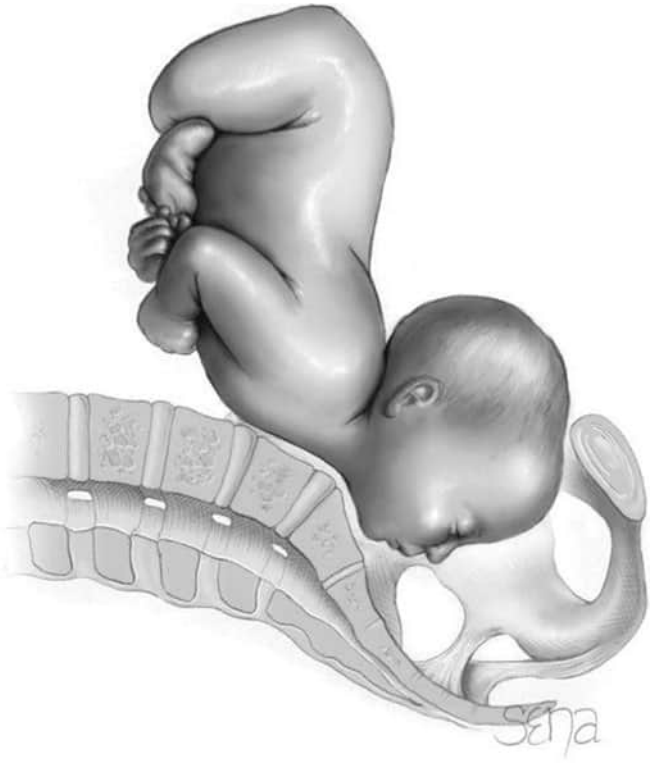

FIGURE 23-4 Face presentation. The chin is directly posterior. Vaginal delivery is impossible unless the chin rotates anteriorly.

Face presentation is diagnosed by vaginal examination and palpation of facial features. Notably, a breech may be mistaken for a face presentation. With careful examination, however, the finger encounters muscular resistance with the anus, whereas the bony, less-yielding jaws and palate are felt through the mouth. The finger, upon removal from the anus, may be stained with meconium. The mouth and malar eminences form a triangular shape, whereas the ischial tuberosities and anus lie in a straight line. Sonography can aid unclear cases (Bellussi, 2017). Used rarely, radiographs demonstrate a hyperextended head with the facial bones at or below the pelvic inlet (Duff, 1981).

Mechanism of Labor

The fetal face may present with the chin (mentum) anteriorly, transversely, or posteriorly, relative to the maternal symphysis pubis (Chap. 22, p. 418). Although some mentum posterior presentations persist, most convert spontaneously to an anterior position, even as late as second-stage labor (Duff, 1981; Sharshiner, 2015).

With the chin anterior, internal rotation of the face brings the chin under the symphysis pubis (Fig. 23-5). Only in this way can the neck traverse the posterior surface of the symphysis pubis. After anterior rotation and descent, the chin and mouth appear at the vulva, and the undersurface of the chin presses against the symphysis. Once the chin clears the symphysis, the neck can flex. The nose, eyes, brow, and occiput then appear in succession over the anterior margin of the perineum. After birth of the head, the occiput sags backward toward the anus. Next, the chin rotates externally to the side toward which it was originally directed, and the shoulders are born as in cephalic presentations. Fortunately temporary, edema and bruising can significantly distort the face.

Instead, if the chin persists posteriorly, the relatively short neck cannot span the anterior surface of the sacrum. Moreover, the fetal brow is pressed against the maternal symphysis pubis. This position precludes the flexion necessary to negotiate the birth canal. Hence, as noted earlier, vaginal birth from a mentum posterior position is impossible unless the shoulders enter the pelvis at the same time, an event that is impossible except for an extremely small or macerated fetus.

Management

During labor, fetal heart rate monitoring is best done with external devices to help avoid face or eye injury. Because face

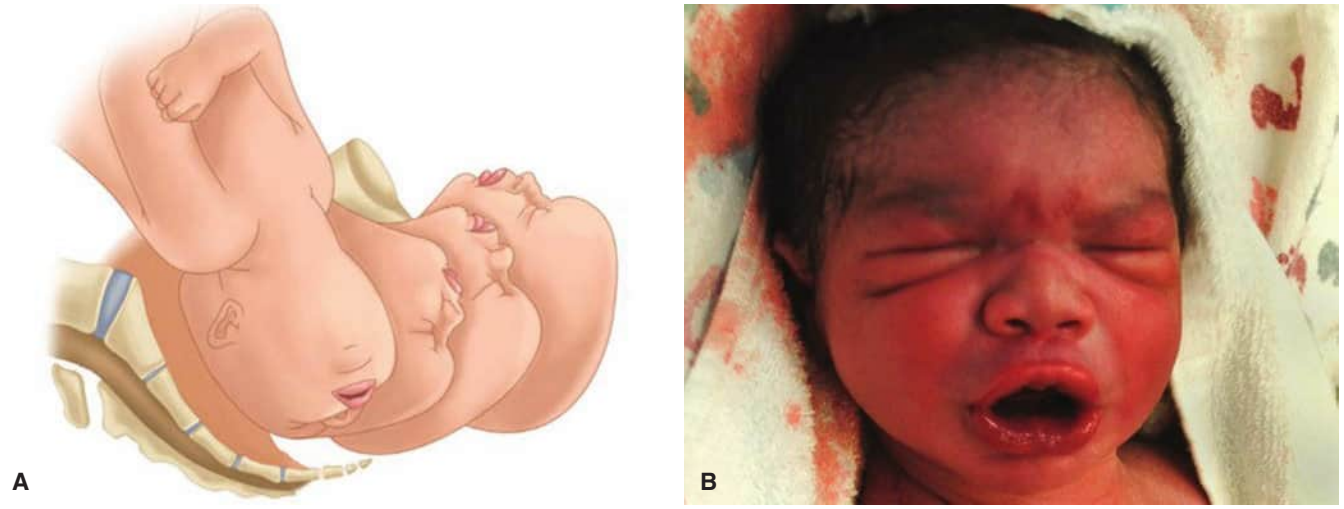

FIGURE 23-5 Face presentation. **A.** Mechanism of labor for right mentoanterior position. **B.** Swollen eyes and lips are common and transient in newborns delivered with face presentation.

presentations among term-size fetuses are more common with some degree of pelvic inlet contraction, cesarean delivery rates are substantially higher than with occiput presentation. If indicated, low or outlet forceps delivery of a mentum anterior face presentation can be completed (Chap. 29, p. 542). Vacuum extraction has been associated with eye trauma and is not recommended (De Bernardo, 2017).

As noted, rotation to a mentum anterior position may occur late in labor. Conversion methods should not be pursued. Namely, attempts to convert a face presentation manually to an occiput one, to rotate a posterior chin to a mentum anterior position, or to complete internal podalic version and extraction are dangerous and not recommended.

Brow Presentation

This uncommon presentation is diagnosed when that portion of the fetal head between the orbital ridge and the anterior fontanel presents at the pelvic inlet. As shown in Figure 23-6, the fetal head thus occupies a position midway between full flexion (occiput) and full extension (face). Rates range from 0.1 to 0.2 percent of births (Gardberg, 2011; Verspyck, 2012).

Risks for persistent brow presentation mirror those for face presentation. A brow presentation is commonly unstable and converts to a face or an occiput presentation (Cruikshank, 1973). The presentation may be recognized by abdominal palpation when both the occiput and chin can be palpated easily, but vaginal examination is usually necessary. The frontal sutures, large anterior fontanel, orbital ridges, eyes, and root of the nose are felt during vaginal examination, but neither the mouth nor the chin is palpable. Sonographic landmarks have been described (Bellussi, 2017).

Except when the fetal head is small or the pelvis is unusually large, engagement of the fetal head and subsequent delivery cannot take place as long as the brow presentation persists. Engagement is impossible until marked molding shortens the occipitomental diameter or, more commonly, until the neck either flexes to an occiput presentation or extends to a face presentation. The considerable molding essential for vaginal delivery of a persistent brow characteristically deforms the head. The caput succedaneum is over the forehead, and it may be so extensive that identification of the brow by palpation is impossible. In these instances, the forehead is prominent and squared, and the occipitomental diameter is diminished. Management principles mirror those for a face presentation.

Transverse Lie

Etiology and Diagnosis

With this, the fetus' long axis lies approximately perpendicular to that of the mother. In a transverse lie, the shoulder is usually

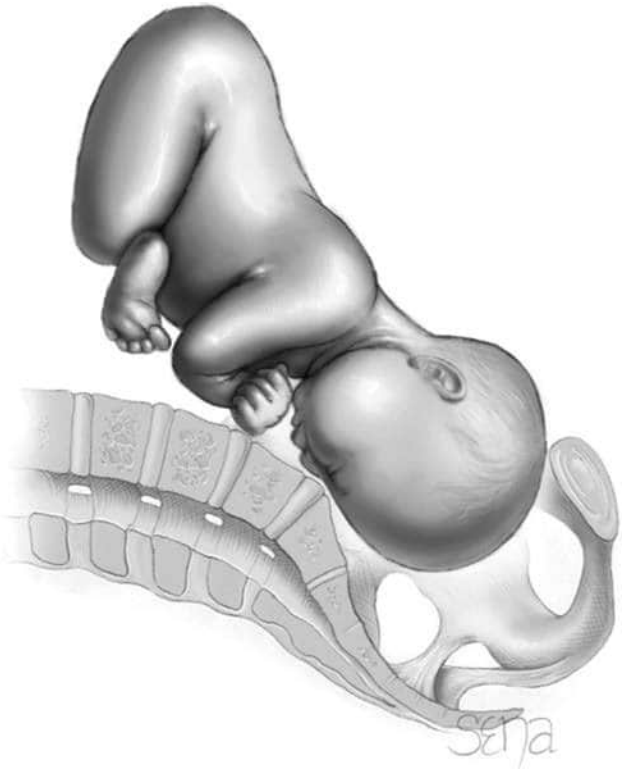

FIGURE 23-6 Brow posterior presentation.

FIGURE 23-7 Transverse lie. Leopold maneuver of a fetus with right acromiodorsoanterior position.

positioned over the pelvic inlet. The head occupies one iliac fossa, and the breech the other. This creates a *shoulder presentation* in which the side of the mother on which the acromion rests determines the designation of the position as right or left acromial. In addition, the back may be directed anteriorly or posteriorly and also superiorly or inferiorly. Thus, it is customary to further distinguish right or left varieties as dorsoanterior and dorsoposterior (Fig. 23-7).

Transverse lie complicates approximately 0.3 percent of births (Cruikshank, 1973; Gemer, 1994). Some of the more common causes include abdominal wall relaxation from high parity, preterm fetus, placenta previa, abnormal uterine anatomy, hydramnios, and contracted maternal pelvis.

A transverse lie is usually recognized easily, often by inspection alone. The abdomen is unusually wide, whereas the uterine fundus extends to only slightly above the umbilicus. No fetal pole is detected in the fundus, and the ballottable head is found on one side and the breech on the other. When the back is anterior, a hard resistance plane extends across the front of the abdomen. When it is posterior, irregular nodules that represent fetal small parts are felt through the mother's abdominal wall. During vaginal examination, in the early stages of labor, if the side of the thorax can be reached, the sequential parallel ribs are felt. With further dilation, the scapula and the clavicle are distinguished on opposite sides of the thorax. The position of the axilla indicates the side of the mother toward which the shoulder is directed.

Mechanism of Labor

Spontaneous delivery of a fully developed newborn is impossible with a persistent transverse lie. After rupture of the membranes, if labor continues, the fetal shoulder is forced into the pelvis, and the corresponding arm frequently prolapses. After some descent, the shoulder is arrested by the margins of the pelvic inlet. As labor continues, the shoulder is impacted firmly in the upper part of the pelvis. The uterus then contracts vigorously in an unsuccessful attempt to overcome the obstacle. With time, a uterine contraction ring rises increasingly higher and becomes more marked. An extreme form is the *Bandl ring*, described in the complication section. With a neglected transverse lie, the uterus will eventually rupture. Even without this complication, maternal and fetal morbidity rates with transverse lie are increased because of the frequent association with placenta previa, umbilical cord prolapse, and fetal manipulations during cesarean delivery.

If the fetus is small—usually <800 g—and the pelvis is large, spontaneous delivery is possible despite persistence of the abnormal lie. The fetus is compressed with the head forced against its abdomen. A portion of the thoracic wall below the shoulder thus becomes the most dependent part, appearing at the vulva. The head and thorax then pass through the pelvic cavity at the same time. The fetus, which is doubled upon itself in a position sometimes referred to as *conduplicato corpore*, is expelled.

Management

Active labor in a woman with a transverse lie typically requires cesarean delivery. With dorsoanterior or back down position, neither the fetal feet nor head occupies the lower uterine segment. A low transverse uterine incision may lead to difficult fetal extraction. Thus, a vertical hysterotomy incision is typically indicated. With dorsoposterior or back up position, one or both feet can be grasped through a low transverse incision and delivered by breech extraction (Chap. 28, p. 527).

Before labor or early in labor, with the membranes intact, attempts at external cephalic version (ECV) are worthwhile. Candidate selection and ECV technique mirror those for the breech fetus and are described in Chapter 28 (p. 528). ECV success rates are high and exceed those for breech fetuses (Correia Costa, 2020; Salzer, 2015).

■ Umbilical Cord Prolapse

Prolapse complicates 0.1 to 0.2 percent of births (Behbehani, 2016; Gibbons, 2014). As noted earlier, umbilical cord prolapse may be more common with pelvis contraction. Most risks stem from an unengaged presenting part and include hydramnios, breech presentation, transverse lie, premature or small fetus with weight <2500 g, preterm rupture of membranes, and multifetal gestation (Hasegawa, 2016). Funic presentation is one in which the umbilical cord is the presenting part. Although rare, it is a potent risk factor for prolapse and merits cesarean delivery prior to labor. Of maternal factors for cord prolapse, grand multiparity, a distorting leiomyoma, or müllerian uterine anomaly are less common reasons (Pagan, 2020).

Umbilical cord prolapse is usually diagnosed clinically. The cord loop is palpated in a position lower in the vaginal canal than the head or beside it. For most cases, prompt manual elevation of the fetal head relieves cord compression. Concurrently,

expeditious transfer to an operating room and preparations for cesarean delivery are completed. Rarely, vaginal or operative vaginal birth is reasonable if it can be completed much more rapidly than emergent cesarean birth (Royal College of Obstetricians and Gynaecologists, 2017).

Compound Presentation

With this, an extremity prolapses alongside the presenting part, and both present simultaneously in the pelvis (Fig. 23-8). Goplerud and Eastman (1953) identified a hand or arm prolapsed alongside the head once in every 700 deliveries. Much less common was prolapse of one or both lower extremities alongside a cephalic presentation or a hand alongside a breech. At Parkland Hospital, compound presentations were identified in only 68 of more than 70,000 singleton fetuses—an incidence of approximately 1 in 1000. Compound presentations form in cases that prevent or delay occlusion of the pelvic inlet and mirror those for other malpresentations.

In most cases, the prolapsed part should be left alone. It typically does not impede labor and often retracts out of the way with descent of the presenting part. If it fails to retract and if it appears to prevent descent of the head, the prolapsed part can be pushed gently upward and the head simultaneously downward by fundal pressure. In cases with a co-presenting hand, the fetus may reflexively retract the hand if pinched by the provider.

In general, rates of perinatal mortality and morbidity are increased, but these mainly stem from effects of associated preterm birth, prolapsed umbilical cord, and traumatic obstetrical procedures. Tebes and coworkers (1999) described a rare case of pressure-induced forearm ischemia and later surgical amputation.

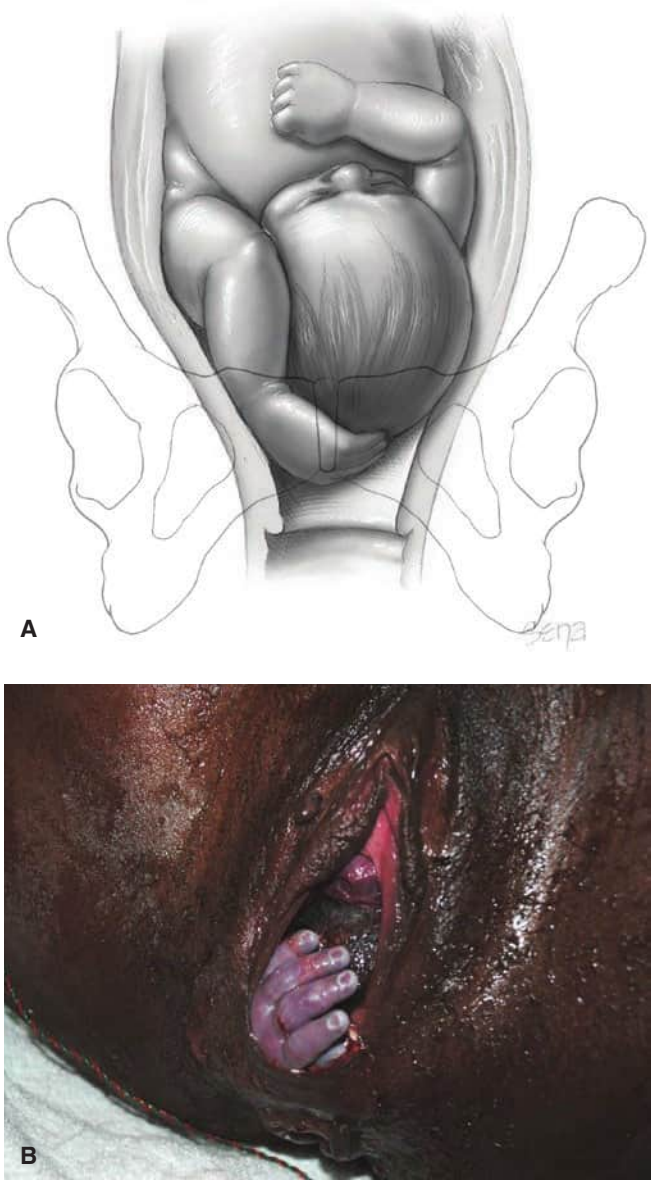

FIGURE 23-8 Compound presentation. **A.** The left hand is lying in front of the vertex. With further labor, the hand and arm may retract from the birth canal, and the head may then descend normally. **B.** Photograph of a small 34-week fetus with a compound presentation that delivered uneventfully with the hand presenting first. Mild bruising resolved uneventfully. (Reproduced with permission from Dr. Elizabeth Mosier.)

COMPLICATIONS WITH DYSTOCIA

Dystocia, especially if labor is prolonged, is associated with a higher incidence of several common obstetrical and neonatal complications. Noted earlier, *maternal infection*, either intrapartum chorioamnionitis or postpartum endomyometritis, is more common with desultory and prolonged labors. *Postpartum hemorrhage* from atony is increased with prolonged and augmented labors. *Uterine tears* at the time of second-stage cesarean delivery also occur at greater incidence if the fetal head is impacted in the pelvis.

Uterine rupture is another risk. Abnormal thinning of the lower uterine segment creates a serious danger during prolonged labor (Delafield, 2018; Ronel, 2012). As described in Chapter 21 (p. 410), the upper segment of the uterus contracts, retracts, and expels the fetus. In response, the softened lower uterine segment and cervix dilate and thereby form a greatly expanded, thinned-out tube through which the fetus can pass. The boundary between these segments is the physiological *retraction ring*. When disproportion is so pronounced that fetal descent arrests, the lower uterine segment becomes increasingly stretched, and the normal *retraction ring* is unusually marked. Seldom encountered today, the *pathological retraction ring of Bandl* is associated with exaggerated thinning of the lower uterine segment. The ring may be seen clearly as a sharp uterine indentation and signifies impending lower segment rupture.

Fistula formation may result from dystocia, in which the presenting part is firmly wedged into the pelvis. Excessive pressure is exerted against tissues lying between the leading part and the pelvic wall. Because of impaired circulation, necrosis may result and become evident several days after delivery as vesicovaginal, vesicocervical, or rectovaginal fistulas (Letchworth, 2018). Most often, pressure necrosis follows a very prolonged second stage. These are rare today except in undeveloped medical systems.

Lower-extremity nerve injury in the mother can follow prolonged second-stage labor. These are discussed in Chapter 36 (p. 644). Fortunately, deficits are mainly sensory, and most resolve within 6 months of delivery in most women.

Similar to the mother, the incidence of peripartum fetal sepsis rises with longer labors. *Caput succedaneum* and *molding* develop commonly and may be impressive (Fig. 22-7, p. 423) (Buchmann, 2008). Mechanical trauma such as nerve injury, fractures, and cephalohematoma also are more frequent and are discussed further in Chapter 33 (p. 608).

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CHAPTER 24

Intrapartum Assessment

Electronic fetal monitoring eclipsed periodic fetoscopic auscultation of the fetal heartbeat in the late 1960s (Hon, 1958). It was hoped that the continuous graph-paper portrayal of the fetal heart rate (FHR), termed *cardiotocography*, would reflect pathophysiological events affecting the fetus. Initially, electronic FHR monitoring was used primarily in complicated pregnancies. Now, more than 85 percent of all live births in the United States undergo electronic FHR monitoring (Ananth, 2013).

ELECTRONIC FETAL MONITORING

Internal (Direct) Electronic Monitoring

Direct FHR measurement is accomplished by attaching a bipolar spiral electrode directly to the fetus (Fig. 24-1). The wire electrode penetrates the fetal scalp, and the second pole is a metal wing on the electrode. The P wave, QRS complex, and T wave of the electrical fetal cardiac signal are amplified and fed into a cardiotachometer for heart rate calculation. The peak R-wave voltage is the most reliably detected portion of the fetal electrocardiogram (ECG). Time (t) in milliseconds between fetal R waves is fed into a cardiotachometer, and a new FHR is set with the arrival of each new R wave (Fig. 24-2). The phenomenon of continuous R-to-R wave FHR computation was known as *beat-to-beat variability*, and is now called *baseline variability*. If present, fetal premature atrial contractions (PACs) cause the cardiotachometer to rapidly and erratically seek new heart rates and create the "spiking" shown Figure 24-3.

Electrical cardiac complexes detected by the fetal electrode include those generated by the mother. However, the amplitude of the maternal ECG signal is diminished when recorded through the fetal scalp electrode. Thus, maternal cardiac signals do not appear on the FHR tracing. However, if the fetus is dead, maternal R waves can be still detected by the scalp

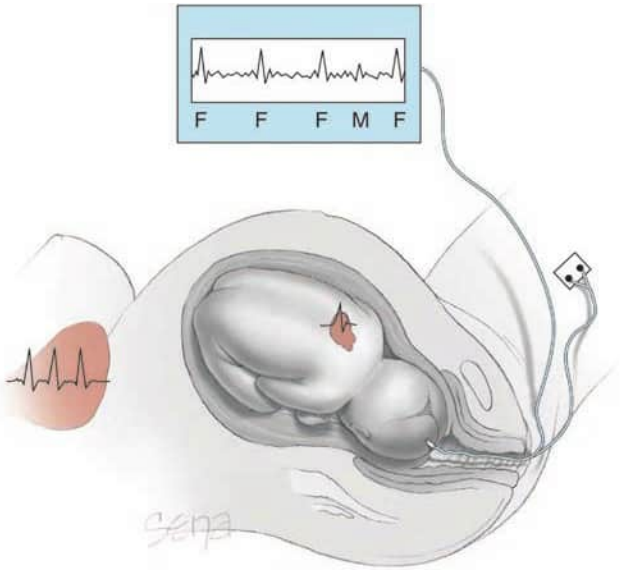

FIGURE 24-1 With internal electronic fetal monitoring a bipolar electrode is attached to the fetal scalp for detection of fetal QRS complexes (F). At times, the maternal heart and its electrical complex (M) also may be detected.

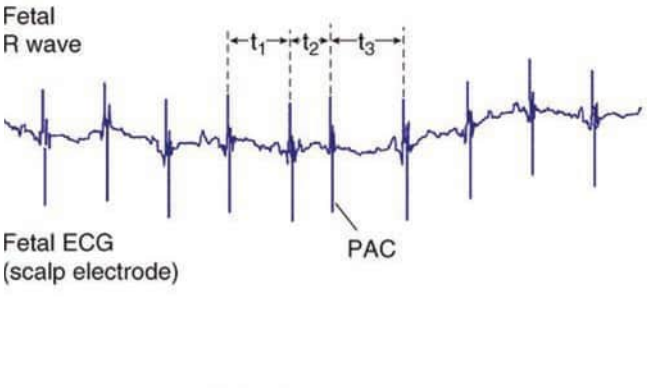

FIGURE 24-2 Fetal electrocardiographic signals from the scalp electrode are used to compute continuous beat-to-beat heart rate. Time intervals (t_1, t_2, t_3) in milliseconds between successive fetal R waves are used by a cardiotachometer to compute instantaneous fetal heart rate. In this example, the t_2 interval has complexes that are close together, which indicates a slighted higher heart rate. This is reflected in the vertical rise on the cardiotachometer graph. ECG = electrocardiogram; PAC = premature atrial contraction.

electrode as the next best signal and are counted by the cardiotachometer (Fig. 24-4).

External (Indirect) Electronic Monitoring

Although it avoids membrane rupture, external monitoring does not provide the precision of internal FHR monitoring (Nunes, 2014). Moreover, in some women, external monitoring may be difficult. For example, fetuses of obese women have a greater amount of unmonitored time compared with those of normal-weight women (Brocato, 2019).

With external monitoring, the FHR is detected through the maternal abdominal wall using the *ultrasound Doppler principle* (Chap. 14, p. 261). The instrument contains a transducer that emits ultrasound and a sensor to detect a shift in frequency of

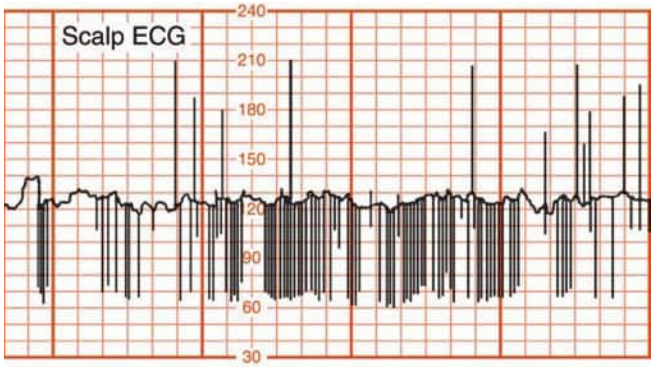

FIGURE 24-3 Standard fetal monitor tracing of heart rate using a fetal scalp electrode. Spiking of the fetal rate reflects premature atrial contractions.

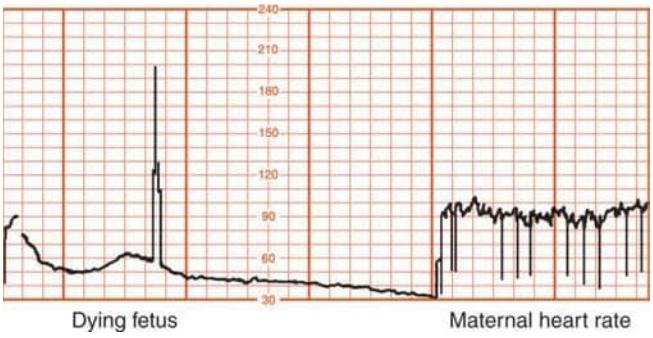

FIGURE 24-4 Placental abruption. The fetal scalp electrode first detects the dying fetus' heart rate. After fetal death, the maternal electrocardiogram complex is detected and recorded.

the reflected sound. The transducer is placed on the maternal abdomen at a site where fetal heart action is best detected. A coupling gel must be applied because air conducts ultrasound waves poorly. The device is held in position by an elastic belt.

Ultrasound Doppler signals are edited electronically before FHR data appear. Reflected ultrasound signals from moving fetal heart valves are analyzed through a microprocessor that compares incoming signals with the most recent previous signal. This process, called *autocorrelation*, is based on the premise that the FHR has regularity, whereas "noise" is random and lacks regularity. Several fetal heart motions must be deemed electronically acceptable by the microprocessor before the FHR is revealed. Such electronic editing has greatly improved tracing quality. Many fetal monitors are capable of interfacing with archival storage systems, which obviates maintaining actual paper tracings.

Other features of current external monitors include the ability to monitor twin fetuses, concurrently assess maternal heart rate, display fetal ECG, and record maternal pulse oximetry values. Wireless, abdominal, dermal-patch, external array systems may improve the interpretability of intrapartum FHR tracings in obese women (Lempersz, 2020; Monson, 2020). Wireless monitors use electrocardiography to accurately measure maternal and fetal heart rates yet allow patient mobility during labor.

Fetal Heart Rate Patterns

The interpretation of FHR patterns can be problematic without definitions and nomenclature. In one study, three Maternal-Fetal Medicine specialists independently interpreted FHR tracings. Agreement was poor for the most ominous tracings and was moderate for less severe patterns (Blackwell, 2011). To help standardize definitions, the National Institute of Child Health and Human Development (NICHD) convened a working group (Table 24-1) (Macones, 2008). The resulting definitions are used in this chapter and have been adopted by the American College of Obstetricians and Gynecologists (2019a). Interobserver agreement improves when these standardized definitions are implemented (Epstein, 2013).

Pattern interpretation derives from the FHR that is portrayed on the monitor or graph paper. Thus, the choice of vertical and horizontal scaling greatly affects patterns. NICHD Workshop scaling parameters recommend that each centimeter

TABLE 24-1. Electronic Fetal Monitoring Definitions

Pattern	Definition
Baseline	• The mean FHR rounded to increments of 5 bpm during a 10-min segment, excluding: —Periodic or episodic changes —Periods of marked FHR variability —Segments of baseline that differ by more than 25 bpm • The baseline must be for a minimum of 2 min in any 10-min segment or the baseline for that time period is indeterminate. In this case, one may refer to the prior 10-min window for determination of baseline. • Normal FHR baseline: 110–160 bpm • Tachycardia: FHR baselines is greater than 160 beats per minute • Bradycardia: FHR baseline is less than 110 beats per minute
Baseline variability	• Fluctuations in the baseline FHR that are irregular in amplitude and frequency • Variability is visually quantified as the amplitude of peak-to-trough in beats per minute —Absent: amplitude range undetectable —Minimal: amplitude range detectable but 5 beats per minutes or fewer —Moderate (normal): amplitude range 6–25 beats per minute —Marked: amplitude range greater than 25 beats per minute
Acceleration	• A visually apparent abrupt increase (onset to peak in less than 30 seconds) in the FHR • At 32 weeks of gestation and beyond, an acceleration has a peak of 15 bpm or more above baseline, with a duration of 15 sec or more but less than 2 minutes from onset to return • Before 32 weeks, an acceleration has a peak of 10 bpm or more above baseline, with a duration of 10 seconds or more but less than 2 minutes from onset to return • Prolonged acceleration lasts 2 minutes or more but less than 10 minutes in duration • If an acceleration lasts 10 minutes or longer, it is a baseline change
Early deceleration	• Visually apparent usually symmetrical gradual decrease and return of the FHR associated with a uterine contraction • A gradual FHR decrease is defined as from the onset to the FHR nadir of 30 seconds or more • The decrease in FHR is calculated from the onset to the nadir of the deceleration • The nadir of the deceleration occurs at the same time as the peak of the contraction • In most cases the onset, nadir, and recovery of the deceleration are coincident with the beginning, peak, and ending of the contraction, respectively
Late deceleration	• Visually apparent usually symmetrical gradual decrease and return of the FHR associated with a uterine contraction • A gradual FHR decrease is defined as from the onset to the FHR nadir of 30 seconds or more • The decrease in FHR is calculated from the onset to the nadir of the deceleration • The deceleration is delayed in timing, with the nadir of the deceleration occurring after the peak of the contraction • In most cases the onset, nadir, and recovery of the deceleration occur after the beginning, peak, and ending of the contraction, respectively
Variable deceleration	• Visually apparent abrupt decrease in FHR • An abrupt FHR decrease is defined as from the onset of the deceleration to the beginning of the FHR nadir of less than 30 seconds • The decrease in FHR is calculated from the onset to the nadir of the deceleration • The decrease in FHR is 15 beats per minute or greater, lasting 15 seconds or greater, and less than 2 minutes in duration • When variable decelerations are associated with uterine contraction, their onset, depth, and duration commonly vary with successive uterine contractions
Prolonged deceleration	• Visually apparent decrease in the FHR below the baseline • Decrease in FHR from the baseline that is 15 beats per minute or more, and less than 2 minutes in duration • If a deceleration last 10 minutes or longer, it is a baseline change
Sinusoidal pattern	• Visually apparent, smooth, sine wave-line undulating pattern in FHR baseline with a cycle frequency of 3–5 per minute which persists for 20 minutes or more

FHR = fetal heart rate.

on the vertical axis represents 30 beats per minute (bpm). Measurement markers on this axis range from 30 to 240 bpm. Along the horizontal axis, the chart recorder moves at a speed of 3 cm/min. The time between each bold vertical line on this axis is 1 minute (see Fig. 24-4).

FHR patterns during labor are dynamic and can interchange rapidly. Although intrapartum evaluation of fetal heart tracings occur every 5 to 30 minutes, tracing interpretation should reflect a longitudinal assessment beyond the current 5- to 30-minute segment (American College of Obstetricians and Gynecologists, 2019b; Robinson, 2008; Vintzileos, 2016). Thus, a full description should include an evaluation of changes or trends over time (Macones, 2008).

Baseline Fetal Heart Activity

This refers to FHR baseline characteristics apart from periodic accelerations or decelerations. Elements include *rate*, *variability*, and distinct FHR patterns such as *sinusoidal* or *saltatory*.

Rate

Beginning at 16 weeks' gestation, the heart rate drops approximately 1 bpm each week (Pillai, 1990; Serra 2009). This continues postnatally such that the average rate is 85 bpm by age 8 years (Tintinalli, 2016). This normal gradual slowing of the FHR is thought to correspond to maturation of parasympathetic (vagal) heart control (Renou, 1969).

The baseline FHR is the approximate mean rate during a 10-minute tracing segment and is rounded to increments of 5 bpm. In any 10-minute window, the minimum interpretable baseline duration must be at least 2 minutes—otherwise the baseline is considered *indeterminate*. For an indeterminate baseline, the previous 10-minute interval is used to determine the baseline heart rate.

If the baseline FHR is <110 bpm, it is termed *bradycardia*. If the baseline rate is >160 bpm, it is called *tachycardia*. The average FHR is considered the result of tonic balance between *accelerator* and *decelerator* influences on cardiac pacemaker cells. In this concept, the sympathetic system is the accelerator influence. The parasympathetic system is the decelerator factor and mediated by vagal slowing of heart rate (Dawes, 1985). Heart rate also is under the control of arterial chemoreceptors such that both hypoxia and hypercapnia can modulate rate. Prolonged hypoxia that is associated with a rising blood lactate level and severe metabolic acidemia induces an extended drop in heart rate (Thakor, 2009).

Bradycardia. In the third trimester, the normal mean baseline FHR ranges between 110 and 160 bpm. But, pragmatically, a rate between 100 and 119 bpm, in the absence of other FHR changes, usually is not representative of fetal compromise. Such mild bradycardias were observed in 2 percent of monitored pregnancies and averaged approximately 50 minutes in duration (Young, 1976). These low baseline heart rates have also been attributed to head compression from occiput posterior or transverse positions, particularly during second-stage labor.

However, fetal bradycardia may stem from congenital heart block or from fetal hypoxia due to maternal or fetal causes (Bravo-Valenzuela, 2018; Lepercq, 2021). For example, Figure 24-4 shows bradycardia in a fetus dying from placental abruption. Less often, sustained maternal hypothermia also can cause fetal bradycardia, but these uniquely involved fetuses apparently are not harmed by several hours of such bradycardia (Spires, 2020).

Tachycardia. This is defined as a baseline FHR >160 bpm. The most common explanation is maternal fever. In some cases, fetal tachycardia may precede overt maternal fever (Gilstrap, 1987). Fetal tachycardia caused by maternal infection typically is not associated with fetal compromise unless it is associated with fetal sepsis or with significant FHR decelerations.

Other causes of fetal tachycardia include fetal compromise, cardiac arrhythmias, and maternal administration of parasympathetic inhibiting (atropine) or sympathomimetic (terbutaline) drugs. Prompt treatment of the compromising event, such as alleviation of maternal fever or volume resuscitation, can result in fetal recovery. The key feature to distinguish fetal compromise in association with tachycardia seems to be concomitant FHR decelerations (Cahill, 2018).

Baseline Variability

This is an important index of cardiovascular function and reflects a sympathetic and parasympathetic "push and pull" mediated by the fetal sinoatrial node. This produces beat-to-beat fluctuations of the baseline FHR (Kozuma, 1997). *Variability* describes these changes during 1 minute, which modify the baseline's waviness (Fig. 24-5). Interpretation of variability is subjective and judges this waviness. The NICHD workshop defined *baseline variability* as irregular fluctuations in the baseline excluding accelerations and decelerations (Macones, 2008). They recommended the criteria shown in Figure 24-5 for quantification of variability. Normal variability shows oscillations that change 6 to 25 bpm. FHR variability increases with advancing gestational age (Serra, 2009; Shuffrey, 2019).

Increased Variability. Several physiological and pathological processes affect variability. Greater variability accompanies fetal breathing and body movements (Dawes, 1981; Zizzo, 2020). Shuffrey and colleagues (2020) showed the FHR had enhanced variation in state 4F (active awake state) compared with 1F (quiet state) and 2F (active state) (Chap. 20, p. 383). However, in one study of 390 fetuses, greater intrapartum variability was associated with abnormal fetal arterial cord blood gas measurements but without increased neonatal morbidity rates (Polnaszek, 2020).

Decreased Variability. *Absent variability* and *minimal variability* are defined as no baseline fluctuation or changes ≤5 bpm. These are shown in Figure 24-5, panels 1 and 2. Of greatest concern, diminished variability can be an ominous sign that indicates a seriously compromised fetus. According to Esplin (2020), metabolic acidemia depresses the fetal brainstem or heart to create the loss of variability. Thus, diminished variability, when it reflects fetal compromise, likely reflects acidemia rather than hypoxia. Severe maternal acidemia also can lower fetal variability, for example, in a mother with diabetic ketoacidosis.

Reduced baseline FHR variability is the single most reliable sign of fetal compromise. Moderate variability is associated with a normal umbilical cord pH in 98 percent of cases (Parer, 2006). Absent or minimal variability is associated with fetal acidemia, but it predicts an umbilical cord pH <7.15 in only 12 to 31 percent of cases (Parer, 2006; Williams, 2003). In a study of 2200 consecutive deliveries, authors concluded that variability by itself could not be used as the only indicator of fetal well-being (Samueloff, 1994). Comorbid fetal tachycardia or FHR decelerations also may help predict fetal acidemia (Esplin, 2020; Vintzileos, 2016).

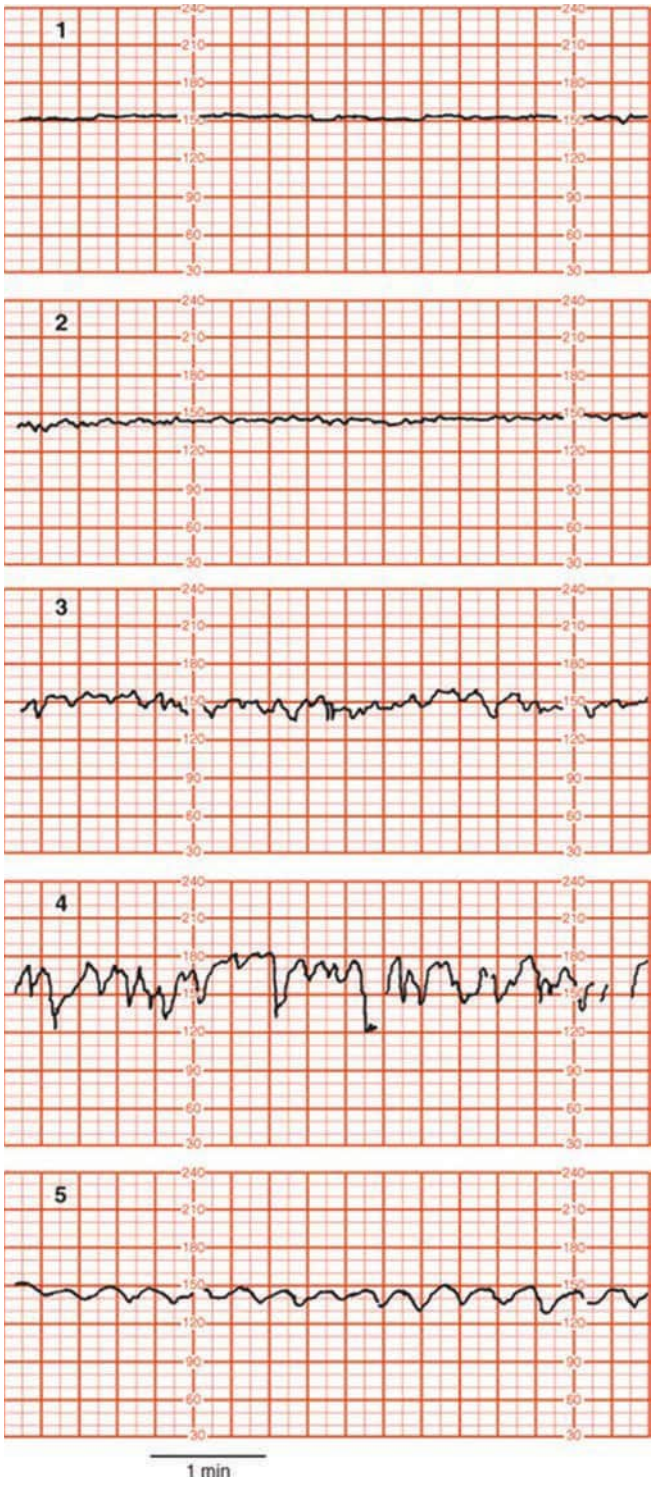

FIGURE 24-5 Baseline fetal heart rate variability shown in the following five panels. **1.** Undetectable, absent variability. **2.** Minimal variability, ≤5 bpm. **3.** Moderate (normal) variability, 6 to 25 bpm. **4.** Marked variability, >25 bpm. **5.** Sinusoidal pattern. This differs from variability in that it has a smooth, sinelike pattern of regular fluctuation and is excluded in the definition of fetal heart rate variability.

Another common cause of diminished variability is administration of some analgesic drugs during labor (Chap. 25, p. 477). These can depress the central nervous system and include narcotics, barbiturates, phenothiazines, tranquilizers, and general anesthetics. As one specific example, variability regularly diminishes within 5 to 10 minutes following intravenous (IV) meperidine administration, and the effects may last 60 minutes or longer (Hill, 2003; Petrie, 1993). IV butorphanol has similar effects (Schucker, 1996). And, chronically administered buprenorphine suppresses FHR and movement (Jansson, 2017). Corticosteroids also decrease fetal movement and thereby dampen variability (Noben, 2019).

Magnesium sulfate can diminish variability and is widely used in the United States for fetal neuroprotection, tocolysis, and seizure prophylaxis in preeclampsia. In a study of nearly 250 term gestations, its administration led to decreased variability but without evidence of adverse neonatal effects (Duffy, 2012). Others echo these findings (Nensi, 2014; Verdurmen, 2017).

In sum, variability is affected by fetal physiology, and its meaning differs depending on clinical setting. A decrease in variability but without decelerations is unlikely to reflect fetal hypoxia (Parer, 2006). A persistently flat FHR baseline—absent variability—within the normal baseline rate range and without decelerations may reflect a prior fetal insult that has resulted in neurological damage (Freeman, 2003).

Cardiac Arrhythmia

When fetal cardiac arrhythmias are first suspected using electronic monitoring, findings can include baseline bradycardia, tachycardia, or most commonly in our experience, *abrupt baseline spiking* (see Fig. 24-3). An arrhythmia can only be documented, practically speaking, when scalp electrodes are used. Some fetal monitors can be adapted to output the scalp electrode signals into an ECG recorder. Because only a single lead is obtained, analysis and interpretation of rhythm and rate disturbances are severely limited.

In one study, rate and rhythm disturbances in 934 normal pregnancies were evaluated between 30 and 40 weeks' gestation. Arrhythmias, episodes of bradycardia <100 bpm, or tachycardia >180 bpm were encountered in 3 percent (Southall, 1980). Most supraventricular arrhythmias carry little significance during labor unless fetal heart failure, as evidenced by hydrops, is coexistent. Many supraventricular arrhythmias disappear in the immediate neonatal period, although some are associated with structural cardiac defects (Api, 2008). Intermittent baseline bradycardia is frequently due to congenital heart block. Conduction defects, most often complete atrioventricular (AV) block, usually are found in association with maternal connective tissue diseases (Chap. 62, p. 1113). Antepartum evaluation of the fetus with an identified arrhythmia and treatment options are discussed in Chapter 19 (p. 368).

Most fetal arrhythmias without comorbid fetal hydrops are inconsequential during labor, but they may hinder interpretation of FHR tracings and thereby necessitate cesarean delivery. Sonographic evaluation of fetal anatomy and echocardiography can be useful. Generally, without evidence of fetal hydrops, neonatal outcome is not measurably improved by pregnancy intervention. At Parkland Hospital, intrapartum fetal cardiac arrhythmias, especially those associated with clear amnionic fluid, are typically managed conservatively.

Sinusoidal Heart Rate

A sinusoidal baseline is one with a sine wave–like undulating pattern with a frequency of 3 to 5 cycles per minute for at least 20 minutes. A true sinusoidal pattern such as that shown in panel 5 of Figure 24-5 can be observed with fetal intracranial hemorrhage, severe fetal asphyxia, or severe fetal anemia. The last may stem from alloimmunization, fetomaternal hemorrhage, twin-twin transfusion syndrome, fetal parvoviral infection, or vasa previa with bleeding. The pathophysiology of sinusoidal patterns is unclear, in part due to varying definitions. One group proposed that the pattern relates to fetal arterial blood pressure and oscillations in the baroreceptor-chemoreceptor feedback mechanism (Ikeda, 1999). Modanlou (1982, 2004) proposed adoption of a strict definition for true sinusoidal FHR that is most likely ominous. This criteria eliminates the influence of maternal medications.

1. Stable baseline FHR of 120 to 160 bpm with regular oscillations
2. Amplitude of 5 to 15 bpm (rarely greater)
3. 2 to 5 cycles per minute
4. Absent variability and accelerations
5. Oscillation of the sinusoidal waveform above or below a baseline
6. No concurrent drugs such as narcotics

Other investigators classify sinusoidal heart rate patterns into mild—amplitude 5 to 15 bpm; intermediate—16 to 24 bpm; and major—≥25 bpm. Increasing amplitude correlates with advancing fetal risk (Murphy, 1991; Neesham, 1993).

Importantly, insignificant sinusoidal patterns have been reported following administration of meperidine, morphine, alphaprodine, and butorphanol (Angel, 1984; Egley, 1991; Epstein, 1982). When due to narcotics, this pattern has a sine frequency of 6 cycles per minute. A sinusoidal pattern also has been described with chorioamnionitis, fetal distress, and umbilical cord occlusion (Murphy, 1991). Investigators have concluded that intrapartum sinusoidal fetal heart patterns are not generally associated with fetal compromise (Johnson, 1981; Young, 1980a). Thus, management is usually dictated by the clinical setting.

Pseudosinusoidal describes intrapartum sine wave–like baseline variation coupled with periods of acceleration. In one study, this pattern was seen in 15 percent of monitored labors (Murphy, 1991). Mild pseudosinusoidal patterns were associated with use of meperidine and epidural analgesia. Intermediate pseudosinusoidal patterns were linked to fetal sucking or transient episodes of fetal hypoxia caused by umbilical cord compression. In another study, 4 percent of fetuses demonstrated sinusoidal patterns transiently during normal labor (Egley, 1991). These authors noted patterns lasting for 90 minutes in some cases.

Periodic Fetal Heart Rate Changes

These refer to visually apparent deviations from baseline. *Acceleration* refers to a rise in FHR above the baseline, and *deceleration* is a drop below the baseline rate. For the latter, terms used in the United States are *early, late,* or *variable* and refer to the temporal relationship between the deceleration and contractions. Waveform shapes also aid pattern recognition and are described subsequently. The NICHD Workshop (2008) considered decelerations to be *recurrent* if they accompanied ≥50 percent of contractions in any 20-minute period.

Accelerations

These are an abrupt FHR increase above the baseline and are defined by the onset-to-peak rise within 30 seconds (American College of Obstetricians and Gynecologists, 2019a). At ≥32 weeks' gestation, an *acceleration* is one that peaks at a point ≥15 bpm above baseline. Its duration is ≥15 seconds but <2 minutes from onset to baseline return (see Table 24-1). Before 32 weeks, a peak ≥10 bpm and duration lasting 10 seconds to 2 minutes is considered normal. *Prolonged acceleration* is one lasting ≥2 minutes but <10 minutes.

Accelerations occur antepartum and intrapartum. Proposed mechanisms for intrapartum accelerations include fetal movement, stimulation by uterine contractions, umbilical cord occlusion, fetal scalp stimulation, scalp blood sampling, and acoustic stimulation. Accelerations are common during labor. These are virtually always reassuring and almost always confirm that the fetus is not acidemic at that moment (Berkus, 1999).

Accelerations reflect intact neurohormonal cardiovascular control mechanisms linked to fetal behavioral states. In one analysis of FHR tracings in nearly 2000 fetuses, 99.8 percent showed sporadic accelerations during labor. FHR accelerations during the first or last 30 minutes of labor were a favorable sign for fetal well-being (Krebs, 1982). Their absence during labor, however, is not necessarily an unfavorable sign unless coincidental with other nonreassuring changes. The chance of acidemia in the fetus that fails to respond to stimulation despite an otherwise nonreassuring pattern approximates 50 percent (Clark, 1984; Smith, 1986).

Early Deceleration

This physiological response shows a gradual FHR decline and then return to baseline that mirrors the contraction (Fig. 24-6). Etiologically, head compression and dural stimulation probably cause vagal nerve activation, which mediates the FHR deceleration (Paul, 1964). Freeman and associates (2003) defined early decelerations as those generally seen in active labor between 4 and 7 cm cervical dilation. In their definition, the degree of deceleration is generally proportional to the contraction strength and rarely falls below 100 to 110 bpm or 20 to 30 bpm below baseline. These decelerations are common during active labor and not associated with tachycardia, loss of variability, or other FHR changes. Early decelerations are considered benign

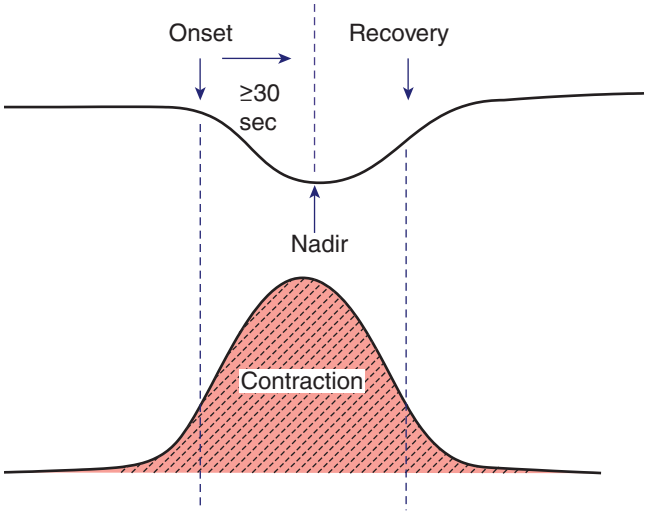

FIGURE 24-6 An early fetal heart rate deceleration characteristically shows a gradual decline and recovery in the heart rate that coincide with the onset and recovery of the contraction. The nadir of the deceleration is ≥30 seconds after the deceleration onset.

and not associated with fetal hypoxia, acidemia, or low Apgar scores.

Late Deceleration

This deceleration is a smooth, gradual, symmetrical decline in the FHR that begins at or after the contraction peak and returns to baseline only after the contraction has ended. It reaches its nadir within 30 seconds of its onset (Fig. 24-7). Typically, a late deceleration's depth is <10 to 20 bpm below baseline. These usually are not accompanied by accelerations.

Late decelerations often reflect poor uterine perfusion or placental dysfunction. In one animal study, uteroplacental perfusion was intentionally compromised, and the lag between contraction onset and late deceleration onset was directly related to basal fetal oxygenation (Myers, 1973). The lower the fetal Po_2 before contractions, the shorter the lag to the late deceleration's onset. This lag reflects the time necessary for the fetal Po_2 to fall below a critical level necessary to stimulate arterial chemoreceptors, which mediate the decelerations.

Late decelerations are the first FHR consequence of uteroplacental-induced hypoxia. Fetal acidemia develops after frequent or prolonged periods of hypoxia. However, late decelerations alone do not predict fetal acidemia (Jia, 2021). Instead, late decelerations plus decreased variability, which itself is an indicator of less activity in the cardioregulatory center of the medulla, are more predictive of fetal acidemia and neonatal morbidity (Cahill, 2018; Holzmann, 2015). Cahill and coworkers (2018) calculated the total area within the below-baseline curves of decelerations. They found that increasing area was more predictive of fetal acidemia than other FHR characteristics.

Generally, any process that produces maternal hypotension, excessive uterine activity, or placental dysfunction can induce late decelerations. The two most common are hypotension from epidural analgesia and uterine hyperactivity from oxytocin stimulation. Maternal hypertension, diabetes, and collagen vascular disorders can cause chronic placental dysfunction. Placental abruption can acutely produce late decelerations.

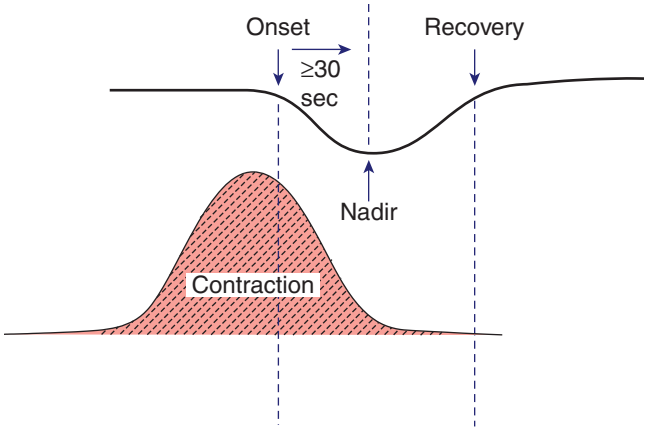

FIGURE 24-7 A late fetal heart rate deceleration characteristically shows a gradual decline in the heart rate that starts at or after the contraction's peak and recovers after the end of the contraction. The deceleration nadir occurs ≥30 seconds after the deceleration's onset.

Variable Deceleration

This is the most frequent deceleration pattern encountered during labor and is attributed to umbilical cord occlusion. In a study of more than 7000 tracings, variable decelerations were identified in 40 percent when labor had progressed to 5 cm dilation and in 83 percent by the end of first-stage labor (Melchior, 1985). The slope of FHR change is abrupt and erratic, giving the waveform its jagged shape (Fig. 24-8). A variable deceleration is defined as a drop in the FHR that begins with the contraction's onset and reaches a nadir in <30 seconds. The deceleration lasts between 15 seconds and 2 minutes, and its depth is ≥15 bpm in amplitude. The onset of deceleration typically varies with successive contractions.

Etiologically, variable deceleration often reflects some degree of umbilical cord occlusion. In one animal study, Hon (1959)

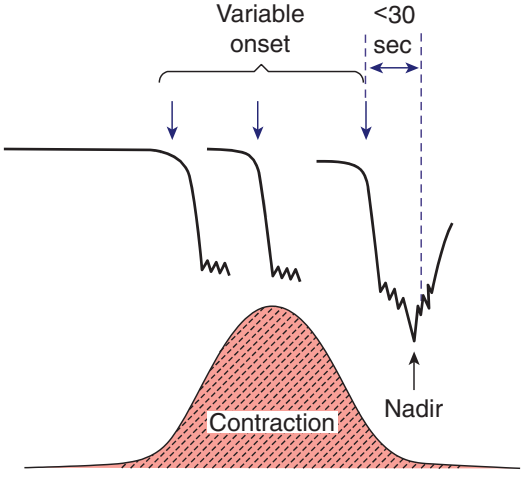

FIGURE 24-8 A variable fetal heart rate deceleration characteristically shows an abrupt drop in the heart rate, and its onset commonly varies with successive contractions. The deceleration depth measures ≥15 bpm, lasts ≥15 seconds, and has an onset-to-nadir phase <30 seconds. Its total duration is <2 minutes.

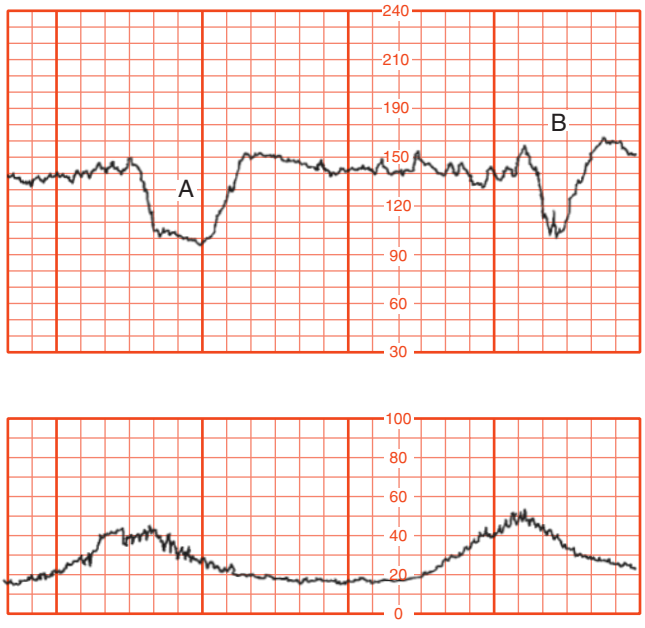

FIGURE 24-9 Variable fetal heart rate decelerations. Deceleration (*B*) exhibits "shoulders" of acceleration compared with deceleration (*A*).

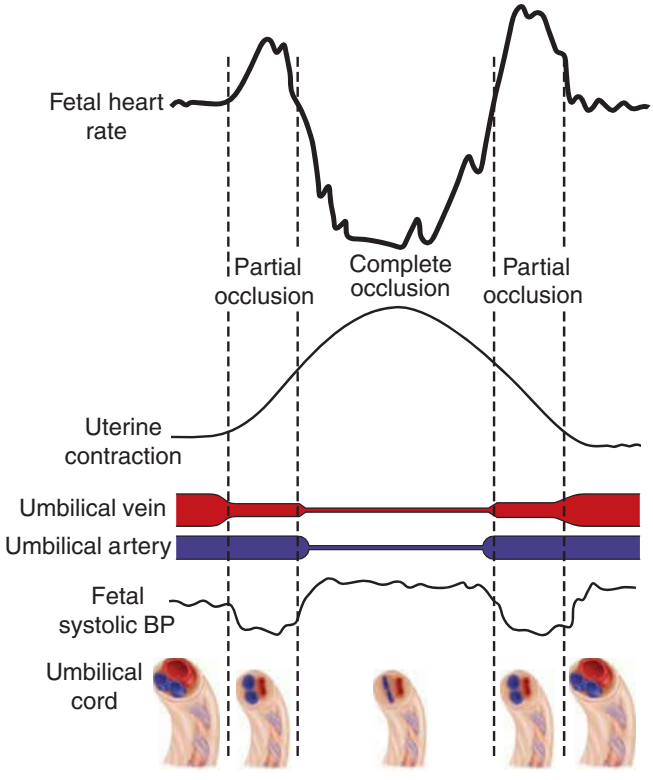

FIGURE 24-10 Schematic representation of the fetal heart rate effects with partial and complete umbilical cord occlusion. Uterine pressures generated early in a contraction cause cord compression predominantly of the thin-walled umbilical vein. The resulting decrease in fetal cardiac output leads to an initial compensatory rise in fetal heart rate. As cord compression intensifies, umbilical arteries are then also compressed. The resulting rise in fetal systolic blood pressure leads to a vagal-mediated fetal heart rate deceleration. As the contraction abates and compression is relieved first on the umbilical arteries, elevated fetal systolic blood pressures drop and the deceleration resolves. A final increase in fetal heart rate is seen as a result of persistent umbilical vein occlusion. With completion of the uterine contraction and cord compression, the fetal heart rate returns to baseline. BP = blood pressure.

assessed the effects of umbilical cord compression on FHR. He found lengthening and deepening of the deceleration curve with longer occlusion times. In another study, variable decelerations in fetal lambs occurred only after umbilical blood flow was reduced by at least 50 percent (Itskovitz, 1983).

Two patterns of variable decelerations are shown in Figure 24-9. The deceleration denoted by "A" is very much like that seen with complete umbilical cord occlusion in experimental animals. However, deceleration "B" differs and displays an acceleration before and after the deceleration component. Lee and coworkers (1975) proposed that this form was caused by differing degrees of cord occlusion. In this scheme, occlusion of only the vein reduces fetal blood return and thereby triggers a baroreceptor-mediated acceleration. With increasing intrauterine pressure and subsequent complete cord occlusion, fetal systemic hypertension develops due to obstructed umbilical artery flow. This stimulates a baroreceptor-mediated deceleration. Presumably, the aftercoming acceleration represents the same events occurring in reverse (Fig. 24-10) (Lee, 1975). Ball and Parer (1992) concluded that variable decelerations are mediated vagally and that the vagal response may be due to chemoreceptor or baroreceptor activity or both. Partial or complete cord occlusion produces an increase in afterload (baroreceptor) and a drop in fetal arterial oxygen content (chemoreceptor). Both result in vagal activity leading to deceleration.

Thus, variable decelerations represent FHR reflexes that reflect either blood pressure changes due to interruption of umbilical flow or changes in oxygenation. It is likely that most fetuses have experienced brief but recurrent periods of hypoxia due to umbilical cord compression during gestation. The great dilemma for the obstetrician in managing variable FHR decelerations is determining when variable decelerations are pathological. According to the American College of Obstetricians and Gynecologists (2019a), recurrent variable decelerations with minimal to moderate variability are *indeterminate*, whereas those with absent variability are *abnormal*.

A *saltatory* FHR baseline is another pattern linked to umbilical cord complications during labor (Fig. 24-11) (Hammacher, 1968). The pattern is rapidly recurring couplets of acceleration and deceleration causing relatively large oscillations of the FHR baseline. We also observed a relationship between cord occlusion and the saltatory pattern in postterm pregnancies (Leveno, 1984). In the absence of other FHR findings, this pattern does not signal fetal compromise.

Prolonged Deceleration

This pattern is defined as an isolated deceleration with a depth >15 bpm and length ≥2 minutes but <10 minutes from onset to return to baseline (Fig. 24-12). Prolonged decelerations are difficult to interpret because they are seen in many different clinical situations. Frequent causes are cervical examination, uterine hyperactivity, cord entanglement, and maternal supine hypotension. Epidural, spinal, or

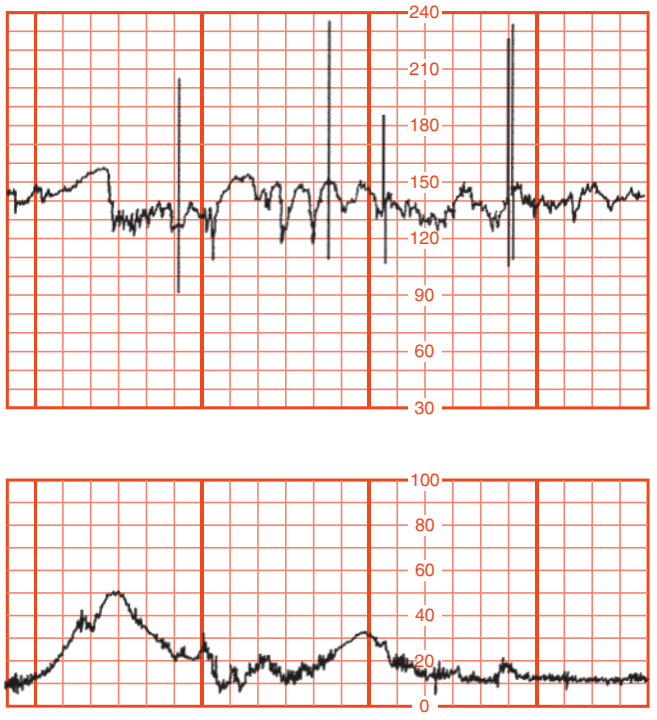

FIGURE 24-11 Saltatory baseline fetal heart rate showing rapidly recurring couplets of acceleration combined with deceleration.

paracervical analgesia may induce a prolonged deceleration (Eberle, 1998). Of women given epidural analgesia during labor in one analysis at Parkland Hospital, prolonged deceleration was noted in 1 percent (Hill, 2003). Other causes include placental abruption, umbilical cord knots or prolapse, maternal hypoperfusion or hypoxia from any cause, maternal seizures, fetal scalp-electrode application, impending birth, or maternal Valsalva maneuver.

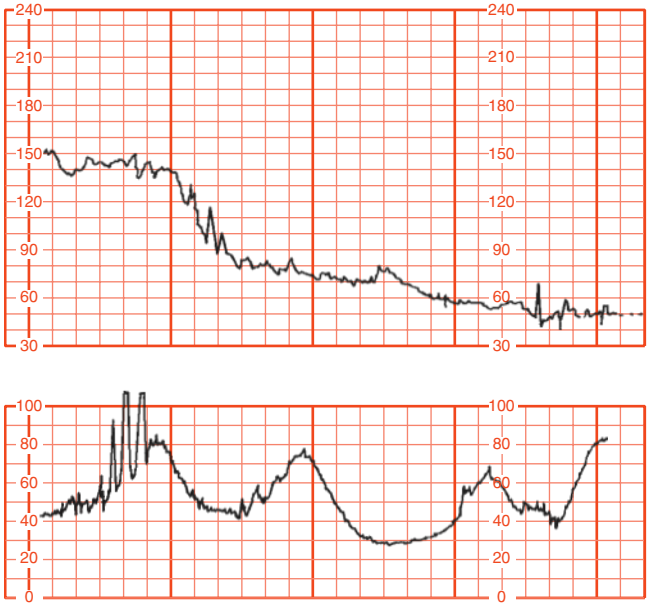

FIGURE 24-12 Prolonged fetal heart rate deceleration due to uterine hyperactivity. Approximately 3 minutes of the tracing are shown, but the fetal heart rate returned to normal after uterine hypertonus resolved. Vaginal delivery later ensued.

The placenta can effectively resuscitate the fetus if the original insult does not recur immediately. Occasionally, such self-limited prolonged decelerations are followed by loss of variability, baseline tachycardia, and even a period of late decelerations. These all resolve as the fetus recovers. Freeman and colleagues (2003) emphasize that the fetus may die during prolonged decelerations. Thus, management of prolonged decelerations can be extremely tenuous. Management of isolated prolonged decelerations is based on bedside clinical judgment, which inevitably will sometimes be imperfect given the unpredictability of these decelerations.

Fetal Heart Rate Patterns During Second-stage Labor

Decelerations are virtually ubiquitous during the second-stage labor. In one study, only 1.4 percent of more than 7000 deliveries lacked decelerations during this stage (Melchior, 1985). Both cord and fetal head compressions are implicated as causes of decelerations and of baseline bradycardia in this stage. In one series, profound, prolonged FHR deceleration in the 10 minutes preceding vaginal delivery was associated with intervention and good fetal outcomes (Boehm, 1975). In a later extension of this series, similarly prolonged second-stage decelerations were also associated with a stillbirth and neonatal death (Herbert, 1981). These experiences attest to the unpredictability of the FHR during second-stage labor.

In the analysis noted earlier by Cahill and associates (2018), an increasing total deceleration area found in the final 120 minutes prior to delivery was most predictive of fetal acidemia. A combination of deceleration area plus a 10-minute period of tachycardia was most predictive of neonatal morbidity. Others have reported similar findings (Krebs, 1981; Picquard, 1988). Gull and colleagues (1996) observed that abrupt FHR decelerations to <100 bpm associated with lost variability for ≥4 minutes predicted fetal acidemia. Thus, second-stage decelerations plus an abnormal FHR baseline (bradycardia or tachycardia and/or absent variability) are associated with greater risk for fetal compromise (Fig. 24-13).

Computerized Interpretation

FHR pattern interpretations are subjective. Thus, the potential for computer assistance to enhance the precision of identifying abnormal patterns appeared promising. The INFANT Collaborative Group (2017) studied whether the addition of computer-based decision-support software for FHR pattern interpretation lowered the number of poor neonatal outcomes. In this large trial, women were randomly assigned to computer-assisted interpretation or to conventional clinical interpretation. Rates of adverse perinatal outcomes that included intrapartum stillbirth, early neonatal death, and neonatal encephalopathy were not improved, and a subset showed no difference in neurological development at 2 years. Cesarean delivery rates were similar in both groups. In a subsequent analysis of 71 adverse outcomes, computer interpretation of FHR tracings was deemed completely valid in only 34 percent of cases. Computer analysis missed a significant portion of decelerations, reduced variability, and tachysystole (Steer, 2019).

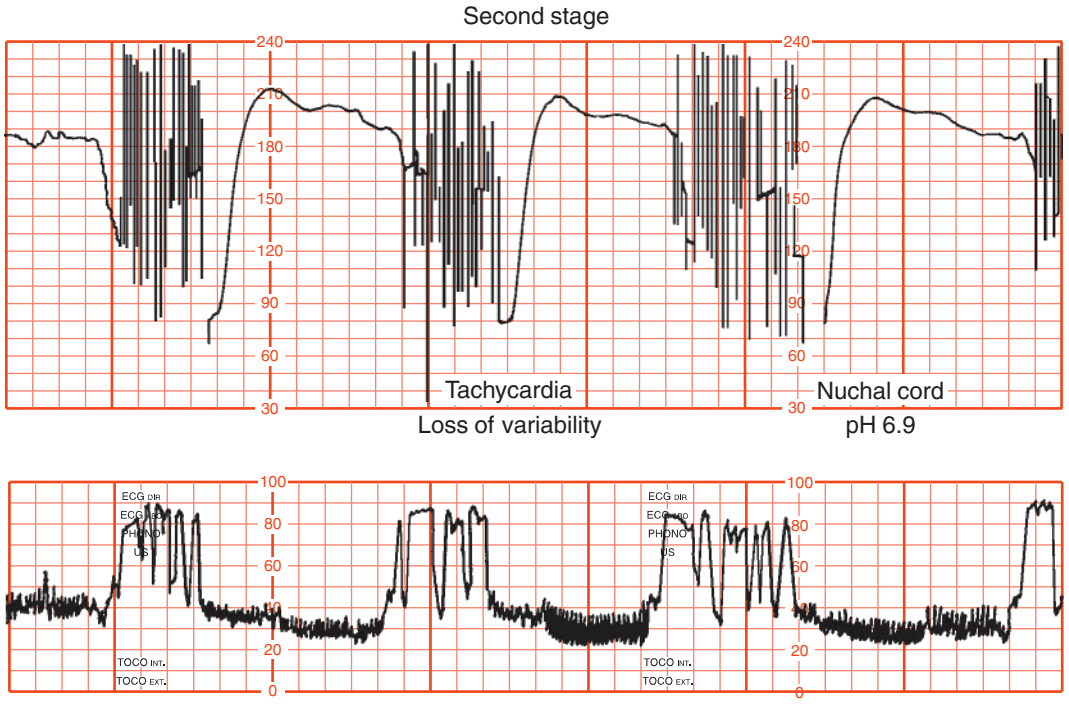

FIGURE 24-13 Cord-compression fetal heart rate decelerations in second-stage labor associated with tachycardia and loss of variability. The umbilical cord arterial pH was 6.9.

OTHER INTRAPARTUM ASSESSMENT TECHNIQUES

Fetal Scalp Blood Sampling

According to the American College of Obstetricians and Gynecologists (2019a), measurements of the pH in capillary scalp blood may help identify the fetus in serious distress. However, this group also emphasizes that neither normal nor abnormal scalp pH results accurately predict neonatal outcome. Although used in other countries, the procedure is not available at most hospitals in the United States.

With sampling, an illuminated endoscope is inserted through the dilated cervix after membrane rupture and is pressed firmly against the fetal scalp. The skin is wiped clean with a cotton swab and coated with a silicone gel, which allows fetal blood to accumulate as discrete globules. An incision is made through the fetal scalp to a depth of 2 mm with a special blade on a long handle. As a drop of blood forms on the surface, it is immediately collected into a heparinized glass capillary tube. The blood pH is measured promptly.

The pH of fetal capillary scalp blood is usually lower than that of umbilical venous blood and approaches that of umbilical arterial blood. In one algorithm, if the pH is ≥7.25, labor is observed, and if between 7.20 and 7.25, the pH measurement is repeated within 30 minutes (Zalar, 1979). If the pH is <7.20, another scalp blood sample is collected immediately, and delivery is performed promptly if the low pH level is confirmed. Otherwise, labor is allowed to continue, and scalp blood samples are repeated periodically.

The only benefits reported for scalp blood pH testing are fewer cesarean deliveries for fetal distress (Young, 1980b). However, Goodwin and coworkers (1994) showed a decrease in the scalp pH sampling rate from approximately 1.8 percent in the mid-1980s to 0.03 percent by 1992. This drop in sampling rate was not associated with a higher cesarean delivery rate for fetal distress. They concluded that scalp blood pH sampling was unnecessary.

Kruger and colleagues (1999) have assessed fetal scalp blood lactate concentration as an adjunct to pH. In one large randomized study, fetuses received scalp blood pH analysis or scalp blood lactate analysis (Wiberg-Itzel, 2008). The authors found either to be equivalent in predicting fetal acidemia. In a secondary analysis, prediction of low Apgar scores or admission to the neonatal intensive care unit did not differ between lactate and pH groups (Stal, 2020). However, cesarean delivery rates were higher in the lactate group.

Scalp Stimulation

Clark and coworkers (1984) have suggested that fetal scalp stimulation is an alternative to scalp blood sampling. This proposal stemmed from the observation that FHR acceleration followed pinching the fetal scalp with an Allis clamp just before obtaining scalp blood and was invariably associated with a normal pH level. However, failure to provoke acceleration was not uniformly predictive of fetal acidemia. In another study of 58 cases in which the FHR accelerated >10 bpm after 15 seconds of digital scalp stroking, 100 percent had a scalp blood pH >7.20 (Elimian, 1997). However, without an acceleration, only 30 percent had a scalp blood pH >7.20. Authors of a recent prospective study concluded that scalp stimulation was a reliable alternative to fetal scalp blood pH determination (Tahir Mahmood, 2018). In our practice, scalp stimulation is

often one element of intrapartum assessment of the fetus with a category II tracing.

Vibroacoustic Stimulation

FHR acceleration in response to vibroacoustic stimulation is another substitute for fetal scalp blood sampling (Edersheim, 1987). The technique uses an electronic artificial larynx placed 1 cm from or directly onto the maternal abdomen (Chap. 20, p. 387). Response to vibroacoustic stimulation is considered normal if the FHR accelerates within 15 seconds after the stimulus and with prolonged fetal movements (Sherer, 1994).

Lin and colleagues (2001) prospectively studied vibroacoustic stimulation in 113 women in labor with either moderate to severe variable or late FHR decelerations. They concluded that this technique effectively predicts fetal acidosis in cases with variable decelerations. In the setting of late decelerations, its prediction of fetal acidosis, however, is limited. Other authors found vibroacoustic stimulation in second-stage labor did not predict neonatal outcome or enhance labor management (Anyaegbunam, 1994).

Skupski and coworkers (2002) performed a metaanalysis of reports on intrapartum fetal stimulation tests. These included fetal scalp puncture for blood pH testing, fetal scalp pinching, vibroacoustic stimulation, and digital stroking of the fetal scalp. Results were similar for all four methods. These authors concluded that intrapartum stimulation tests were useful to exclude fetal acidemia. They cautioned, however, that these tests are "less than perfect."

Fetal Pulse Oximetry

Using technology similar to that of adult pulse oximetry, this tool measures fetal oxyhemoglobin saturation once membranes are ruptured. A unique padlike sensor is inserted through the cervix and positioned against the fetal face. Using fetal pulse oximetry, the lower limit for normal fetal oxygen saturation is generally considered to be 30 percent (Gorenberg, 2003; Stiller, 2002). However, when measured in umbilical arterial blood, fetal oxygen saturation normally varies greatly.

In one large trial of this technology, women with term fetuses that developed abnormal FHR patterns were assigned to conventional FHR monitoring alone or FHR monitoring plus continuous fetal pulse oximetry (Garite, 2000). The use of fetal pulse oximetry significantly reduced the cesarean delivery rate for nonreassuring fetal status from 10.2 to 4.5 percent. No neonatal benefits or adverse effects were associated with fetal pulse oximetry. Based on these observations, the U.S. Food and Drug Administration (FDA) approved marketing of the Nellcor N-400 Fetal Oxygen Monitoring System. However, three subsequent trials compared fetal pulse oximetry with standard care. In each, neonatal outcomes were similar between study arms. In one, the addition of oximetry significantly reduced cesarean delivery rates for fetal indications (East, 2006). However, two studies found no difference in cesarean delivery rates between the two study arms (Bloom, 2006; Klauser, 2005). Because of these findings, in 2005, the manufacturer discontinued device sales in the United States.

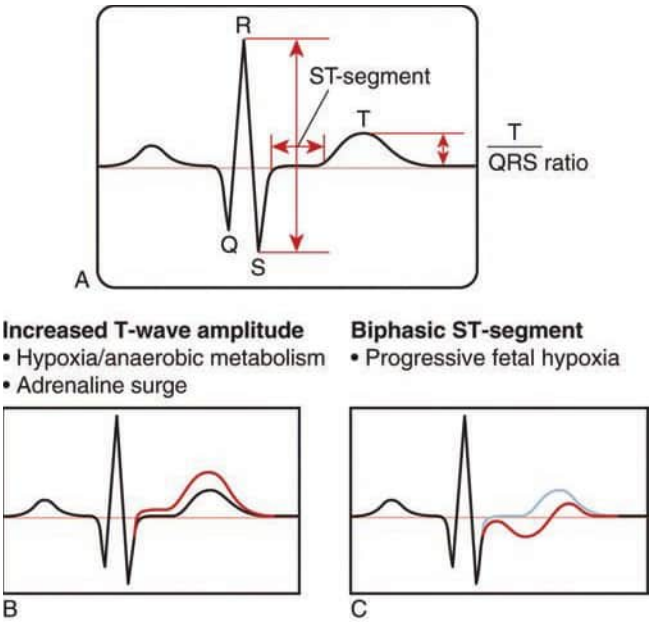

FIGURE 24-14 A. Generation of T:QRS ratio from a normal ST segment. **B.** ST-segment elevation in hypoxic conditions. **C.** Biphasic ST-segment waveform with progressive fetal hypoxia.

Fetal Electrocardiography

As fetal hypoxia worsens, the fetal ECG changes. Namely, the mature fetus with hypoxemia develops an elevated ST segment and a progressive rise in the T-wave height that can be expressed as a T:QRS ratio (Fig. 24-14) (Devoe, 2006). Increasing T:QRS ratios are thought to reflect fetal cardiac ability to adapt to hypoxia and appear before neurological damage. Further worsening of hypoxia then leads to progressively negative ST-segment deflection that creates a biphasic form. It is reasonable to consider that ST-segment abnormalities might occur late in the course of fetal compromise. Indeed, it has been hypothesized that ST-segment changes reflect myocardial tissue hypoxia.

Because of these findings, these parameters have been evaluated as an adjunct to conventional fetal monitoring. The technique requires internal FHR monitoring and special equipment to process the fetal ECG. In 2005, the manufacturer—Neoventa Medical—received FDA approval for their ST-segment analysis program named the *STAN system*.

Several studies have evaluated ST-segment changes with fetal monitoring. In one randomized trial of 2400 pregnancies, neonatal outcomes were not improved compared with those in which conventional FHR monitoring alone was used (Westgate, 1993). However, the cesarean delivery rate for fetal distress declined in those with ST-segment analysis. Subsequent studies revealed conflicting data regarding lower rates of operative delivery, fetal acidemia, and neonatal encephalopathy (Amer-Wåhlin, 2001; Becker, 2012; Doria, 2007).

In a trial by the NICHD, 5532 women were randomly assigned to an ST-segment analysis and 5576 to standard intrapartum management. The primary outcome was a composite of one or more of seven events associated with fetal compromise (Belfort, 2015). In the ST-segment analysis group, clinician

actions were directed by predetermined guidelines. These stipulated that intervention should be withheld, that is, expectant management adopted, for at least 60 minutes despite the presence of minimal variability; variable decelerations lasting ≥60 seconds or dropping to a level ≥60 bpm; recurrent late decelerations; or prolonged decelerations lasting >2 minutes, so long as no ST-segment abnormality was present. These guidelines did not pertain to the standard group. Notably, in the ST-segment analysis group, 55 (20 percent) of the 287 cesarean deliveries performed for fetal indications were done even though trial guidelines indicated that labor could continue. In these cases, physicians likely perceived the FHR patterns to reflect those formerly accepted in their usual practice as nonreassuring. These results showed that STAN system had no effect on neonatal outcome or cesarean delivery rates (Belfort, 2015). A subsequent systematic review reached similar conclusions (Neilson, 2015). These results have essentially eliminated use of ST-segment analysis in the United States, but it is still used in Europe.

NONREASSURING FETAL STATUS

The term *fetal distress* is too broad and vague to be applied with any precision to clinical situations (American College of Obstetricians and Gynecologists, 2019d). Uncertainty regarding the diagnosis based on FHR pattern interpretation has given rise to descriptions such as *reassuring* or *nonreassuring*. The former suggests confidence in the health of the fetus. In contrast, a nonreassuring designation suggests inability to remove doubt. However, these assessments are subjective judgments that are inevitably imperfect and must be recognized as such. The American College of Obstetricians and Gynecologists (2019d) recommends use of these terms followed by a description of the findings.

The difficulty in assigning a nonreassuring label to FHR patterns stems in part from the fact that these patterns reflect fetal physiology more so than pathology. Heart rate control stems from interconnected mechanisms that depend on blood flow and oxygenation. Moreover, these mechanisms are influenced by the preexisting state of fetal oxygenation. Chronic placental insufficiency is one example. Thus, normal labor is a process of repeated fetal hypoxic events and can infrequently lead to significant acidemia (Rogers, 1998).

Diagnosis

Identification of nonreassuring fetal status based on FHR patterns is imprecise. One study of interobserver agreement with FHR pattern interpretation found that consensus varied (Ayres-de-Campos, 1999). Specifically, experts agreed on 62 percent of normal patterns, 42 percent of suspicious patterns, and only 25 percent of pathological patterns. In another study, 17 experts reviewed 50 tracings on two occasions, at least 1 month apart. Approximately 20 percent changed their own interpretations, and approximately 25 percent did not agree with the interpretations of their colleagues (Keith, 1995).

In an attempt to resolve this imprecision, the NICHD recommended a three-tier system for FHR pattern classification (Table 24-2). The American College of Obstetricians and Gynecologists (2019b) has recommended its use. To assess this tiered system, Jackson and associates (2011) studied 48,444 women in labor and found that category I patterns were observed in 99.5 percent of tracings. Category II patterns were found in 84.1 percent, and category III patterns were seen in 0.1 percent

TABLE 24-2. Three-Tier Fetal Heart Rate Interpretation System

Category I—Normal

Include all of the following:

- Baseline rate: 110–160 bpm
- Baseline FHR variability: moderate
- Late or variable decelerations: absent
- Early decelerations: present or absent
- Accelerations: present or absent

Category II—Indeterminate

Include all FHR tracings not categorized as category I or III.

Category II tracings may represent an appreciable fraction of those encountered in clinical care. Examples include any of the following:

Baseline rate

- Bradycardia not accompanied by absent baseline variability
- Tachycardia

Baseline FHR variability

- Minimal baseline variability
- Absent baseline variability not accompanied by recurrent decelerations
- Marked baseline variability

Accelerations

- Absence of induced accelerations after fetal stimulation

Periodic or episodic decelerations

- Recurrent variable decelerations accompanied by minimal or moderate baseline variability
- Prolonged deceleration ≥2 min but <10 min
- Recurrent late decelerations with moderate baseline variability
- Variable decelerations with other characteristics, such as slow return to baseline, "overshoots," or "shoulders"

Category III—Abnormal

Include either:

- Absent baseline FHR variability and any of the following:
  Recurrent late decelerations
  Recurrent variable decelerations
  Bradycardia
- Sinusoidal pattern

bpm = beats per minute; FHR = fetal heart rate.
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(54 women). During labor, 84 percent of women had a mix of categories. The American College of Obstetricians and Gynecologists and the American Academy of Pediatrics (2019d) has concluded that a category I or II tracing with a 5-minute Apgar score >7 or with normal arterial blood acid–base values is not consistent with an acute hypoxic-ischemic event.

Other studies have evaluated this three-tiered system. In one, the incidence of umbilical cord acidemia (pH ≤7.10) was correlated retrospectively with FHR characteristics during the 30 minutes preceding delivery. None of the three categories demonstrated a significant association with cord blood acidemia (Cahill, 2012). Sholapurkar (2012) has challenged the validity of the three-tier system because most abnormal FHR patterns fall into the indeterminate category II. It was suggested that this resulted from most FHR decelerations being inappropriately classified as *variable* and attributed to cord compression.

Parer and King (2010) compared this situation in the United States with that of other countries in which a consensus on classification and management has been reached by their professional societies. These authors note that the NICHD three-tier system is inadequate because category II contains a vast heterogenous mixture of patterns that prevents development of a management strategy. Weissbach and associates (2018) found that duration of category II tracings does not predict perinatal asphyxia, but the individual components of diminished variability and fetal tachycardia are predictive.

Parer and Ikeda (2007) had previously proposed a color-coded five-tier system for both FHR interpretation *and* management. Two subsequent reports have compared the five- and three-tier systems. In one, the two systems were similar in FHR interpretations for tracings that were either very normal or very abnormal (Bannerman, 2011). The other study found that the five-tier system had better sensitivity than the three-tier one (Coletta, 2012). It is apparent that despite decades of electronic FHR monitoring, a consensus on FHR pattern interpretation and diagnosis is still lacking (Parer, 2011).

■ Meconium in the Amnionic Fluid

Obstetricians have long realized that meconium during labor is an inaccurate predictor of fetal distress or asphyxia. Indeed, although 12 to 22 percent of labors are complicated by meconium, only a few are linked to neonatal mortality. In an investigation from Parkland Hospital, meconium was found to be a "low-risk" obstetrical hazard because the perinatal mortality rate attributable to meconium was only 1 death per 1000 live births (Nathan, 1994).

Three etiological theories may explain the tenuous association between meconium passage and neonatal mortality. First, fetuses may pass meconium in response to hypoxia, and meconium therefore signals fetal compromise (Walker, 1953). Second, however, in utero passage of meconium may represent normal gastrointestinal tract maturation under neural control (Mathews, 1979). A final theory posits that common but transient umbilical cord entrapment leads to vagal stimulation, increased bowel peristalsis, and meconium passage (Hon, 1961).

Jovanovic and Nguyen (1989) observed that meconium aspirated into fetal lungs during gasping caused aspiration syndrome only in asphyxiated animals. Ramin and associates (1996) studied almost 8000 pregnancies with meconium-stained amnionic fluid delivered at Parkland Hospital. Meconium aspiration syndrome was significantly associated with fetal acidemia at birth. Further analysis of umbilical blood gases suggested that the fetal compromise associated with meconium aspiration syndrome was an acute event. This is because most acidemic fetuses had abnormally elevated P_{CO_2} values rather than a pure metabolic acidemia. Other significant correlates of aspiration included cesarean delivery, forceps to expedite delivery, intrapartum FHR abnormalities, depressed Apgar scores, and need for assisted ventilation at delivery.

Ramin and colleagues (1996) hypothesized that the pathophysiology of meconium aspiration syndrome includes, but is not limited to, fetal hypercarbia, which stimulates fetal respiration leading to aspiration of meconium into the alveoli. Lung parenchymal injury is secondary to acidemia-induced alveolar cell damage. In this pathophysiological scenario, meconium in amnionic fluid is a fetal environmental hazard rather than a marker of preexisting compromise. This proposed pathophysiological sequence is not all-inclusive, because it does not account for approximately half of the cases of meconium aspiration syndrome in which the fetus is not acidemic at birth.

Thus, the high incidence of meconium observed in the amnionic fluid during labor often represents normal physiological fetal passage of gastrointestinal contents. Although normal, such meconium becomes an environmental hazard when fetal acidemia from hypercarbia supervenes. Importantly, such acidemia occurs acutely, and therefore meconium aspiration is unpredictable and likely unpreventable.

Growing evidence indicates that many newborns with meconium aspiration syndrome have suffered chronic hypoxia before birth (Ghidini, 2001). In one study, 60 percent of neonates diagnosed with meconium aspiration syndrome had umbilical artery blood pH ≥7.20, which implies that the syndrome was unrelated to the neonatal condition at delivery (Blackwell, 2001). Similarly, comorbid markers of chronic hypoxia, such as elevated fetal erythropoietin levels and increased nucleated red blood cell counts in newborns, suggest that chronic hypoxia is involved in many meconium aspiration syndrome cases (Dollberg, 2001; Jazayeri, 2000).

Previously, routine obstetrical management of a newborn with meconium-stained amnionic fluid included intrapartum suctioning of the oropharynx and nasopharynx. Current recommendations state that newborns with meconium-stained amnionic fluid, regardless of their vigor, should no longer routinely receive intrapartum suctioning (American College of Obstetricians and Gynecologists, 2021; Wyckoff, 2015). Suctioning is reserved for those with airway obstruction. They also recommend that an appropriately credentialed team with full resuscitation skills be available (Chap. 32, p. 586).

■ Management Options

Initial management of variant FHR patterns aims to correct any fetal insult, if possible. Suggestions are listed in Table 24-3. The woman is moved to a lateral position, and supplemental oxygen is provided by mask. Correcting maternal hypotension

TABLE 24-3. Some Resuscitative Measures for Category II or Category III Tracings

Fetal Heart Rate Abnormality[a]	Interventions[b]
Recurrent late decelerations Minimal or absent FHR variability	Initial actions: lateral decubitus positioning; administer maternal oxygen; intravenous fluid bolus; reduce uterine contraction frequency
Prolonged decelerations or bradycardia Tachysystole with category II or III tracing	Initial actions plus discontinue oxytocin or prostaglandins; consider terbutaline
Recurrent variable decelerations Prolonged decelerations or bradycardia	Initial actions plus consider amnioinfusion; with cord prolapse, manually elevate the presenting part while preparing for immediate delivery

[a]Simultaneous evaluation of the suspected cause(s) is also an important step in management of abnormal FHR tracings.
[b]The combination of multiple interventions simultaneously may be appropriate and potentially more effective than doing them individually or serially.
FHR = fetal heart rate.

caused by regional analgesia and discontinuing oxytocin both serve to improve uteroplacental perfusion. Vaginal examination excludes a prolapsed cord or impending delivery. Simpson and James (2005) assessed the benefits of three maneuvers in 52 women with fetal oxygen saturation sensors already in place. They provided IV hydration with 500 to 1000 mL of lactated Ringer solution given over 20 minutes; lateral versus supine positioning; and administration of supplemental oxygen at 10 L/min using a nonrebreathing mask. Each of these maneuvers significantly raised fetal oxygen saturation levels. A randomized trial comparing oxygen via face mask to room air showed no difference in resolution of recurrent decelerations (75 percent versus 86 percent), time to resolution of recurrent decelerations, and total deceleration area (Raghuraman, 2020b).

Tocolysis

Terbutaline sulfate given to relax the uterus can be a temporizing maneuver in the management of nonreassuring FHR patterns during labor. A single 250-μg IV or subcutaneous injection is used to inhibit uterine contractions and thereby improve fetal oxygenation. One study described 368 pregnancies in which terbutaline was used to relieve contractions in preparation for cesarean delivery that was already planned for nonreassuring fetal status (Cook, 1994). Compared with a group not receiving tocolysis, the treated group had fewer 5-minute Apgar scores <7. Small IV doses of nitroglycerin—60 to 180 μg—also have reported benefit (Mercier, 1997). In one comparator study, both agents resolved tachysystole, but nitroglycerin lowered mean arterial blood pressures (Pullen, 2007). Two systematic reviews both noted that data were limited and reached differing views on tocolysis benefits (Bullens, 2015; Leathersich, 2018). The American College of Obstetricians and Gynecologists (2019b) cites that evidence is insufficient to recommend tocolysis for nonreassuring FHR patterns. We consider terbutaline during labor stimulation to resolve tachysystole-associated prolonged decelerations. However, the chance of success is balanced against terbutaline's side effects should cesarean delivery be needed for unresolved bradycardia. Namely, β agonist–related maternal tachycardia exacerbates the tachycardia associated with surgery itself. We consider maternal cardiopulmonary disease, poorly controlled hyperthyroidism, and maternal or fetal tachycardia with loss of variability to be contraindications.

Amnioinfusion

Early studies infused saline through an intrauterine pressure catheter in laboring women who had either variable or prolonged decelerations attributed to cord compression (Miyazaki, 1983, 1985). Such therapy improved the FHR pattern and decreased cesarean delivery rates for fetal indications. For variable decelerations, other studies also support amnioinfusion to reduce variable deceleration frequency, improve neonatal outcome, and lower cesarean delivery rates (Hofmeyr, 2012; Raghuraman, 2020a). The American Academy of Pediatrics and the American College of Obstetricians and Gynecologists (2017) conclude that amnioinfusion is a reasonable approach to treat repetitive variable decelerations but not late decelerations. As a prophylactic tool in known cases of oligohydramnios, evidence does not support amnioinfusion to prevent cord compression-related decelerations (Nageotte, 1991; Ogundipe, 1994). Last, attempts to flush out or dilute thick meconium are not recommended (Fraser, 2005; Xu, 2007).

Despite differing amnioinfusion protocols, most provide a 500- to 800-mL bolus of warmed normal saline, which is followed by a continuous infusion of 3 mL/min (Owen, 1990; Pressman, 1996). Rinehart and colleagues (2000) administered a 500-mL bolus of normal saline at room temperature alone or this bolus plus a continuous infusion at 3 mL/min. They included 65 women with variable decelerations and found neither method to be superior. Potential amnioinfusion complications are summarized in Table 24-4 from a U.S. survey of fellowship and residency directors (Wenstrom, 1995).

TABLE 24-4. Complications Associated with Amnioinfusion from a Survey of 186 Obstetrical Units

Complication	Percent
Uterine hypertonus	14
Abnormal fetal heart rate tracing	9
Chorioamnionitis	4
Maternal cardiac or respiratory compromise	2
Uterine rupture	2
Maternal death	1
Other: cord prolapse, abruption	5

Fetal Heart Rate Patterns and Brain Injury

Studies attempting to correlate FHR patterns with brain injury have primarily examined infants identified in medicolegal actions. Phelan and Ahn (1994) reported that among 48 fetuses later found to be neurologically impaired, a persistent nonreactive FHR tracing was already present at the time of admission in 70 percent. They concluded that fetal neurological injury occurred predominantly before arrival to the hospital. When they looked retrospectively at FHR patterns in 209 brain-injured newborns, they concluded that there was not a single unique pattern associated with fetal neurological injury (Ahn, 1996). Others have reported the same conclusion (Nakao, 2020; Phelan, 2000). In a review of literature published between 1966 and 2006 on the effect of FHR monitoring to prevent perinatal brain injury, the summary found no benefit (Graham, 2006).

FHR patterns necessary for perinatal brain damage have been studied in animals. Myers (1972) described the effects of complete and partial asphyxia in rhesus monkeys (Fig. 24-15). Complete asphyxia was produced by total occlusion of umbilical blood flow that led to prolonged deceleration. Fetal arterial pH did not drop to 7.0 until approximately 8 minutes after complete cessation of oxygenation and umbilical flow. At least 10 minutes of such prolonged deceleration were required before surviving fetuses demonstrated brain damage.

The most common FHR pattern during labor—due to umbilical cord occlusion—requires considerable time to significantly affect the fetus in experimental animals. Clapp and colleagues (1988) partially occluded the umbilical cord for 1 minute every 3 minutes in fetal sheep. Rocha and associates (2004) totally occluded the umbilical cord for 90 seconds every 30 minutes for 3 to 5 hours a day for 4 days without producing necrotic brain cell injury. Results from such studies suggest that the effects of umbilical cord entrapment depend on the degree, the duration, and the frequency of such occlusions.

The contribution of intrapartum events to subsequent neurological handicaps has been greatly overestimated, as discussed in Chapter 33 (p. 601). For brain damage, the fetus must be exposed to much more than a brief period of hypoxia. Moreover, the hypoxia must cause profound, just barely sublethal metabolic acidemia. Because of this, the American College of Obstetricians and Gynecologists (2019d) has recommended umbilical cord blood gases be obtained when cesarean delivery is performed for fetal compromise or when a low 5-minute Apgar score, severe fetal-growth restriction, an abnormal FHR tracing, or multifetal gestation is present (Chap. 32, p. 593).

Until recently, the prognosis for moderately affected newborns with hypoxic-ischemic encephalopathy (HIE) was poor. More recently, studies show that brain cooling administered to newborns suffering neonatal HIE could ameliorate the development of subsequent cerebral palsy (Chap. 33, p. 602).

Benefits of Electronic Fetal Heart Rate Monitoring

Several false assumptions underlie the expectation of improved perinatal outcome with electronic FHR monitoring. One is that nonreassuring fetal status is a slowly developing phenomenon and that electronic monitoring permits early detection of the compromised fetus. Another presumption is that all fetal injury develops in the hospital. In reality, most neurologically damaged fetuses suffer insults before arrival at labor units. The very term *fetal monitor* implies that this inanimate technology in some fashion "monitors." The assumption is made that if a dead or damaged fetus is delivered, the tracing strip must provide some clue, because this device was monitoring fetal condition. These assumptions led to expectations that all neonatal deaths or injuries were preventable.

By the end of the 1970s, questions regarding the efficacy, safety, and costs of electronic monitoring were being voiced. Banta and Thacker (2002) reviewed the benefits, or lack thereof, of electronic FHR monitoring. More recently, a review of 13 randomized trials involving more than 37,000 women concluded that electronic FHR monitoring was associated with fewer neonatal seizures but a higher rate of cesarean and operative vaginal deliveries (Alfirevic, 2017). However, rates of perinatal mortality or cerebral palsy did not decline. Grimes and Peipert (2010) concluded that such monitoring has failed as a public health screening program. They noted that the positive-predictive value of electronic FHR monitoring for fetal death in labor or cerebral palsy is near zero and reflects that "almost every positive test result is wrong."

Epidemiologically, two large studies in the United States reported a decline in neonatal mortality rates due to electronic

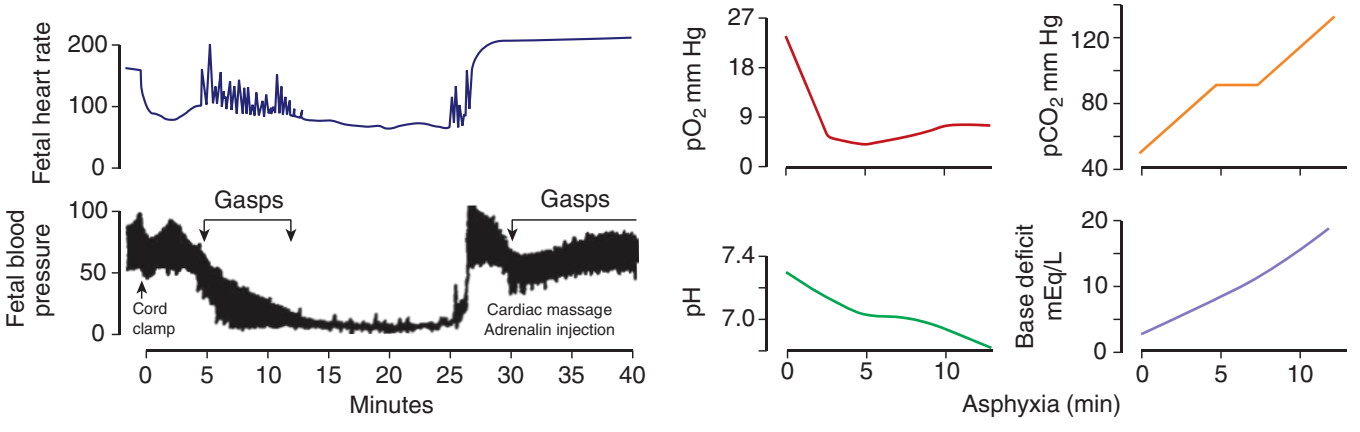

FIGURE 24-15 Prolonged deceleration in a rhesus monkey shown with blood pressure and biochemical changes during total occlusion of umbilical cord blood flow.

FHR monitoring. However, the highest effect was seen in preterm neonates (Ananth, 2013; Chen, 2011). Of note, caution must be used in interpreting these studies, as epidemiological association does not establish causation (Resnik, 2013).

At admission for labor, most women with low-risk pregnancies are monitored for a short time. In one study, 3752 low-risk women in spontaneous labor were randomly assigned at admission to either FHR auscultation or 20 minutes of electronic FHR monitoring (Mires, 2001). Electronic FHR monitoring did not improve neonatal outcome. Moreover, its use resulted in a greater number of interventions, including operative delivery. A similar study echoed these neonatal outcomes (Impey, 2003). Last, admission FHR monitoring for low-risk pregnancy is associated with a higher cesarean delivery rate but not improved neonatal outcomes in one Cochrane review (Devane, 2017).

At Parkland Hospital in July 1982, an investigation began to ascertain whether all women during labor should undergo electronic monitoring (Leveno, 1986). In alternating months, universal electronic FHR monitoring was rotated with selective FHR monitoring, which was the prevailing practice. During the 3-year investigation, more than 17,000 labors were managed using universal electronic FHR monitoring, and these outcomes were compared with a similar-sized cohort of women selectively monitored electronically. No significant differences were found in any perinatal outcome. With universal monitoring, a small but significant increase in the cesarean delivery rate for fetal distress was noted. Thus, greater application of electronic FHR monitoring at Parkland Hospital did not improve perinatal results but did slightly raise the frequency of cesarean delivery for fetal distress. More recently, a Cochrane Database review found that intermittent auscultation was associated with a higher cesarean delivery rate compared with continuous monitoring (Martis, 2017).

Current Recommendations

Methods most commonly used for intrapartum FHR monitoring include intermittent auscultation with a fetal stethoscope or a Doppler ultrasound device, or continuous electronic monitoring of FHR and uterine contractions. Evidence has not identified the most effective method nor the frequency or duration of fetal surveillance that ensures optimum results. That said, Table 24-5 summarizes current guidelines from the American Academy of Pediatrics and American College of Obstetricians and Gynecologists (2017). Intermittent auscultation or continuous electronic monitoring is considered an acceptable method of intrapartum surveillance in both low- and high-risk pregnancies. The recommended interval between checking the heart rate, however, is longer in the uncomplicated pregnancy. When auscultation is used, it is recommended that it be performed after a contraction and for 60 seconds. It also is recommended that a 1-to-1 nurse–patient ratio be used if auscultation is employed. The position taken by the American College of Obstetricians and Gynecologists (2019b) acknowledges that available data do not show a clear benefit to the use of electronic monitoring over intermittent auscultation. At Parkland Hospital, all high-risk labors are continuously monitored electronically. In low-risk pregnancies, both intermittent auscultation and continuous electronic monitoring are used depending on clinical circumstances, including the woman's desire to ambulate.

TABLE 24-5. Guidelines for Methods of Intrapartum Fetal Heart Rate Monitoring

Surveillance	Low-Risk Pregnancies	High-Risk Pregnancies
Acceptable methods		
Intermittent auscultation	Yes	Yes[a]
Continuous electronic monitoring (internal or external)	Yes	Yes[b]
Evaluation intervals		
First-stage labor (active)	30 min	15 min[a,b]
Second-stage labor	15 min	5 min[a,c]

[a]Preferably before, during, and after a uterine contraction.
[b]Includes tracing evaluation and charting at least every 15 min.
[c]Tracing should be evaluated at least every 5 min.

INTRAPARTUM SURVEILLANCE OF UTERINE ACTIVITY

Analysis of electronically measured uterine activity permits some generalities concerning the relationship of certain contraction patterns and labor outcome. However, uterine muscle efficiency to bring about delivery varies greatly. Thus, caution should be exercised before diagnosing true labor or its absence solely from a monitor tracing.

With *internal monitoring* of contractions, amniotic fluid pressure is measured between and during contractions. An intrauterine pressure catheter is placed into the uterus with its distal tip above the presenting part. The catheter tip contains a pressure sensor and allows calculation of intrauterine pressure with each contraction (Fig. 24-16). With *external monitoring*, uterine contractions can be measured by a displacement transducer in which the transducer button, or "plunger," is held against the

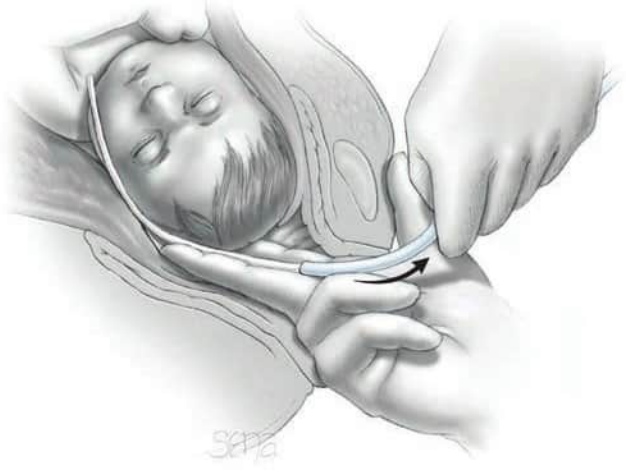

FIGURE 24-16 Placement of an intrauterine pressure catheter to monitor contractions and their pressures. The catheter, contained within the light blue introducer, is inserted into the uterus and placed along one side of the fetal head. The catheter is then gently advanced into the uterus, and the introducer is withdrawn.

maternal abdominal wall. As the uterus contracts, the button moves in proportion to the strength of the contraction. This movement is converted into a measurable electrical signal that indicates the *relative* intensity of the contraction. It has generally been accepted that internal monitoring provided a more accurate measure of intensity. That said, in a randomized trial comparing internal versus external monitoring of uterine contractions in 1456 women, the two methods yielded equivalent operative delivery rates and neonatal outcomes (Bakker, 2010).

Patterns of Uterine Activity

Caldeyro-Barcia and Poseiro (1960), from Montevideo, Uruguay, were pioneers in elucidating the patterns of spontaneous uterine activity throughout pregnancy. Waves of uterine activity were usually measured using intraamnionic pressure catheters. But early in their studies, as many as four simultaneous intramyometrial microballoons also were used to record uterine pressure. Contraction intensity was defined as the rise in this pressure above a resting pressure baseline. These investigators also introduced the concept of *Montevideo units* to define uterine activity (Chap. 23, p. 435). With this definition, uterine performance is the product of contraction intensity in mm Hg multiplied by the number of contractions in a 10-minute span. For example, three contractions in 10 minutes, each with 50-mm Hg intensity, would equal 150 Montevideo units.

According to Caldeyro-Barcia and Poseiro (1960), clinical labor usually commences when uterine activity reaches values between 80 and 120 Montevideo units. This translates into approximately three contractions of 40 mm Hg every 10 minutes. Importantly, no clear-cut division marks labor onset, which is a gradual and progressive transition.

In first-stage labor, uterine contractions progressively grow in intensity from approximately 25 mm Hg at labor commencement to 50 mm Hg at its end. At the same time, the frequency advances from three to five contractions per 10 minutes, and uterine baseline tone rises from 8 to 12 mm Hg. Uterine activity is further enhanced during second-stage labor, aided by maternal pushing. Contraction intensity of 80 to 100 mm Hg is typical, and the uterus contracts as frequently as five to six times each 10 minutes. Hauth and coworkers (1986) quantified uterine contraction pressures in 109 women at term who received oxytocin for labor induction or augmentation. Most of these women achieved 200 to 225 Montevideo units, and 40 percent had up to 300 units to effect delivery. The authors suggested that these levels of uterine activity should be sought before consideration of cesarean delivery for presumed dystocia (Chap. 23, p. 436).

Interestingly, the duration of uterine contractions—60 to 80 seconds—does not lengthen appreciably from early active labor through the second stage (Bakker, 2007; Pontonnier, 1975). Presumably, this duration constancy serves fetal respiratory gas exchange. During a uterine contraction, as the intrauterine pressure exceeds that of the intervillous space, respiratory gas exchange is halted. This leads to functional fetal "breath holding," which has a 60- to 80-second limit that remains relatively constant.

Caldeyro-Barcia and Poseiro (1960) also observed empirically that uterine contractions are clinically palpable only after their intensity exceeds 10 mm Hg. Moreover, until the intensity of contractions reaches 40 mm Hg, the uterine wall can readily be depressed by the finger. At greater intensities, the uterine wall then becomes so hard that it resists easy depression. Uterine contractions usually are not associated with pain until their strength exceeds 15 mm Hg. Presumably, this is the minimum pressure required to distend the lower uterine segment and cervix.

Hendricks (1968) observed that "the clinician makes great demands upon the uterus." The uterus is expected to remain well relaxed during pregnancy, to contract effectively but intermittently during labor, and then to remain in a state of almost constant contraction for several hours postpartum. Figure 24-17 demonstrates an example of normal uterine

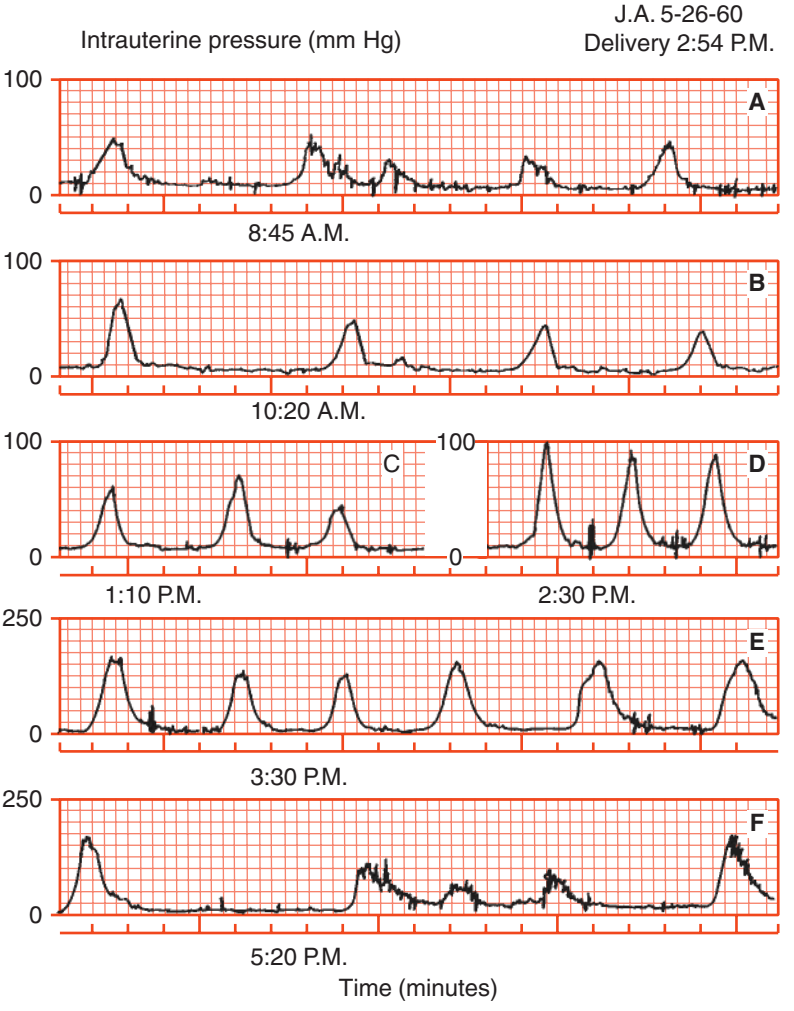

FIGURE 24-17 Intrauterine pressure recorded through a single catheter. **A.** Prelabor. **B.** Early labor. **C.** Active labor. **D.** Late labor. **E.** Spontaneous activity ½ hour postpartum. **F.** Spontaneous activity 2½ hours postpartum. (Redrawn from Hendricks CH: Uterine contractility changes in the early puerperium. Clin Obstet Gynecol 1968 Mar;11(1):125–144.)

activity during labor. Uterine activity progressively and gradually rises from early through late labor. Interestingly, uterine contractions after birth are identical to those resulting in delivery of the newborn. Logically, the uterus that performs poorly before delivery is also prone to atony and puerperal hemorrhage.

Uterine Contraction Terminology

Terms to describe uterine contractions have been recommended by the American College of Obstetricians and Gynecologists (2019b). *Normal uterine activity* is defined as five or fewer contractions in 10 minutes, averaged during a 30-minute span. *Tachysystole* is more than five contractions in 10 minutes, averaged over 30 minutes. Tachysystole can be applied to spontaneous or induced labor. The term *hyperstimulation* was abandoned.

Stewart and associates (2012) prospectively studied uterine tachysystole in 584 women undergoing labor induction with misoprostol at Parkland Hospital. A higher rate of adverse neonatal outcomes was not associated with an increasing number of contractions per 10 minutes or per 30 minutes. Counts of six or more contractions in 10 minutes, however, were significantly associated with FHR decelerations.

Electronic Fetal Monitoring Complications

Electrodes for FHR evaluation and catheters for uterine contraction measurement are both associated with infrequent but potentially serious complications. Rarely, an intrauterine pressure catheter may lacerate a fetal vessel in the placenta during placement. Also with insertion, placental and possibly uterine perforation can cause hemorrhage, abruption, and spurious recordings that have resulted in inappropriate management. Severe cord compression has been described from entanglement with the pressure catheter. Injury to the fetal scalp or breech by a FHR electrode is rarely severe. However, face presentations pose risk for eye or mouth trauma.

Both the fetus and the mother may be at greater risk of infection from internal monitoring (Faro, 1990). Scalp wounds from the electrode may become infected, but subsequent cranial osteomyelitis is rare (Brook, 2005; Eggink, 2004; McGregor, 1989). Certain maternal infections that include human immunodeficiency virus (HIV), herpes simplex virus, and hepatitis B and C virus are relative contraindications to internal FHR monitoring (American Academy of Pediatrics, 2017).

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CHAPTER 25

Obstetrical Analgesia and Anesthesia

Obstetrical anesthesia presents unique challenges. Labor begins without warning, and anesthesia may be required within minutes of a full meal. Vomiting with aspiration of gastric contents is a constant threat. The usual physiological adaptations of pregnancy require special consideration, especially with disorders such as preeclampsia, placental abruption, or sepsis.

Obstetrical analgesia and anesthesia have become extraordinarily safe over the past 40 years (Hawkins, 2011). Anesthetic-related maternal mortality rates decreased more than 60 percent during this time, and from 2007 to 2017, only 0.4 percent of 6765 maternal deaths were due to anesthesia complications (Petersen, 2019). Creanga and colleagues (2017) reported the contribution of anesthetics to pregnancy-associated deaths has declined markedly in the United States (Fig. 25-1). Approximately two thirds of deaths associated with general anesthesia were caused by induction problems or intubation failures during cesarean delivery. Deaths associated with regional analgesia were caused by spinal or epidural blocks reaching higher than planned spinal levels—26 percent; respiratory failure—19 percent; and drug reaction—19 percent.

Of factors contributing to improved obstetrical anesthesia safety, the increased use of regional analgesia for labor and delivery is the most significant. For general anesthesia, the improved case-fatality rate is especially notable considering that this method is now used for the highest-risk patients and for emergencies with decision-incision intervals <15 minutes (Bloom, 2005). In addition, the incidence of aspiration, hypoxia, or other respiratory events has declined during the past three decades. This is likely due to use of difficult-airway algorithms, advanced airway equipment, and increased in-house anesthesia staffing (Davies, 2017; Lim, 2018). Despite these encouraging results with general anesthesia, rising complications with regional analgesia techniques are now reported (Davies, 2017).

GENERAL PRINCIPLES

Obstetrical Anesthesia Services

Every obstetrician should be proficient in local and pudendal analgesia for select circumstances. However, it is preferable for

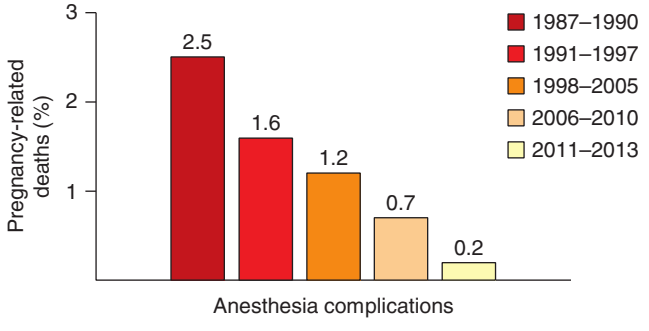

FIGURE 25-1 Contribution of anesthetic complications to pregnancy-associated deaths—United States, 1987–2013.

TABLE 25-1. Maternal Factors That May Prompt Anesthetic Consultation

Anatomical abnormalities of the face, neck, or spine
Thyromegaly
Cardiac, pulmonary, renal, hepatic, or neurological disease
Bleeding disorders
Prior anesthetic complications
Class III obesity (BMI ≥40 kg/m^2)
Obstetrical complications likely to lead to operative delivery
Severe pregnancy-associated hypertension
Obstetrical hemorrhage

BMI = body mass index.

an anesthesiologist or anesthetist to provide rapid and reliable pain relief to allow the obstetrician to focus attention on the laboring woman and her fetus.

The American College of Obstetricians and Gynecologists (2019b) and the American Society of Anesthesiologists (2016) have reaffirmed prior directives that a woman's request for labor pain relief is sufficient indication for its provision. Identification of any of the risk factors shown in Table 25-1 should prompt consultation and collaboration with anesthesia personnel. The resulting plan should ideally minimize the need for emergency anesthesia in this high-risk group.

Goals for optimizing obstetrical anesthesia services have been established by the American College of Obstetricians and Gynecologists (2019b) and the American Society of Anesthesiologists (2016). To achieve these goals, the following is a partial list of requisites:

1. Availability of a licensed practitioner credentialed to administer an appropriate anesthetic whenever necessary and to maintain support of vital functions in an obstetrical emergency
2. Availability of anesthesia personnel to permit the start of cesarean delivery within 30 minutes of the decision to perform the procedure (decision–incision time)
3. Anesthesia personnel immediately available to support an emergency cesarean delivery during the active labor of a woman attempting vaginal birth after prior cesarean (Chap. 31, p. 578)
4. Appointment of a qualified anesthesiologist to be responsible for all anesthetics administered
5. Availability of a qualified physician with obstetrical privileges to perform operative vaginal or cesarean delivery during anesthesia administration
6. Availability of equipment, facilities, and support personnel equal to that provided in a surgical suite
7. Immediate availability of personnel, other than the surgical team, to assume responsibility for resuscitation of a depressed newborn (Chap. 32, p. 586).

To meet these goals, 24-hour in-house anesthesia staffing is usually necessary. Providing such service in smaller facilities is more challenging. This is underscored by the fact that approximately 40 percent of all hospitals providing obstetrical care have fewer than 500 deliveries per year (American Academy of Pediatrics, 2017). Bell and coworkers (2000) calculated the financial burden that may be incurred to provide 24/7 obstetrical anesthesia coverage. They concluded that such coverage could not operate profitably at their tertiary referral institution, given the average indemnity and Medicaid reimbursement for labor epidural analgesia. Compounding this burden, some third-party payers have denied reimbursement for epidural analgesia in the absence of a specific medical indication—an approach repudiated by the American College of Obstetricians and Gynecologists (2019b).

■ Principles of Pain Relief

Labor pain caused by uterine contractions and cervical dilation is transmitted through visceral afferent sympathetic nerves entering the spinal cord from T_{10} through L_1. Later, perineal stretching transmits painful stimuli through the pudendal nerve and sacral nerves from S_2 through S_4. Cortical responses to pain and anxiety are complex and may be influenced by multiple factors.

Labor pain is a highly individual response to variable stimuli that are uniquely received and interpreted (Hawkins, 2010). These stimuli are modified by emotional, motivational, cognitive, social, and cultural circumstances. Specific modifiers are maternal expectations for her childbirth experience, age, antepartum labor education, and quality of emotional support. Major causes of dissatisfaction with pain relief are perceived labor pain and delay in ameliorating the pain (Yurashevich, 2019).

A mother's physiological responses to labor pain may influence maternal and fetal well-being and labor progress. First, a higher metabolic rate leads to more oxygen consumption and the resultant hyperventilation may induce hypocarbia. Second, the sympathetic nervous system response to pain leads to elevated circulating catecholamine levels. These in turn raise cardiac output and vascular resistance, which may raise maternal blood pressure. Catecholamines also directly can adversely affect uterine activity and uteroplacental blood flow. Last, pain, stress, and anxiety cause release of stress hormones such as cortisol and endorphins. Effective analgesia attenuates or eliminates these responses.

ANALGESIA AND SEDATION DURING LABOR

If uterine contractions cause discomfort, pain relief with a narcotic such as meperidine, plus an antiemetic tranquilizer such as promethazine, is appropriate. With a successful program of analgesia and sedation, discomfort usually is felt at the acme of a uterine contraction, and the mother can rest quietly between contractions. Appropriate drug selection and administration from the medications shown in Table 25-2 safely accomplishes these objectives.

■ Parenteral Agents

Meperidine and Promethazine

Meperidine, 50 to 100 mg, with promethazine, 25 mg, may be administered intramuscularly (IM) at intervals of 2 to

TABLE 25-2. Typical Parenteral Analgesic Agents for Labor Pain

Agent	Usual Dose	Frequency	Onset	Neonatal Half-Life
Meperidine	25–50 mg (IV) 50–100 mg (IM)	Every 1–2 hr Every 2–4 hr	5 min 30–45 min	~18–20 hr ~60 hr
Fentanyl	50–100 µg (IV)	Every 1 hr	1 min	~5 hr
Remifentanil	0.15–0.5 µg/kg (PCA)	Every 2 min	<1 min	10 min
Butorphanol	1–2 mg (IV or IM)	Every 4 hr	1–2 min (IV) 10–30 min (IM)	~5 hr
Morphine	2–5 mg (IV) 10 mg (IM)	Every 4 hr	5 min 30–40 min	~7 hr

IV = intravenously; IM = intramuscularly; PCA = patient-controlled analgesia.

4 hours. Analgesia is maximal 30 to 45 minutes after an IM injection. An almost immediate effect is achieved by giving meperidine intravenously (IV) in doses of 25 to 50 mg every 1 to 2 hours. In an earlier study, meperidine was found to be the most common opioid used worldwide for pain relief in labor (Bricker, 2002). Tsui and associates (2004) found meperidine to be superior to placebo for pain relief in the first stage of labor. In a randomized investigation at Parkland Hospital, IV patient-controlled analgesia (PCA) with meperidine was found to be an inexpensive and reasonably effective method for labor analgesia (Sharma, 1997). Women received 50-mg meperidine with 25-mg promethazine IV as an initial bolus. Thereafter, an infusion pump was set to deliver 15 mg of meperidine every 10 minutes as needed until delivery. Neonatal sedation, as measured by need for naloxone treatment in the delivery room, was identified in 3 percent of newborns.

Meperidine readily crosses the placenta, and its depressant effect in the fetus closely follows peak maternal analgesia. The active metabolite of meperidine, normeperidine, has a half-life of approximately 72 hours in the neonate. Therefore, other opioids discussed below are favored for labor analgesia. (American College of Obstetricians and Gynecologists, 2019b).

Butorphanol

This synthetic opioid-receptor agonist-antagonist narcotic, given in 1- to 2-mg IV doses every 4 hours as needed, compares favorably with meperidine for labor analgesia. Its major side effects are somnolence, dizziness, and dysphoria. Neonatal respiratory depression is less than with meperidine. Importantly, the two drugs are not given contiguously because butorphanol antagonizes the narcotic effects of meperidine. Hatjis and Meis (1986) described a transient sinusoidal fetal heart rate pattern following butorphanol administration, but no short-term maternal or neonatal adverse sequelae were noted (Chap. 24, p. 451).

Fentanyl

This short-acting and potent synthetic opioid may be given in doses of 50 to 100 µg IV every hour. Its main disadvantage is a short duration of action, which requires frequent dosing or use of a PCA pump. Atkinson and coworkers (1994) reported that butorphanol provided better initial analgesia than fentanyl and was associated with fewer requests for additional medication or for epidural analgesia.

Remifentanil

This ultrashort-acting opioid can be given using a PCA pump (see Table 25-2). Remifentanil is administered through a dedicated IV cannula to avoid bolus dosing, which can lead to apnea. Both respiratory monitoring and 1:1 nursing-to-patient ratio help watch for apneic spells, which occur in 25 percent of treated women (Stocki, 2014). In the RemiPCA SAFE Network Study, moderate maternal hypoxia (SaO_2 <94 percent) was documented in a fourth of women (Melber, 2019). A multicenter randomized study showed PCA-administered remifentanil halved the proportion of women subsequently requesting epidural analgesia compared with IM meperidine (Wilson, 2018).

Parenteral Agent Safety

Parenteral sedation is not without risks. Hawkins and colleagues (1997) reported that 4 of 129 maternal anesthetic-related deaths were from such sedation. One was from aspiration, two from inadequate ventilation, and one from overdosage.

Narcotics used during labor may cause newborn respiratory depression. Naloxone is a narcotic antagonist capable of reversing respiratory depression induced by opioid narcotics. It acts by displacing the narcotic from specific receptors in the central nervous system. After adequate ventilation has been established, naloxone may be given to a newborn whose mother received narcotics. Naloxone is contraindicated in a newborn of a narcotic-addicted mother because withdrawal symptoms may be precipitated (American Academy of Pediatrics, 2017).

■ Nitrous Oxide

A self-administered mixture of 50-percent nitrous oxide (N_2O) and oxygen may provide satisfactory analgesia during labor (Zafirova, 2018). Some preparations are premixed in a single cylinder (Entonox), and in others, a blender mixes the two gases from separate tanks (Nitronox). The gases are connected to a breathing circuit through a valve that opens only when the patient inspires. The use of intermittent nitrous oxide did not alter the rate of epidural analgesia but did improve birth experience satisfaction rates (Bobb, 2016; Lim, 2018). Maternal side effects include nausea, vomiting, dizziness, and drowsiness. Neonatal Apgar scores or umbilical cord blood gas results did not differ in women using

TABLE 25-3. Commonly Used Local Anesthetic Agents in Obstetrics

Anesthetic Agent[a]	Usual Concentration (%)	Usual Volume (mL)	Onset	Average Duration (min)	Maximum Dose (mg)	Clinical Use
Aminoesters[b]						
2-Chloroprocaine	2	10–20	Rapid	30–60	800	Local infiltration or pudendal block
	3	10–20		30–60		Epidural for cesarean or forceps delivery
Aminoamides[b]						
Bupivacaine	0.0625–0.125	5–10	Slow	60–90	175	Epidural for labor
	0.5	10–20		90–150		Epidural for cesarean
	0.75	1.5–2		60–120		Spinal for cesarean
Lidocaine	1–1.5	10–20	Rapid	30–60	300	Local infiltration or pudendal block
	1.5–2	5–20		60–90		Epidural for cesarean
	5	1.5–2		45–60		Spinal for D & C or puerperal tubal
Ropivacaine	0.08–0.2	5–10	Slow	60–90	200	Epidural for labor
	0.5–1	10–30		90–150	250	Epidural for cesarean

[a]Without epinephrine.
[b]Esters are hydrolyzed by plasma cholinesterases and amides by hepatic clearance.
D & C = dilation and curettage.
From Chestnut, 2020; Lin, 2017.

nitrous oxide compared with those selecting other pain management methods or no analgesia in labor (Likis, 2014).

NERVE BLOCKS

Various nerve blocks provide pain relief during labor and/or delivery. These include pudendal, paracervical, and neuraxial blocks such as spinal, epidural, dural-puncture epidural, and combined spinal-epidural techniques.

Anesthetic Agents

Commonly used nerve block anesthetics are summarized in Table 25-3. The dose of each agent varies widely and is dependent on the particular nerve block and physical status of the woman. The onset, duration, and quality of analgesia can be enhanced by increasing the anesthetic agent's dose, concentration, and volume or by altering its delivery mode. With their use, safety tenets include incremental boluses of the agent and carefully monitoring for early warning signs of adverse effects. Appropriate equipment and personnel to manage these reactions must be immediately available.

Local analgesic agents are manufactured in more than one concentration and ampule size, and this raises the potential for dosing errors. Most often, serious toxicity follows inadvertent intravenous, subarachnoid, or subdural injection. Systemic toxicity from local anesthetics typically manifests in the central nervous and cardiovascular systems. For this reason, before epidural analgesia is initiated, a mixture of a small amount of local anesthetic drug and epinephrine is given as a test dose. Epinephrine with its associated tachycardia is used as a marker to help identify incorrect placement if it occurs. A sudden significant elevation in the maternal heart rate or blood pressure within 1 to 2 minutes after administration suggests intravenous catheter placement. A block extending over wider than expected spinal levels and/or dense motor blockade indicate inadvertent catheter placement into the subarachnoid or into the subdural space.

Central Nervous System Toxicity

Early symptoms are those of *stimulation*, but as serum levels rise, *depression* follows. Symptoms may include lightheadedness, dizziness, tinnitus, metallic taste, and numbness of the tongue and mouth. Patients may also show bizarre behavior, slurred speech, and muscle fasciculation and excitation. Ultimately, generalized convulsions and loss of consciousness could result.

For neural and cardiac toxicity treatment, a rapid IV infusion of 20-percent intralipids effectively disassociates anesthetic drugs from neural and myocardial cell membranes. For patients weighing >70 kg, a 100-mL bolus dose of lipid emulsion is given. Boluses can be repeated once or twice every 5 minutes for persistent cardiac instability. The initial bolus is followed by a 200-mL infusion over 15 minutes (Neal, 2018).

For convulsions, an airway is established, and oxygen delivered. To halt seizures, lorazepam, 4 mg IV slowly, is administered and may be repeated once after 10 to 15 minutes. Alternatively, diazepam, 5 to 10 mg IV every 10 to 15 minutes up to a total dose of 30 mg, can be used. Succinylcholine abolishes the peripheral manifestations of the convulsions and allows tracheal intubation. Magnesium sulfate, administered according to the regimen for eclampsia, also controls convulsions (Chap. 41, p. 719).

Abnormal fetal heart rate patterns such as late decelerations or persistent bradycardia may develop from maternal hypoxia and lactic acidosis. With arrest of convulsions, oxygen administration, and other supportive measures, the fetus usually

recovers more quickly in utero than following immediate cesarean delivery. Moreover, the mother is better served if delivery is delayed until the intensity of hypoxia and metabolic acidosis has diminished.

Cardiovascular Toxicity

These manifestations generally develop later than those from cerebral toxicity, and they may not develop at all because they are induced by higher serum drug levels. The exception is bupivacaine, which is associated with the development of neurotoxicity and cardiotoxicity at virtually identical levels (Catterall, 2018). Fortunately, bupivacaine is mostly used in dilute epidural solutions, and use of 0.75-percent solution is limited to a small dose for spinal analgesia. Similar to neurotoxicity, cardiovascular toxicity is characterized first by stimulation and then by depression. Accordingly, hypertension and tachycardia are soon followed by hypotension, cardiac arrhythmias, and impaired uteroplacental perfusion. As before, 20-percent intralipids serve as the rescue.

Hypotension is managed initially by turning the woman onto either side to avoid aortocaval compression. A crystalloid solution is infused rapidly along with vasopressors. Emergency bedside cesarean delivery is considered if maternal vital signs have not been restored within 4 minutes of cardiac arrest, and the goal is delivery within 5 minutes (Chap. 50, p. 897). However, as with convulsions, the fetus is likely to recover more quickly in utero once maternal cardiac output is reestablished.

■ Pudendal Block

Pain with vaginal delivery arises from stimuli from the lower genital tract. These are transmitted primarily through the pudendal nerve, the peripheral branches of which provide sensory innervation to the perineum, anus, vulva, and clitoris (Chap. 2, p. 21). The pudendal nerve passes beneath the posterior surface of the sacrospinous ligament just as the ligament attaches to the ischial spine. Sensory nerve fibers of the pudendal nerve are derived from ventral branches of the S_2 through S_4 nerves.

The pudendal nerve block is a relatively safe, simple method of analgesia for vaginal delivery (Sultan, 2021). As shown in Figure 25-2, a tubular introducer is used to sheath and guide a 15-cm, 22-gauge needle into position near the pudendal nerve. The end of the introducer is placed against the vaginal mucosa just beneath the tip of the ischial spine. The introducer allows 1.0 to 1.5 cm of needle to protrude beyond its tip, and the needle is pushed beyond the introducer tip into the mucosa. A mucosal wheal is made with 1 mL of 1-percent lidocaine solution or an equivalent dose of another local anesthetic (see Table 25-3). To guard against intravascular infusion, aspiration is attempted before this and all subsequent injections. The needle is then advanced until it touches the sacrospinous ligament, which is infiltrated with 3 mL of lidocaine. The procedure is repeated on the other side.

Within 3 to 4 minutes of injection, the successful pudendal block will allow pinching of the lower vagina and posterior vulva without pain. If delivery occurs before the pudendal block becomes effective and an episiotomy is indicated, the fourchette, perineum, and adjacent vagina can be infiltrated with 5 to 10 mL of 1-percent lidocaine solution directly at the planned episiotomy site. The pudendal block usually has become effective by the time of repair.

The maximum recommended total dose of lidocaine is 4.5 mg/kg and not to exceed 300 mg (see Table 25-3). For a 50-kg woman, this would equal 225 mg (4.5 mg/kg × 50 kg). Thus, if 1-percent lidocaine is used, the calculated allowed amount would be: 225 mg ÷ 10 mg/mL = 22.5 mL. Of note, for any drug solution, 1 percent = 10 mg/mL.

Pudendal block usually does not provide adequate analgesia when delivery requires extensive obstetrical manipulation. Parenteral or neuraxial anesthesia is usually necessary when complete visualization of the cervix and upper vagina or manual exploration of the uterine cavity is indicated.

Infrequently, complications may follow this block. As previously described, intravascular injection of a local anesthetic agent may cause serious systemic toxicity. Hematoma formation from perforation of a blood vessel is most likely when there is a coagulopathy (Lee, 2004). The addition of a corticosteroid injected along with the local anesthetic did not decrease the incidence of pudendal neuralgia at 3 months (Labat, 2017). Rarely, severe infection may originate at the injection site. The infection may spread posteriorly to the hip joint, into the gluteal musculature, or into the retropsoas space (Svancarek, 1977).

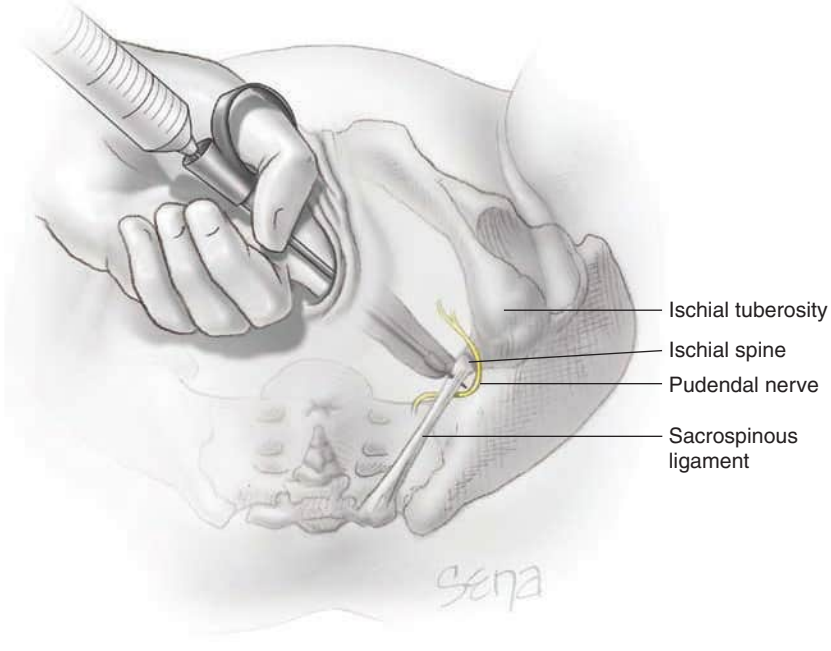

FIGURE 25-2 Local infiltration of the pudendal nerve. Transvaginal technique showing the needle extended beyond the needle guard and passing through the sacrospinous ligament to reach the pudendal nerve.

Paracervical Block

The cervix, vagina, and uterus are richly supplied by nerves of the uterovaginal plexus (Fig. 2-12, p. 25). This plexus lies within the connective tissue lateral to the uterosacral ligaments. Thus, injections are most effective if placed immediately lateral to the insertion of the uterosacral ligaments into the uterus (Rogers, 1998). For paracervical blockade, usually 1-percent lidocaine or 3-percent chloroprocaine, 5 to 10 mL, is injected into the cervix laterally at 4 and 8 o'clock positions. This block usually provides satisfactory pain relief during first-stage labor. However, because the pudendal nerves are not blocked, additional analgesia is required for delivery. The block may have to be repeated during labor because these anesthetics are relatively short acting.

Fetal bradycardia is a worrisome complication that develops in approximately 15 percent of these blocks (Rosen, 2002). Bradycardia usually develops within 10 minutes and may last up to 30 minutes. Doppler studies have shown an increase in the pulsatility index of the uterine arteries following paracervical blockade (Chap. 14, p. 262). These observations support the hypothesis of drug-induced arterial vasospasm as a cause of fetal bradycardia (Manninen, 2000). Thus, paracervical block should not be used in situations of potential fetal compromise. For all of these reasons, we do not use this block at Parkland Hospital.

NEURAXIAL ANALGESIA

Neuraxial Regional Blocks

Epidural, spinal, dural-puncture epidural, or combined spinal-epidural techniques are the most common methods used for relief of pain during labor and/or delivery in the United States. Nearly 75 percent of mothers receive neuraxial anesthesia for pain relief (Butwick, 2018a). Among first births, 68 percent of women who delivered vaginally received neuraxial pain relief compared with 57 percent of women delivering their second or higher number child. Antepartum education programs improve the understanding of labor analgesia and increase its use by 30 percent in Hispanic women who traditionally choose labor epidural analgesia less often (Togioka, 2019). Butwick and associates (2018b) showed women are more likely to receive neuraxial analgesia with higher class of obesity—class I, 72 percent; class II, 73 percent; and class III, 76 percent.

As a brief review, the epidural space lies just outside the dural sac. The dura mater encases the subarachnoid space, which contains the cauda equina of the spinal cord and cerebrospinal fluid (CSF) (Fig. 25-3). Spinal and intrathecal anesthesia are synonymous, and agents are injected into the subarachnoid space.

Epidural analgesia via a catheter in the epidural space is typically used for relief of labor pain, although it can also be used for *anesthesia* during operative vaginal and cesarean delivery. *Spinal analgesia* is typically given as a single intrathecal injection of a local anesthetic at the time of operative vaginal or cesarean delivery. Variations of these two basic approaches are described in the subsequent sections.

Spinal (Subarachnoid) Block

Introduction of a local anesthetic into the subarachnoid space to effect analgesia offers a short procedural time, rapid blockade onset, and high success rate of inducing analgesia. The subarachnoid space is smaller during pregnancy likely because of internal vertebral venous plexus engorgement (see Fig. 25-3A). As a result, compared with nonpregnant women, the same amount of anesthetic agent in the same volume of solution produces a higher-level blockade in parturients.

Vaginal Delivery

Spinal analgesia involving only lower spinal levels can be used for operative vaginal delivery. The level of analgesia should extend to the T_{10} dermatome, which corresponds to the level of the umbilicus. Blockade to this level provides excellent relief from the pain of uterine contractions. The spinal block provides also excellent analgesia to the lower uterine segment, vagina, and perineum.

Several local anesthetic agents have been used for spinal analgesia (see Table 25-3). Addition of dextrose to any of these agents creates a hyperbaric solution, which is heavier and denser than CSF. A sitting position causes a hyperbaric solution to settle caudally, whereas a lateral position will have a greater effect on the dependent side. Lidocaine given in a hyperbaric solution produces excellent analgesia and has the advantage of a rapid onset and relatively short duration. Isobaric bupivacaine provides satisfactory analgesia for more than 1 hour. Single-dose spinal analgesia is usually administered when the cervix is fully dilated, and all other criteria for safe operative vaginal delivery have been fulfilled (Chap. 29, p. 533). Preanalgesic IV hydration with 1 L of crystalloid solution will prevent or minimize hypotension in many cases.

Cesarean Delivery

A level of sensory blockade extending to the T_4 dermatome is desired for cesarean delivery. A dose of 10 to 12 mg of bupivacaine in a hyperbaric solution is administered. The addition of 20 to 25 μg of fentanyl improves the quality and prolongs the duration of the spinal block, reduces shivering, and minimizes referred pain. In addition, 0.1 to 0.2 mg of intrathecal morphine can be added for pain control postoperatively.

With intrathecal morphine, the risk for respiratory depression should be considered. The Society of Obstetric Anesthesia and Perinatology recommends postoperative respiratory monitoring based on dose, patient risk factors, and perioperative risk factors. A low-dose regimen, defined as >50 μg and ≤ 150 μg, in women with no risk factors requires respiratory rate and sedation checks postoperatively for the first 12 hours. In women with additional risk factors, these safeguards are conducted postoperatively for the first 24 hours, and additional monitoring with pulse oximetry or capnography is considered. Last, this monitoring method is also recommended in all women receiving doses >150 μg (Bauchat, 2019).

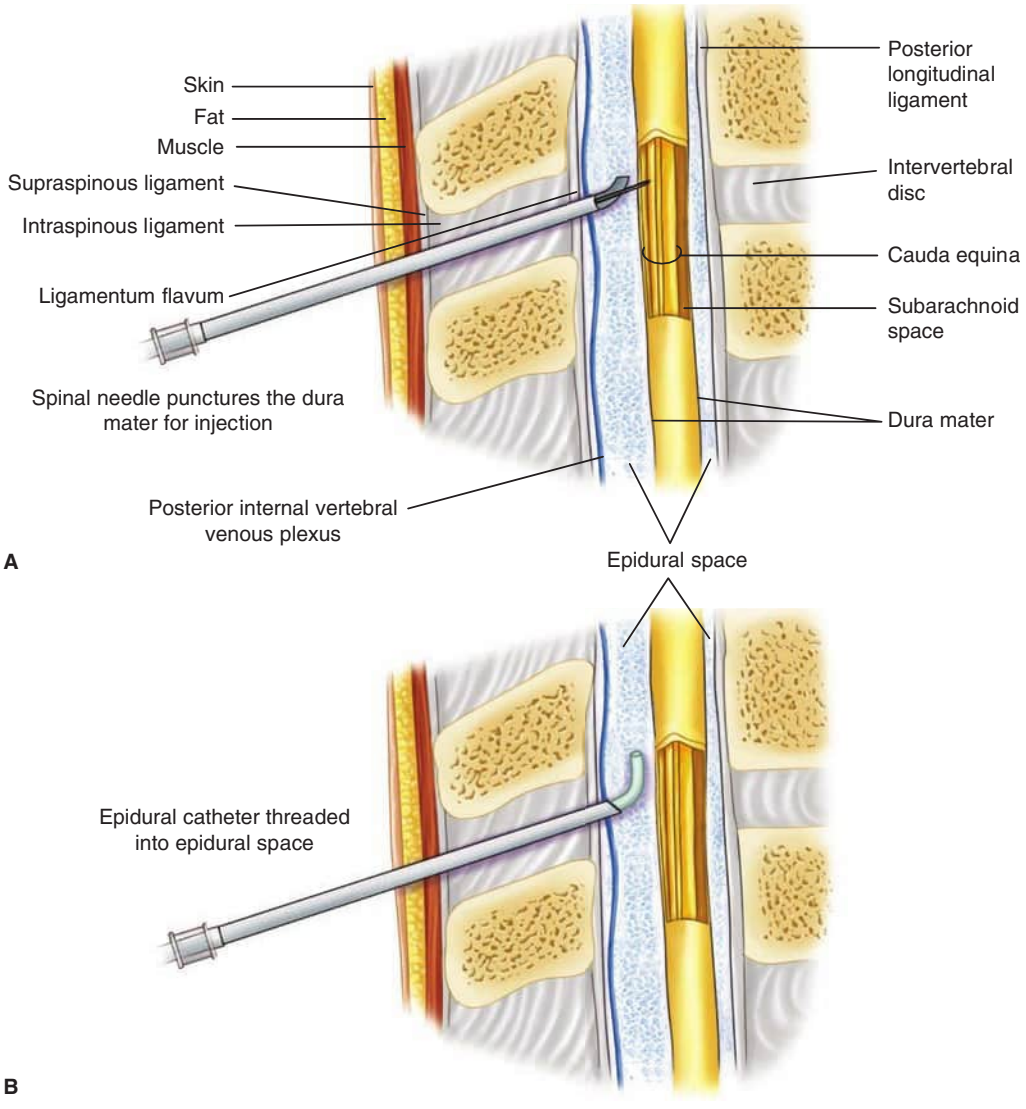

FIGURE 25-3 Neuraxial analgesia. **A.** Combined spinal-epidural analgesia. **B.** Epidural analgesia.

Complications

Shown in Table 25-4 are some of the more common complications associated with neuraxial analgesia.

Hypotension. This common complication may develop soon after injection of the local anesthetic agent. It stems from vasodilation caused by sympathetic blockade and is compounded by obstructed venous return due to uterine compression of the vena cava. In the supine position, even in the absence of maternal hypotension, placental blood flow may still be significantly diminished. Treatment includes uterine displacement by left lateral patient positioning, rapid IV crystalloid infusion, and IV vasopressors.

One systematic review concluded that vasopressors should be given only in the setting of hypotension (Fitzgerald, 2020). For treatment, phenylephrine is now the preferred drug to treat hypotension from neuraxial analgesia. It is a pure alpha agonist and raises blood pressure solely through vasoconstriction. Maternal bradycardia develops more frequently with

TABLE 25-4. Complications of Neuraxial Analgesia

Fever >38°C
Hypotension—highest with spinal analgesia (~50%)
Fetal heart rate abnormalities
High spinal level
Increased QT interval—with spinal analgesia in postterm pregnancies
Inadequate analgesia (~10%)
Postdural puncture headache (1–3%)
Nerve injury—arachnoiditis
Pruritus—with addition of opioids

From American College of Obstetricians and Gynecologists, 2019b; American Society of Anesthesiologists, 2016; D'Angelo, 2014; Karahan, 2020; Maronge, 2018.

phenylephrine than with ephedrine or norepinephrine (Sharkey, 2019; Veeser, 2012). Although ephedrine was believed to correct hypotension without reducing blood flow, phenylephrine is associated with better umbilical cord blood gases (Ngan Kee, 2017). A metaanalysis of 36 randomized trials also suggests that both agents have comparable efficacy but that phenylephrine yields a lower rate of fetal acidosis (Xu, 2018). For administration, prophylactic infusions of phenylephrine are effective and may require less physician intervention compared with intermittent boluses (Ngan Kee, 2004). As another potential agent, norepinephrine may improve cardiac output with its beta-adrenergic effects but also is associated with a lower cord arterial pH compared with phenylephrine (Chen, 2021; Mohta, 2019).

High Spinal Blockade. Most often, complete spinal blockade follows administration of an excessive dose of local anesthetic. However, it can also develop with inadvertent delivery of a small amount of local anesthetic drugs into the subdural space. This small potential space lies between the dura mater and arachnoid mater and outside the subarachnoid space. Because of its limited capacity, even small volumes will reach higher spinal levels. Hypotension and apnea develop quickly and must be immediately treated to prevent cardiac arrest. In the undelivered woman: (1) the uterus is immediately displaced laterally to minimize aortocaval compression, (2) effective ventilation is established, preferably with tracheal intubation, and (3) IV fluids and vasopressors are given to correct hypotension.

Postdural Puncture Headache. Leakage of CSF from the dural puncture site can lead to postdural puncture headache. Presumably, when the woman sits or stands, the diminished CSF volume creates traction on pain-sensitive central nervous system structures. An alternative mechanism is compensatory cerebral vasodilation in response to CSF loss—the *Monro-Kellie hypothesis* (Mokri, 2001).

The incidence of obstetrical postdural puncture headache in women undergoing spinal analgesia ranges from 0.2 to 1 percent (Maronge, 2012; Sprigge, 2008). This rate is similar to the overall occurrence of postdural puncture headaches, which approximates 1 headache per 200 blocks. A study of 567 postpartum hospital encounters showed that 40 percent of presentations for headache are due to neuraxial anesthesia, and these visits most often occur within 7 days of delivery (Rodriguez, 2020).

Procedural preventive steps include using a small-gauge spinal needle and avoiding multiple punctures. In a prospective, randomized study of five different spinal needles, Sprotte and Whitacre needles had the lowest risks of associated postdural puncture headaches (Vallejo 2000). Rates are high with inadvertent dural puncture during epidural analgesia and approximate 0.2 to 1 percent (Introna, 2012; Maronge, 2018). No strong evidence supports placing a woman flat on her back or providing vigorous hydration to prevent headache (Arevalo-Rodriguez, 2016). A prophylactic blood patch performed within 24 hours of dural puncture does not diminish either the incidence of postdural puncture headache or the need for a subsequent therapeutic blood patch (Scavone, 2004).

If a headache develops, administration of caffeine, which is a cerebral vasoconstrictor, has limited efficacy (Katz, 2017). With severe headache, an *epidural blood patch* is most effective and preferred treatment. Autologous blood is obtained aseptically by venipuncture, and 10 to 20 mL is injected into the epidural space at or below the site of dural puncture. This site is selected because the blood will spread more readily in the cephalad direction. Further CSF leakage is halted by either mass effect or clot formation. Relief is immediate, and complications are uncommon.

If a headache does not have the pathognomonic postural characteristics or persists despite treatment with a repeat blood patch, other diagnoses should be considered. Chisholm and Campbell (2001) described a case of superior sagittal sinus thrombosis that manifested as a postural headache. Chan and Paech (2004) reported persistent CSF leak in three women. Smarkusky and colleagues (2006) described pneumocephalus, which caused immediate cephalgia. Last, intracranial and intraspinal subarachnoid hematomas have developed after spinal analgesia (Bi, 2021; Maronge, 2018; Moore, 2019).

Convulsions. Rarely, postdural puncture cephalgia is associated with temporary blindness and convulsions. Shearer and associates (1995) described eight such cases in 19,000 regional analgesia procedures done at Parkland Hospital. It is presumed that these also are caused by hypotension from CSF leak. Immediate treatment of seizures and epidural blood patch were usually effective.

Bladder Dysfunction. With neuraxial analgesia, bladder sensation is likely to be obtunded and bladder emptying impaired for several hours after delivery. As a consequence, bladder distention is a frequent postpartum complication, especially if appreciable volumes of IV fluid are given. Millet (2012) randomized 146 women with neuraxial analgesia to either intermittent or continuous bladder catheterizations and found that the intermittent method was associated with significantly greater rates of bacteriuria.

Arachnoiditis and Meningitis. Local anesthetics used for neuraxial blocks are required to be free of methylparaben or other preservatives. This practice, coupled with aseptic technique and disposable equipment, has made meningitis and arachnoiditis rare (Centers for Disease Control and Prevention, 2010; Maronge, 2018).

Contraindications to Spinal Analgesia

Shown in Table 25-5 are absolute contraindications to spinal analgesia. Obstetrical complications that are associated with maternal hypovolemia and hypotension—for example, severe hemorrhage—are contraindications to spinal blockade. The additive deleterious cardiovascular effects of spinal blockade plus acute blood loss in nonpregnant patients have been documented (Kennedy, 1968).

Severe preeclampsia is another obstetrical complication in which decreased blood pressure can be encountered when neuraxial analgesia is used (Wallace, 1995). These effects are mitigated by judicial dosing of anesthetic solutions. Perhaps related, Ulubaşoğlu and colleagues (2018) reported that preeclamptic

TABLE 25-5. Absolute Contraindications to Spinal Analgesia

Refractory hypotension
Maternal coagulopathy
Thrombocytopenia <70,000/μL
Untreated maternal bacteremia
Skin infection at site of needle placement
Increased intracranial pressure
Prophylactic low-molecular-weight heparin within 12 hours

women undergoing general anesthesia required more antihypertensive medication than those with spinal analgesia.

Disorders of coagulation that result in poor hemostasis also preclude the use of neuraxial analgesia. Women with a bleeding diathesis such as von Willebrand disease or hemophilias carry an increased risk for subarachnoid hematoma formation (Chap. 59, p. 1062). Rare subdural hematomas may mimic postdural puncture headaches (Lim, 2016). However, neuraxial analgesia can be safely performed in these patients following factor replacement and normalization of levels (Choi, 2009; Katz, 2015). As discussed earlier, these patients should receive consultation with an anesthesiologist prior to labor.

The use of anticoagulation to prevent or treat venous thromboembolism is frequently encountered during the peripartum period. No randomized studies guide the management of anticoagulation at the time of delivery, but consensus opinion is provided by the Society for Anesthesia and Perinatology (Leffert, 2018). Briefly, women receiving >10,000 units/d of unfractionated heparin are individually assessed regarding timing and dose of last injection. Thromboprophylaxis with low-molecular-weight heparin (LMWH) should have a 12-hour delay. Therapeutic doses of LMWH merit a 24-hour delay. This is discussed further in Chapter 55 (p. 985). Spinal analgesia is also contraindicated if there is infection at the needle entry site.

Other maternal conditions may pose relative contraindications to neuraxial analgesia. Many women with neurological disorders such as Chiari malformation or pseudotumor cerebri may be candidates for neuraxial analgesia after consultation with an anesthesiologist and neurologist. Women with severe aortic stenosis or pulmonary hypertension also have a relative contraindication to spinal analgesia due to the deleterious effects of hypotension and diminished preload and afterload (Chap. 52, p. 926).

■ Epidural Analgesia

Relief of labor and childbirth pain, including cesarean delivery, can be accomplished by injection of a local anesthetic agent into the epidural space (see Fig. 25-3B). This potential space contains areolar tissue, fat, lymphatics, and the internal vertebral venous plexus. Entry for obstetrical analgesia is usually through a lumbar intervertebral space. Although only one injection may be given, usually an indwelling catheter is placed for subsequent bolus administration or continuous infusion (Billingham, 2018). Infusions use a volumetric pump controlled either by the patient or by a caregiver. Under appropriate physician supervision, labor and delivery nursing personnel with specific training in the management of epidural infusions should be able to adjust dosage and also discontinue infusions.

■ Continuous Lumbar Epidural Analgesia

Complete analgesia for the pain of labor and vaginal delivery necessitates a block from the T_{10} to the S_4 dermatomes. For cesarean delivery, a block extending from the T_4 to the S_1 dermatomes is desired. The effective spread of anesthetic depends upon the catheter tip location and the dose, concentration, and volume of anesthetic agent used. Individual variations in anatomy or synechiae or septa in the epidural space may preclude a completely satisfactory block. Last, the catheter tip may migrate from its original location during labor.

Technique

One example of the sequential steps and techniques for performance of epidural analgesia is detailed in Table 25-6. Before injection of the local anesthetic therapeutic dose, a test dose is given containing small amounts of lidocaine and epinephrine. The woman is observed for features of toxicity from intravascular injection and for signs of either subarachnoid or subdural injection. If these are absent, analgesia is initiated with a full dose of the anesthetic alone. Analgesia is maintained by a continuous infusion or by programmed intermittent boluses delivered by infusion pump (Billingham, 2018). The addition of a short-acting, lipid-soluble narcotic—fentanyl or sufentanil—lowers the required amount of local anesthetic drug needed to achieve analgesia. This helps preserve motor function (Lyons, 1997). One popular regimen is 0.0625- to 0.125-percent bupivacaine with 2-μg/mL fentanyl.

As with spinal blockade, close monitoring, including the level of analgesia, must be performed by trained personnel. Appropriate resuscitation equipment, drugs, and personnel must be available during administration of epidural analgesia.

Complications

As shown in Table 25-4, certain problems are inherent to epidural analgesia.

High Spinal Blockade. Dural puncture with inadvertent and unrecognized either subarachnoid or subdural injection may cause total spinal blockade. In a study of more than 18,000 women, the incidence of recognized accidental dural puncture at the time of epidural analgesia was 0.91 percent (Sprigge, 2008). Management of this complication is described earlier (p. 474).

Ineffective Analgesia. Using currently popular continuous or intermittent epidural infusion regimens, 90 percent of women rate their pain relief as good to excellent (Sharma, 1997). In a study of almost 2000 parturients, Hess and associates (2001) found that 12 percent complained of three or more episodes of

TABLE 25-6. Technique for Labor Epidural Analgesia

Obtain informed consent and consult the obstetrician
Monitoring includes the following:
Blood pressure every 1–2 minutes for 15 minutes after giving a bolus of local anesthetic
Continuous maternal heart rate monitoring during analgesia induction
Continuous fetal heart rate monitoring
Continual verbal communication
Hydration with 500–1000 mL of Ringer lactate solution
The woman assumes a lateral decubitus or sitting position
The epidural space is identified by the needle's loss of resistance during insertion
The epidural catheter is threaded 3–5 cm into the epidural space
After a negative aspiration, a test dose of 3 mL of 1.5% lidocaine with 1:200,000 epinephrine is injected between contractions. Epinephrine is injected after careful aspiration to avert intravascular injection and after a uterine contraction. This minimizes the chance of confusing tachycardia that results from labor pain with that of tachycardia from intravenous injection of the test dose.
A positive test dose manifests as symptoms of an intravascular injection of lidocaine and epinephrine, which are tinnitus, circumoral numbness, dizziness, heart rate increase >20 bpm in 1 minute. Another potential symptom is an inability to raise the lower extremities against gravity in 4 min, which reflects the effects of a subarachnoid space injection.
If the test dose is negative, 10–15 mL of 0.0625–0.125% bupivacaine are injected to achieve a sensory T_{10} level
After 15–20 minutes, the block is assessed using loss of sensation to cold or pinprick. If no block is evident, the catheter is replaced. If the block is asymmetrical, the epidural catheter is withdrawn 0.5–1.0 cm and an additional 3–5 mL of 0.25% bupivacaine is injected. If the block remains inadequate, the catheter is replaced.
The woman is positioned in the lateral or semilateral position to avoid aortocaval compression
Subsequently, maternal blood pressure is recorded every 5–15 minutes. The fetal heart rate is monitored continuously
The level of analgesia and intensity of motor blockade are assessed at least hourly

pain or pressure. Its efficacy was more likely to decrease with rising body mass index (Dresner, 2006). Inadequate analgesia may result in patient dissatisfaction. Catheter replacement should be considered.

Moreover, a poorly functioning epidural catheter cannot be used for additional dosing of local anesthetic drugs for intrapartum cesarean delivery. Such conversion of labor epidural analgesia to cesarean delivery anesthesia has an approximately 20 percent failure rate. This necessitates placement of a new regional block or general anesthesia (Mankowitz, 2016). In a Maternal Fetal Medicine Units (MFMU) Network study, 4 percent of women initially given epidural analgesia required a general anesthetic for cesarean delivery (Bloom, 2005).

Also at times, perineal analgesia for vaginal delivery is difficult to obtain, especially when lower volumes of epidural local anesthetic drugs are used. With this situation, additional doses can be given, or a pudendal block may be added.

Hypotension. Sympathetic blockade from epidurally injected analgesic agents may cause peripheral vasodilation with resulting hypotension and diminished cardiac output. Hypotension is more common—20 percent—in women with an admission pulse pressure <45 mm Hg compared with 6 percent in those whose pulse pressure is >45 mm Hg (Miller, 2013). Pulse pressure is calculated by subtracting diastolic from systolic blood pressure measurements. Obese women also have significantly higher rates of hypotension (Vricella, 2011). In normal gravidas, hypotension induced by epidural analgesia usually can be prevented by rapid IV infusion of 500 to 1000 mL of crystalloid solution as described for spinal analgesia. Maintaining a lateral position also minimizes hypotension. Despite these precautions, hypotension is the most frequent side effect and is severe enough to require treatment in a third of women (Sharma, 1997).

Central Nervous Stimulation. Convulsions are an uncommon but serious complication. Described earlier, the immediate management involves infusion of 20-percent intralipids and treatment with lorazepam or diazepam (p. 470).

Fever. Some women develop intrapartum fever following epidural analgesia. Many studies are limited by the inability to control for other risk factors, such as labor length, duration of ruptured membranes, and number of vaginal examinations. With this in mind, the frequency of intrapartum fever associated with epidural analgesia is 10 to 15 percent above the baseline rate (Lieberman, 2002).

The two general theories concerning the etiology of maternal hyperthermia are *maternal-fetal infection* or *dysregulation of body temperature* (American College of Obstetricians and Gynecologists, 2019b). A study of placental histopathology in women given epidural analgesia identified intrapartum fever only when there was placental inflammation (Dashe, 1999). This suggests that fever is due to infection. Sharma (2014) randomized 400 nulliparas with labor epidural analgesia to receive 2 g cefoxitin prophylactically versus placebo. It was hypoth-

esized that epidural-related fever was due to infection and that prophylactic antimicrobials should significantly reduce the rate of fever. Approximately equal proportions—40 percent—of women developed fever ≥38°C during labor. This result suggests that infection is unlikely to cause the fever associated with epidural analgesia during labor. Whatever the mechanism, women with persistent fever are usually treated with antimicrobials for presumed chorioamnionitis.

The other proposed mechanisms include alteration of the hypothalamic thermoregulatory set point, impaired peripheral thermoreceptor input to the central nervous system with selective blockade of warm stimuli, or imbalance between heat production and heat loss. Del Arroyo and colleagues (2019) suggested that bupivacaine blocks release of antipyretic interleukins.

Back Pain. An association between epidural analgesia and back pain has been reported by some. In a prospective cohort study, Butler and Fuller (1998) reported that back pain after delivery was common with epidural analgesia, however, persistent pain was infrequent. Based on their systematic review, Lieberman and O'Donoghue (2002) concluded that available data do not support an association between epidural analgesia and development of de novo, long-term backache.

Miscellaneous Complications. A spinal or epidural hematoma is a rare complication of an epidural catheter (Grant, 2007). These are considered neurological emergencies, and treatment is usually surgical. Epidural abscesses are rare, and the most common pathogen is *Staphylococcus aureus* (McQuaid, 2018). These may be managed conservatively with IV antibiotics, but surgical intervention may be necessary. For both conditions, timely neurosurgical consultation is important. Uncommonly, the plastic epidural catheter is sheared off (Noblett, 2007). Computed tomography can localize the retained fragment. For a tip left in the epidural space, surveillance is reasonable in the absence of symptoms. With neurological changes or with fragments in the subarachnoid space, neurosurgical consultation is recommended (Mitra, 2007). Last, an association of epidural analgesia and autism spectrum disorder seems unlikely (Mikkelsen, 2021).

Effect on Labor

Most studies, including five combined randomized trials from Parkland Hospital shown in Table 25-7, report that epidural analgesia prolongs labor and increases the use of oxytocin stimulation (Sharma, 2004). Alexander and associates (2002) examined the effects of epidural analgesia on the Friedman (1955) labor curve (Chap. 22, p. 424). There were 459 nulliparas randomly assigned to receive patient-controlled epidural analgesia or patient-controlled IV meperidine. Compared with original Friedman criteria, epidural analgesia prolonged the active phase of labor by 1 hour. In a cohort study, similar labor durations were observed for both spinal-epidural and epidural analgesia (Poma, 2019).

The effect of labor epidural on the second stage is unclear. Prolongation of the second stage was particularly true in earlier studies, at a time when higher concentrations of local anesthetic drugs were used. This association has been attributed to local-anesthetic-induced motor blockade and resultant impaired maternal expulsive efforts. Chestnut and associates (1999) reported that, with epidural analgesia, operative vaginal delivery occurred more frequently because of prolonged second-stage labor. In a systematic review, Anim-Somuah and colleagues (2018) reported that epidural analgesia prolongs the first stage by 32 minutes and the second stage by 15 minutes. Craig and coworkers (2015) randomly assigned 310 nulliparous women with labor epidural analgesia to receive 0.125-percent bupivacaine plus fentanyl or epidural fentanyl alone during second-stage labor. Epidural bupivacaine analgesia did cause motor blockade during the second stage, however, the duration of the second stage was not longer. Neither obstetrical nor neonatal outcomes were different between the two groups. Patient satisfaction was high with both methods.

TABLE 25-7. Selected Labor Events in 2703 Nulliparous Women Randomized to Epidural Analgesia or Intravenous Meperidine Analgesia

Event[a]	Epidural Analgesia n = 1339	Intravenous Meperidine n = 1364	*p* value
Labor outcomes			
First-stage duration (hr)[b]	8.1 ± 5	7.5 ± 5	0.011
Second-stage duration (min)	60 ± 56	47 ± 57	<0.001
Oxytocin after analgesia	641 (48)	546 (40)	<0.001
Type of delivery			
SVD	1027 (77)	1122 (82)	<0.001
Forceps	172 (13)	101 (7)	<0.001
Cesarean	140 (10.5)	141 (10.3)	0.92

[a]Data are presented as n (%) or mean ± SD.
[b]First stage = initiation of analgesia to complete cervical dilation.
SVD = spontaneous vaginal delivery.

Fetal Heart Rate. Hill and associates (2003) examined the effects of epidural analgesia with 0.25-percent bupivacaine on fetal heart rate patterns. Compared with IV meperidine, no worrisome effects were identified. Reduced beat-to-beat variability and fewer accelerations were more common in fetuses whose mothers received meperidine (Chap. 24, p. 450). Based on their systematic review, Reynolds and coworkers (2002) reported that epidural analgesia was associated with improved neonatal acid-base status compared with meperidine.

Cesarean Delivery Rates. A contentious issue in the past was whether epidural analgesia increased the risk for cesarean delivery. Early evidence that it did was from an era when dense motor blockade resulted from high concentrations of local

TABLE 25-8. Cesarean Delivery (CD) Rates in Laboring Women Receiving Epidural Analgesia or Intravenous Meperidine

Study	Odds Ratio[a]	CD Incidence Higher with
Ramin (1995)	1.20 (0.73–1.97)	Epidural
Sharma (1997)	0.77 (0.31–1.91)	Meperidine
Gambling (1998)	1.13 (0.65–1.97)	Epidural
Lucas (2001)	1.05 (0.68–1.63)	Epidural
Sharma (2002)	0.81 (0.41–1.61)	Meperidine
Adjusted	1.04 (0.81–1.34)	

[a]Shown with 95-percent confidence intervals.

anesthetic agents. Now however, with the administration of *dilute* anesthetic solutions, the risk for cesarean delivery is not increased.

Several studies conducted at Parkland Hospital were designed to answer this and related questions. From 1995 to 2002, a total of 2703 nulliparas at term and in spontaneous labor were enrolled in five trials to evaluate epidural analgesia techniques compared with IV meperidine. The results from these are summarized in Table 25-8 and show that epidural analgesia does not significantly raise cesarean delivery rates (Sharma, 2004). The American College of Obstetricians and Gynecologists (2019b) and the American Society of Anesthesiologists (2016) also conclude that epidural analgesia is not associated with a greater cesarean delivery rate.

Timing of Epidural Placement. Earlier studies indicated that epidural placement in early labor was linked to a higher risk of cesarean delivery (Lieberman, 1996; Rogers, 1999; Seyb, 1999). These observations prompted at least five randomized trials, which showed that the timing of epidural placement has no effect on the risk of cesarean birth, forceps delivery, or fetal malposition (Chestnut, 1994a,b; Luxman, 1998; Ohel, 2006; Wong, 2005, 2009). Thus, withholding epidural placement until some arbitrary cervical dilation has been attained serves only to deny women maximal labor pain relief.

Safety

Among nearly 20,000 women who received epidural analgesia in the MFMU Network study cited earlier, no anesthesia-related maternal deaths were reported (Bloom, 2005). Ruppen and colleagues (2006) reviewed data from 27 studies involving 1.4 million pregnant women who received epidural analgesia. Their calculated adverse-event rates were 1:145,000 for deep epidural infection, 1:168,000 for epidural hematoma, and 1:240,000 for persistent neurological injury. More recently, the Society for Obstetric Anesthesia and Perinatology established the Serious Complication Repository Project (D'Angelo, 2014). During a 5-year period, more than 228,000 women had neuraxial analgesia. There were no maternal deaths related to anesthesia, but two each were attributed to cardiac arrest and myocardial infarction. There were four cases of epidural abscess or meningitis, 58 high-spinal-level neuraxial blocks (1 in 4000), 27 neurological injuries, and 16 respiratory arrests (1 in 10,000).

Contraindications

As with spinal analgesia, contraindications are listed in Table 25-5.

Thrombocytopenia. Although low platelet counts are intuitively worrisome, the level at which epidural bleeding *might* develop is unknown. Epidural hematomas are rare, and their incidence was estimated to be 0 to 0.6 percent in women whose platelet count is <70,000/μL (Goodier, 2015; Lee, 2017). The American College of Obstetricians and Gynecologists (2019b) and Society for Obstetric Anesthesia and Perinatalogy (Bauer, 2021) have concluded that women with a platelet count of ≥70,000/μL may be candidates for neuraxial analgesia.

Anticoagulation. Women receiving anticoagulation therapy who are given regional analgesia are at increased risk for spinal cord hematoma and compression (Chap. 55, p. 985). The American College of Obstetricians and Gynecologists (2019b) has concluded the following:

1. With prophylactic unfractionated heparin (UFH) in a dose of 5000 units twice daily, regional analgesia is not contraindicated.
2. With an intermediate dose of UFH (7500 to 10,000 units), it is likely low risk to proceed with neuraxial analgesia at a point more than 12 hours after the last dose.
3. With a high dose of UFH (>20,000 units), it is likely low risk to use regional analgesia at a point more than 24 hours after the last dose if the activate partial thromboplastin time (aPTT) is within normal range or the anti-Xa level is undetectable.
4. With thromboprophylaxis with LMWH, needle or catheter placement or removal should be delayed 12 hours or more.
5. With treatment doses of LMWH, placement or removal of a neuraxial catheter should be delayed for 24 hours.

Severe Preeclampsia-Eclampsia. Concerns with neuraxial analgesia in women with severe preeclampsia include hypotension as well as hypertension from pressor agents given to correct hypotension. Additionally, pulmonary edema may follow infusion of large volumes of crystalloid. These risks are outweighed by the disadvantages of general anesthesia (American College of Obstetricians and Gynecologist, 2020). Of these, tracheal intubation may be difficult because of upper airway edema. Also, general anesthesia can lead to severe, sudden hypertension that can cause pulmonary or cerebral edema or intracranial hemorrhage.

With improved techniques for infusion of dilute local anesthetics into the epidural space, most have come to favor epidural blockade for labor and delivery in women with severe preeclampsia. In a study from Parkland Hospital, Lucas and associates (2001) randomly assigned 738 women with hypertension to epidural analgesia or patient-controlled IV analgesia during labor. A standardized protocol for prehydration,

incremental epidural administration, and ephedrine use was employed. They concluded that labor epidural analgesia was safe in women with hypertensive disorders.

Thrombocytopenia is seen with severe preeclampsia complicated by hemolysis, elevated liver enzyme levels, low platelet count—HELLP syndrome (Chap. 40, p. 689). Discussed earlier and in general, it seems safe to use neuraxial techniques if the platelet count is ≥70,000/μL (American College of Obstetricians and Gynecologists, 2019b, 2020).

Women with severe preeclampsia can have remarkably diminished intravascular volume compared with normal pregnancy (Zeeman, 2009). Conversely, total body water volume is increased because of the capillary leak caused by endothelial cell activation (Chap. 40, p. 693). This imbalance is manifested as pathological peripheral edema, proteinuria, ascites, and total lung water. For all of these reasons, aggressive volume replacement raises the risk for pulmonary edema, especially in the first 72 hours postpartum (American College of Obstetricians and Gynecologists, 2019b). In one study, 3.5 percent of women with severe preeclampsia developed pulmonary edema when preloaded without a protocol limit to the volume infused (Hogg, 1999).

The risk of pulmonary edema can be reduced or obviated with judicious prehydration—usually with 500 to 1000 mL of crystalloid solution. Specifically, in the study by Lucas and colleagues (2001) cited earlier, no instances of pulmonary edema developed among the women in whom the infused crystalloid preload volume was limited to 500 mL. Moreover, vasodilation produced by epidural blockade is less abrupt if the analgesia level is achieved slowly with dilute solutions of local anesthetic agents.

With vigorous IV crystalloid therapy, cerebral edema also may develop (Chap. 40, p. 701. Last, most cases of pharyngolaryngeal edema are related to aggressive volume therapy (Heller, 1983).

Epidural Opioid Analgesia

Opioids alone usually will not provide adequate analgesia, and they are often used as an adjunct to a local anesthetic agent such as bupivacaine (Wang, 2020). This combination lowers the local anesthetic drug concentration needed to achieve analgesia, which in turn creates a less dense motor blockade. Other benefits are rapid onset of pain relief and a decrease in shivering. Common side effects include pruritus and urinary retention. Nalbuphine, a mixed opioid agonist/antagonist, will abolish these symptoms without affecting the analgesic action. When neuraxial morphine is given for postoperative pain, monitoring for respiratory depression is necessary as discussed earlier (p. 472) (Bauchat, 2019).

Combined Spinal–Epidural Techniques

The combination of spinal and epidural techniques (CSE) has risen in popularity and may provide rapid and effective analgesia for labor and then for cesarean delivery. An epidural needle is first placed in the epidural space. A small-gauge spinal needle is then introduced through the epidural needle into the subarachnoid space—this is called the *needle-through-needle technique* (see Fig. 25-3A). A single bolus of an opioid, a local anesthetic, or sometimes a combination is injected into the subarachnoid space. A subarachnoid opioid bolus results in the rapid onset of profound pain relief with virtually no motor blockade (Poma, 2019). The spinal needle is withdrawn, and an epidural catheter is then placed into the epidural space. The epidural catheter remains and permits repeated analgesia dosing.

Miro and associates (2008) compared epidural analgesia with CSE analgesia for labor in 6497 women and found the overall outcomes and complications to be similar. Poma and coworkers (2019) also found comparable analgesia results with epidural or CSE techniques. They noted that subarachnoid sufentanil was associated with lower uterine contractility, but labor duration was not affected. A greater incidence of fetal heart rate abnormalities related to uterine hypertonus has been reported with CSE analgesia (Abrão, 2009; Beamon, 2014). The analgesia failure rate is 11.6 percent for traditional labor epidural and 6.6 percent for CSE (Booth, 2016). Although CSE provides a faster onset of labor analgesia, the intrathecal injection of local anesthetic drugs and/or narcotic may cause hypotension and pruritus.

Continuous Spinal Analgesia During Labor

The technique of continuous spinal analgesia for relief of labor pain is seldom used because of postdural puncture headaches (American College of Obstetricians and Gynecologists, 2019b). With redesigned needles and catheters, Arkoosh (2008) randomized 429 women to either continuous spinal or conventional epidural analgesia during labor. Complication rates between these two neuraxial techniques did not differ.

Dural-Puncture Epidural Analgesia

Gaining popularity, this technique is similar to CSE, but initial steps differ. First, a single dural puncture is made using a 25-gauge spinal needle placed through the epidural needle shaft (see Fig. 25-3A). No anesthetic is injected, but the needle can help confirm correct subarachnoid space placement by the drip of CSF from its distal hub. After removal of the spinal needle, the epidural catheter is threaded into the epidural space (see Fig. 25-3B). The dural puncture allows for a small amount of local anesthetic drugs to be translocated from the epidural space to the subarachnoid space. This aids a faster onset of pain relief than traditional epidural analgesia. Without the intrathecal injection, dural-puncture epidural analgesia is associated with fewer side effects than CSE analgesia and provides better block quality than an epidural (Chau, 2017). A review of five studies with 581 patients showed dural puncture epidural technique was associated with a faster onset of analgesic effects, a reduction in provider-initiated boluses "top-ups," and better sacral coverage. The incidence of post-dural puncture headache was not significantly increased (Heesen, 2019). A study confirmed fewer top-ups and a greater local anesthetic drug sparing effect evaluating the combined use of this technique and the intermittent bolus drug delivery mode (Song, 2021).

Local Infiltration Analgesia

A local block is occasionally useful to augment an inadequate or "patchy" regional block that was given emergently. Rarely, local infiltration may be needed to perform an emergency cesarean delivery to save the life of a fetus in the absence of anesthesia support. Two methods are described here.

In one technique, the skin is infiltrated along the proposed incision, and the subcutaneous, muscle, and rectus sheath layers are injected as the abdomen is opened. Injection of large volumes into the fatty layers, which are relatively devoid of nerve supply, is avoided to limit the total dose of local anesthetic needed.

Cooper and coworkers described using 52 mL of 0.5-percent lidocaine with 1:200,000 epinephrine. This delivered 260 mg of lidocaine. Related to lidocaine toxicity, higher lidocaine volumes can be used when paired with epinephrine, because vasoconstriction lowers the intravascular transfer of anesthetic. The maximum dose is 7 mg/kg. Others have used 1-percent procaine with or without epinephrine (Larsen, 1971; Ranney, 1975).

A second technique involves a field block of the major branches supplying the abdominal wall, to include the 10th, 11th, and 12th intercostal nerves and the ilioinguinal and genitofemoral nerves (Nandagopal, 2001). As shown in Figure 25-4, the former group of nerves is located at a point midway between the costal margin and iliac crest in the midaxillary line. The latter group is found at the level of the external inguinal ring. A total of four skin punctures, two on each side, are made. First, at the intercostal block site, the needle is directed medially, and injection is carried down to the transversalis fascia, avoiding injection of the subcutaneous fat. Five mL of 0.5-percent lidocaine with epinephrine are injected. The needle is redirected but not removed, and similar dosing is delivered to sites located at a 45-degree angle cephalad and caudad. The other side is then injected. Second, at the ilioinguinal and genitofemoral sites, the injection is started at a spot 2 to 3 cm lateral from the pubic tubercle at a 45-degree angle. Last, the skin overlying the planned incision is injected.

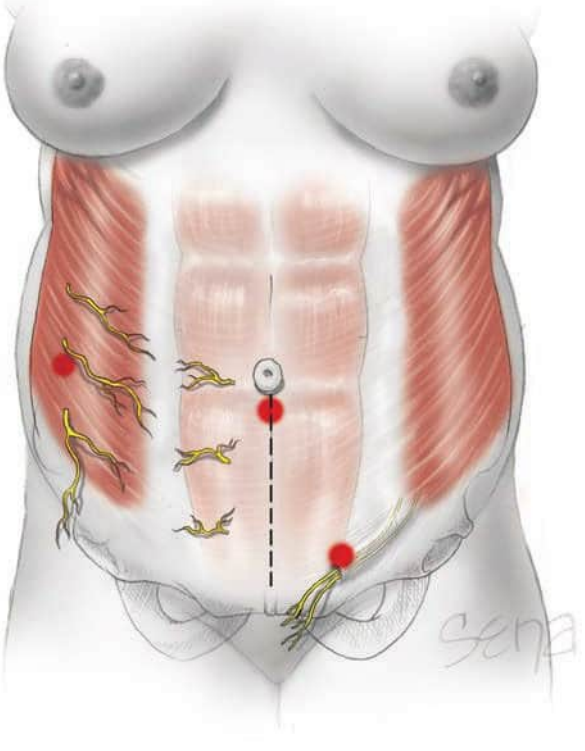

FIGURE 25-4 Local anesthetic block for cesarean delivery. The first injection site is halfway between the costal margin and iliac crest in the midaxillary line to block the 10th, 11th, and 12th intercostal nerves. A second injection at the external inguinal ring blocks branches of the genitofemoral and ilioinguinal nerves. Although not shown, both sites are infiltrated bilaterally. The final site is along the line of proposed skin incision.

Transversus Abdominis Plane Block

This block may be used for those with suitable training (Young, 2012). It is usually performed under ultrasound guidance and involves injection of a local anesthetic into the transversus abdominis plane (TAP) between the internal oblique and transversus abdominis muscles (Fig. 2-2, p. 14). The nerves lying in this plane supply the anterior abdominal wall at the T_6 to L_1 dermatomes. Ng and colleagues (2018) concluded that high- versus low-dose local anesthetics performed comparably.

Local infiltration or TAP blocks can be used also for postoperative pain control. The TAP block in one trial was not superior to local wound infiltration (Tawfik, 2017). Gao and associates (2019) demonstrated that pain relief with the TAP block was comparable with that from patient-controlled IV analgesia. Another study found that the TAP block was equivalent to intrathecal morphine for postoperative pain (Kwikiriza, 2019). Last, Prabhu and coworkers (2018) reported that a liposomal bupivacaine incisional block was not superior to placebo.

GENERAL ANESTHESIA

Trained personnel and specialized equipment—including fiberoptic intubation—are mandatory for the safe use of general anesthesia. A common cause of death cited is failed intubation. The latter occurs in approximately 1 of every 390 general anesthetics administered to pregnant women (Kinsella, 2015).

This relatively higher mortality rate suggests that neuraxial analgesia is the preferred method of pain control and should be used unless contraindicated (American College of Obstetricians and Gynecologists, 2019b; American Society of Anesthesiologists, 2016). In two reports from the MFMU Network, 93 percent of more than 54,000 cesarean deliveries were performed using neuraxial analgesia (Bloom, 2005; Brookfield, 2013). Racial and ethnic disparities exist, and a higher incidence of general anesthesia use is seen among non-white women (Butwick, 2014; Lange, 2017). It is often used for emergent cesarean delivery for acute fetal distress (Metogo, 2021). In contrast, with obstetrical anesthesiologist subspecialists, the overall likelihood that neuraxial analgesia will be used is higher (Cobb, 2019).

Patient Preparation

Before anesthesia induction, several steps should be taken to help minimize complication risks. First, antacid administration shortly before anesthesia induction has probably decreased mortality rates from general anesthesia more than any other

single practice. The American Society of Anesthesiologists Task Force on Obstetrical Anesthesia (2016) recommends timely administration of a nonparticulate antacid, an H_2-receptor antagonist, or metoclopramide. For many years, we have recommended administration of 30 mL of Bicitra—sodium citrate with citric acid—a few minutes before anesthesia induction by either general or major neuraxial block. If more than 1 hour has passed after the first dose was given and anesthesia has not yet been induced, a second dose is given.

Lateral uterine displacement also is provided as the uterus may compress the inferior vena cava and aorta when the mother is supine. With uterine displacement, the duration of general anesthesia has less effect on neonatal condition than if the woman remains supine (Crawford, 1972).

Last, because functional reserve lung capacity is diminished, and oxygen consumption is increased, the pregnant woman becomes hypoxemic more rapidly during periods of apnea than do nonpregnant patients. Obesity exacerbates this tendency. To minimize hypoxia between the time of muscle relaxant injection and intubation, nitrogen is replaced by oxygen in the lungs. This preoxygenation is accomplished by administering 100-percent oxygen via face mask for 2 to 3 minutes before anesthesia induction. In an emergency, four vital capacity breaths of 100-percent oxygen via a tight breathing circuit will provide similar benefit (Norris, 1985). High-flow nasal oxygen was found to be inferior to administration by face mask (Shippam, 2019; Tan, 2019).

Induction of Anesthesia

Drugs used to induce general anesthesia include propofol, etomidate, and ketamine. Propofol has the undesirable side effect of hypotension. Etomidate is associated with fewer hemodynamic changes. Ketamine also may be used for induction of general anesthesia in hemodynamically unstable women.

Intubation

Immediately after a patient is rendered unconscious, a muscle relaxant is given to aid intubation. *Succinylcholine,* a rapid-onset and short-acting agent, is used. Cricoid pressure—the *Sellick maneuver*—is applied by a trained assistant to occlude the esophagus from the onset of induction until intubation is completed. Before the operation begins, proper placement of the endotracheal tube must be confirmed.

As discussed, and although uncommon, failed intubation is a major cause of anesthesia-related maternal mortality. A history of prior difficult intubation and a careful anatomical assessment of the neck and the maxillofacial, pharyngeal, and laryngeal structures may help predict intubation complications. Even in cases in which the initial airway assessment was unremarkable, edema may develop intrapartum and present considerable challenges. Morbid obesity is a major risk factor for failed or difficult intubation.

The American Society of Anesthesiologists Task Force on Obstetric Anesthesia (2016) stresses the importance of appropriate preoperative preparation. This includes the immediate availability of specialized equipment such as different-shaped laryngoscopes, laryngeal mask airways, and video laryngoscopes, as well as equipment for transtracheal ventilation and awake oral intubation with a fiberoptic bronchoscope.

Following failed intubation, the woman is ventilated by mask and cricoid pressure is applied to reduce the aspiration risk. Surgery may proceed with mask ventilation, or the woman may be allowed to awaken. In those cases in which the woman has been paralyzed and in which ventilation cannot be reestablished by insertion of an oral airway, by laryngeal mask airway, or by use of a fiberoptic laryngoscope, then a life-threatening emergency exists (Eskander, 2019). To restore ventilation, percutaneous or even open cricothyrotomy is performed, and jet ventilation begun. Failed intubation drills have been recommended to optimize response to such an emergency.

Inhalational Anesthetics

Once the endotracheal tube is secured, a volatile halogenated agent is given to provide amnesia and analgesia. The most commonly used volatile anesthetics in the United States include *desflurane* and *sevoflurane.* These gases can also produce uterine relaxation when given in high concentrations. These are used when relaxation is a requisite, such as for internal podalic version of the second twin, breech decomposition, ex utero intrapartum treatment (EXIT) procedures, and replacement of the acutely inverted uterus.

Extubation

The endotracheal tube may be safely removed only if the woman is conscious to a degree that enables her to follow commands and is capable of maintaining oxygen saturation with spontaneous respiration. Consideration should be given to emptying the stomach via a nasogastric tube before extubation. As induction has now become safer, extubation may be relatively more perilous. Of 15 anesthesia-related deaths of pregnant women from 1985 to 2003 in Michigan, none occurred during induction, whereas five resulted from hypoventilation or airway obstruction during emergence, extubation, or recovery (Mhyre, 2007).

Fasting

Data are insufficient regarding fasting times for clear liquids and the risk of pulmonary aspiration during labor. The American Society of Anesthesiologists Task Force on Obstetrical Anesthesia (2016) and the American College of Obstetricians and Gynecologists (2017) recommend that modest amounts of clear liquids such as water, clear tea, black coffee, carbonated beverages, and pulp-free fruit juices be allowed in uncomplicated laboring women. As discussed in Chapter 30 (p. 550), enhanced recovery after surgery (ERAS) protocols provide consumption of these same liquids up to 2 hours before scheduled surgery (Wilson, 2018b). Obvious solid foods should be avoided. A fasting period of 6 to 8 hours, depending on the type of food ingested, is recommended for uncomplicated parturients undergoing elective cesarean delivery or puerperal tubal ligation. The amount of gastric fluid—2 mL/kg—in nonlaboring women is almost the same as that in nonpregnant

women (Van de Putte, 2019). However, pregnancy is associated with horizontal shift of the stomach and a reduced esophageal sphincter tone. Our policy at Parkland Hospital is to allow clear liquids in low-risk uncomplicated laboring women in whom vaginal delivery is anticipated.

Aspiration

Massive gastric acidic inhalation may cause pulmonary insufficiency from aspiration pneumonitis (Mandell, 2019). Such pneumonitis has in the past been the most common cause of anesthetic deaths in obstetrics and therefore deserves special attention. To minimize this risk, antacids should be given routinely, intubation should be accompanied by cricoid pressure, and regional analgesia should be employed when possible.

Pathophysiology

In 1952, Teabeaut demonstrated experimentally that if the pH of aspirated fluid was below 2.5, severe chemical pneumonitis developed. It was later demonstrated that the gastric fluid pH of nearly half of women tested intrapartum was <2.5 (Taylor, 1966). The right mainstem bronchus usually offers the simplest pathway for aspirated material to reach the lung parenchyma, and therefore, the right lower lobe is most often involved. In severe cases, involvement is bilateral and widespread.

The woman who aspirates may develop evidence of respiratory distress immediately or several hours after aspiration, depending in part on the material aspirated and the severity of the response. Aspiration of a large amount of solid material causes obvious signs of airway obstruction. Smaller particles without acidic liquid may lead to patchy atelectasis and later to bronchopneumonia.

When highly acidic liquid is inspired, decreased oxygen saturation along with tachypnea, bronchospasm, rhonchi, rales, atelectasis, cyanosis, tachycardia, and hypotension are likely to develop. At the injury sites, there is pulmonary capillary leakage and exudation of protein-rich fluid containing numerous erythrocytes into the lung interstitium and alveoli. This causes decreased pulmonary compliance, shunting of blood, and severe hypoxemia.

Suspicion of aspiration demands close monitoring for evidence of pulmonary damage. Respiratory rate and oxygen saturation as measured by pulse oximetry are the most sensitive and earliest indicators of injury. Radiographic changes may not appear immediately and may be variable. Therefore, chest radiographs alone should not be used to exclude aspiration.

Treatment

Inhaled fluid should be immediately and thoroughly wiped from the mouth and removed from the pharynx and trachea by suction. Saline lavage may further disseminate the acid throughout the lung and is not recommended. If large particulate matter is inspired, bronchoscopy may be indicated to relieve airway obstruction. Use of corticosteroid therapy or prophylactic antimicrobial administration are not supported by clinical or experimental evidence (Mandell, 2019). If infection develops, however, vigorous treatment is given. Etiological agents have shifted from anaerobic or mixed infections to bacteria causing community- or hospital-acquired pneumonitis (Metlay, 2019). These infections are discussed in Chapter 54 (p. 962). If acute respiratory distress syndrome develops, mechanical ventilation with positive end-expiratory pressure may prove lifesaving (Chap. 50, p. 885).

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CHAPTER 26

Induction and Augmentation of Labor

Today, several pharmacological agents permit labor to be induced or augmented. *Induction* implies stimulation of contractions before the spontaneous onset of labor, with or without ruptured membranes. When the cervix is closed and uneffaced, labor induction is often preceded by *cervical ripening*, a process to soften and open the cervix. This is somewhat of a misnomer in that cervical ripening, per se, may also be a means of labor induction. *Augmentation* refers to enhancement of spontaneous contractions that are considered inadequate because of failed cervical dilation and poor fetal descent. This chapter presents indications and methods for labor induction or augmentation and for cervical ripening.

LABOR INDUCTION

Indications

In the United States, the incidence of labor induction rose from 9.5 percent in 1991 to 27 percent in 2019 (Martin, 2019). Induction is indicated when the benefits to either mother or fetus outweigh those of pregnancy continuation. The more common indications include membrane rupture without labor, gestational hypertension, oligohydramnios, nonreassuring fetal status, postterm pregnancy, and various maternal medical conditions such as chronic hypertension and diabetes (American College of Obstetricians and Gynecologists, 2019a).

Methods to induce or augment labor are contraindicated by most conditions that preclude spontaneous labor or delivery. Maternal contraindications are an abnormally implanted placenta or a prior uterine incision type that is associated with a high rupture risk. Uncommon conditions are active genital herpes infection, contracted or distorted pelvic anatomy, or cervical cancer. Fetal factors include appreciable macrosomia, severe hydrocephalus, malpresentation, or nonreassuring fetal status.

Risks

Some maternal complications associated with labor induction are chorioamnionitis, uterine rupture, and postpartum hemorrhage from uterine atony. Earlier nonrandomized studies suggested a particularly higher risk for cesarean delivery in nulliparas undergoing labor induction (Luthy, 2004; Yeast, 1999). More recent ones, however, cite comparable or even lower rates of cesarean delivery when induced labor is compared with spontaneous labor (Middleton, 2020; Souter, 2019).

These studies used spontaneous labor as the comparator, which may be less suitable than using expectant management as the comparator. In the ARRIVE trial—A Randomized Trial of Induction Versus Expectant Management-more than 6000 low-risk nulliparas at 39 weeks' gestation were randomly assigned to labor induction or expectant management groups (Table 26-1) (Grobman, 2018; Tita, 2021). Primary outcome, which was the rate of severe neonatal morbidity or death, did not differ between cohorts. However, the cesarean delivery rate in the induction arm was significantly lower than that in the expectantly managed cohort—18.6 versus 22.2 percent, respectively. Rates

TABLE 26-1. Selected Maternal and Perinatal Outcomes with Labor Induction Versus Expectant Management in Low-Risk Nulliparous Women—the ARRIVE Trial

Factor	Induction (%) (n = 3059)	Expectant (%) (n = 3037)	*p* value
Maternal outcome[a]			
Cesarean delivery	18.6	22.2	<0.001
Operative vaginal delivery	7.3	8.5	0.07
Hypertensive disorder	9.1	14.1	<0.001
Chorioamnionitis	13.3	14.1	0.35
Postpartum hemorrhage	4.6	4.5	0.81
Perinatal outcome[b]	4.3	5.4	0.049
Respiratory support	3.0	4.2	
Apgar score ≤3 at 5 min	0.4	0.6	
Seizure	0.4	0.1	
Meconium aspiration	0.6	0.9	
Birth trauma	0.5	0.6	
Perinatal death	0.1	0.1	

[a]Secondary outcomes.
[b]Composite outcomes.
ARRIVE = A Randomized Trial of Induction Versus Expectant Management.

of chorioamnionitis, postpartum hemorrhage, and peripartum infection were not significantly different. In a metaanalysis of six cohort studies, elective induction at 39 weeks' gestation had a significantly lower risk of cesarean delivery and these other morbidities compared with expectant management (Grobman, 2019).

With induction, the overall associated risk of uterine rupture is low but is highest with a prior uterine scar (Landon, 2004). The American College of Obstetricians and Gynecologists (2019c) recommends against the use of prostaglandins for preinduction cervical ripening or for labor induction in women with a prior uterine incision. It recognizes labor induction with oxytocin as an option but also notes the higher potential rupture rate and lower VBAC rate. Oxytocin augmentation may be used in those undergoing TOLAC, although evidence for higher rupture rates are conflicting.

Amniotomy is often selected to augment labor (p. 494). Of other potential risks, women whose labor is managed with amniotomy have a higher incidence of chorioamnionitis compared with those in spontaneous labor (American College of Obstetricians and Gynecologists, 2019a).

In some, but not all studies, uterine atony and associated postpartum hemorrhage are more common in women undergoing induction or augmentation (Grobman, 2018; Widmer, 2020). And as discussed in Chapter 42 (p. 733), atony with intractable hemorrhage, especially following cesarean delivery, is a frequent indication for peripartum hysterectomy. In a study from Parkland Hospital, labor induction was associated with 17 percent of 553 unanticipated peripartum hysterectomies (Hernandez, 2013).

■ Elective Labor Induction

Until recently, the American College of Obstetricians and Gynecologists (2019a) did not recommend elective labor induction at term for convenience. Occasional exceptions are risk of rapid labor, psychosocial indications, or logistics that factor family support availability and distance from the hospital. Importantly, several studies have shown that elective delivery before 39 completed weeks' gestation is associated with significant adverse neonatal morbidity (Chiossi, 2013; Salemi, 2016; Tita, 2009).

This proscription against elective induction at term was reconsidered following publication of the previously cited ARRIVE trial. Because of the results from that trial, the American College of Obstetricians and Gynecologists (2018) and the Society for Maternal-Fetal Medicine (2019) conclude that offering elective induction to low-risk, well-dated nulliparas at 39 weeks' gestation is reasonable. These women must meet the criteria for the ARRIVE trial, and it is recommended to combine shared decision-making with consideration of available resources.

■ Factors Affecting Induction Success

Several factors affect the ability of labor induction to achieve vaginal delivery. Favorable factors include younger age, multiparity, body mass index (BMI) <30, favorable cervix, and birthweight <3500 g (Freret, 2021; Sievert, 2017). In many cases, the uterus is simply poorly prepared for labor. One example is an "unripe" or "unfavorable" cervix. Indeed, investigators with the *Consortium on Safe Labor* reported that elective induction resulted in vaginal delivery in 97 percent of multiparas and 76 percent of nulliparas. Induction was more often successful with a "ripe cervix" (Laughon, 2012).

Failure of induction is likely strongly influenced by the induction duration, especially with an unfavorable cervix (Spong, 2012). In one study, labor duration to reach the active phase and to complete dilation was adversely affected by a higher BMI (Kominiarek, 2011). Similar findings were

TABLE 26-2. Some Commonly Used Regimens Compared with Oxytocin Infusion for Preinduction Cervical Ripening and/or Labor Induction

Techniques	Agent	Route/Dose	Compared with Oxytocin
Pharmacological			
Prostaglandin E_2	Dinoprostone gel, 0.5 mg (Prepidil) Dinoprostone insert, 10 mg (Cervidil)	Cervical 0.5 mg; repeat in 6 hr; permit 3 doses total Posterior fornix, 10 mg	1. Shorter I-D times with oxytocin infusion than oxytocin alone 1. Insert has shorter I-D times than gel 2. 6–12 hr interval from last insert to oxytocin infusion
Prostaglandin E_1[a]	Misoprostol tablet, 100 or 200 μg (Cytotec)[b]	Vaginal, 25 μg; repeat 3–6 hr prn Oral, 50–100 μg; repeat 3–6 hr prn	1. Contractions within 30–60 min 2. Success comparable to oxytocin for ruptured membranes at term and/or favorable cervix 3. Tachysystole common with vaginal doses >25 μg
Mechanical			
Transcervical 36F Foley catheter	30-mL balloon	Transcervical	1. Improves Bishop scores rapidly 2. 80-mL balloon more effective 3. Combined with oxytocin infusion is superior to PGE_1 vaginally 4. With EASI, results improved and possible decreased infection rate
Hygroscopic dilators	Laminaria, hydrogel	Intracervical	1. Rapidly improves Bishop score 2. May not shorten I-D times with oxytocin 3. Uncomfortable, requires speculum and placement on an examination table

[a]Off-label use.
[b]Tablets must be divided for 25- and 50-μg dose, but drug is evenly dispersed.
EASI = extraamnionic saline infusion at 30–40 mL/hr; I-D = induction-to-delivery.

reported for women with diabetes (Hawkins, 2017). Simon and Grobman (2005) concluded that a latent phase as long as 18 hours allowed most women undergoing labor induction to achieve a vaginal delivery without a significantly increased risk of maternal or neonatal morbidity. Rouse and associates (2000) recommend a minimum of 12 hours of uterine stimulation with oxytocin after membrane rupture, whereas Kawakita and coworkers (2016) recommend up to 15 hours for multiparas.

PREINDUCTION CERVICAL RIPENING

As noted, a soft cervix—described as "ripe" or "favorable"—is important to successful labor induction. However, some estimates of favorability are highly subjective (Feltovich, 2017). Still, pharmacological and mechanical methods can enhance cervical qualities in a process of *preinduction cervical ripening*.

Some of the techniques may have benefits compared with oxytocin induction alone (Table 26-2). Namely, some are able to initiate labor and may effect delivery when used alone. However, few data support the premise that any of these methods lower cesarean delivery rates or lessen maternal or neonatal morbidity compared with women in whom these methods are not used.

■ Cervical "Favorability"

One quantifiable method to predict labor induction outcomes is the score described by Bishop (1964) and presented in Table 26-3. As favorability or Bishop score rises, the rate of induction to effect vaginal delivery also increases. A *Bishop score* >8 conveys a high likelihood for a successful induction, and a score ≤6 is considered unfavorable (American College of Obstetricians and Gynecologists, 2019a).

TABLE 26-3. Bishop Scoring System Used for Assessment of Inducibility

	Cervical Factor				
Score	Dilatation (cm)	Effacement (%)	Station (–3 to +2)	Consistency	Position
0	Closed	0–30	–3	Firm	Posterior
1	1–2	40–50	–2	Medium	Midposition
2	3–4	60–70	–1	Soft	Anterior
3	≥5	≥80	+1, +2	—	—

Laughon and coworkers (2011) attempted to simplify the Bishop score by performing a regression analysis on 5610 nulliparas with term singletons at 38 to 42 weeks' gestation. Cervical dilation, station, and effacement were significantly associated with successful vaginal delivery. Thus, a simplified Bishop score had a similar or improved positive- or negative-predictive value compared with that of the original Bishop score. Others have reported similar findings when consistency and position are omitted (Ivars, 2016; Raghuraman, 2016).

Transvaginal sonographic measurement of cervical length has been evaluated as a Bishop score alternative (Feltovich, 2017). However, data from a metaanalysis of 31 trials showed overall low sensitivity and specificity and limited predictive utility to forecast successful induction (Verhoeven, 2013).

Pharmacological Agents

Prostaglandin analogues make up available options. These can also stimulate contractions and thereby aid subsequent labor induction or augmentation. Importantly, in most studies of preinduction cervical ripening, oxytocin infusion either is initiated with the ripening agent or follows cervical change.

Prostaglandin E_2

Dinoprostone is a synthetic analogue of prostaglandin E_2 (PGE_2). It is commercially available in three forms: a gel, a time-release vaginal insert, and a 20-mg suppository (see Table 26-2). The gel and time-release vaginal insert formulations are indicated only for cervical ripening before labor induction. *Importantly, the 20-mg suppository is not indicated for cervical ripening.* It instead is used for pregnancy termination between 12 and 20 weeks' gestation and for evacuation of the uterus after fetal demise up to 28 weeks.

Local application of the PGE_2 gel form—*Prepidil*—is available in a 2.5-mL syringe for an intracervical application of 0.5 mg of dinoprostone. With the woman supine, the tip of a prefilled syringe is placed intracervically, and the gel is deposited just below the internal cervical os. After application, the woman remains reclined for 30 minutes. Doses may be repeated every 6 hours, with a maximum of three doses recommended in 24 hours.

A 10-mg dinoprostone vaginal insert—*Cervidil*—also is approved for cervical ripening. This is a thin, flat, rectangular polymeric wafer held within a small, white, mesh polyester sac (Fig. 26-1). The sac has a long attached tail to allow easy removal from the vagina. The insert provides slower release of medication—0.3 mg/hr—than the gel form. Cervidil is used as a single dose placed transversely in the posterior vaginal fornix. Lubricant is used sparingly, if at all, because it can coat the device and hinder dinoprostone release. Following insertion, the woman remains recumbent for at least 2 hours. The insert is removed after 12 hours or with labor onset and at least 30 minutes before the administration of oxytocin. Since the active drug is encased in a mesh sac, one benefit is the ability for removal if fetal heart rate abnormalities or tachysystole develop.

Most metaanalyses of dinoprostone efficacy report a reduced time to delivery within 24 hours. However, they do not consistently show a reduction in the cesarean delivery rate.

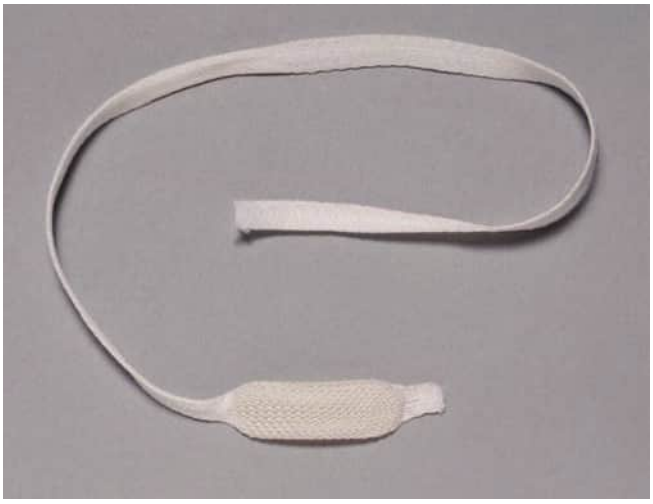

FIGURE 26-1 Cervidil vaginal insert contains 10 mg of dinoprostone designed to release approximately 0.3 mg/hr during a 10-hour period.

Thomas and colleagues (2014) provided a Cochrane review of 70 trials that included 11,487 women given vaginal prostaglandins or either placebo compared with no treatment. They noted a higher vaginal delivery rate within 24 hours when prostaglandins were used. They also reported a threefold greater risk of tachysystole accompanied by fetal heart rate changes, but cesarean delivery rates were not significantly decreased. Similar results were noted in another Cochrane review of intracervical dinoprostone gel (Boulvain, 2008). Compared with placebo or no treatment, a reduced risk of cesarean delivery was found only in a subgroup of women with an unfavorable cervix and intact membranes.

Last, the Foley catheter versus vaginal PGE_2 gel for induction of labor at term—PROBAAT-P and M trials—were unblinded, randomized trials comparing these two options (Jozwiak, 2011, 2013, 2014). The cesarean delivery rate did not differ, a finding consistent with accompanying metaanalyses.

Side Effects

Uterine tachysystole follows vaginally administered PGE_2 in 1 to 5 percent of women (Hawkins, 2012). Although definitions of abnormal uterine activity vary among studies, most use the definition recommended by the American College of Obstetricians and Gynecologists (2019b). *Uterine tachysystole* is defined as >5 contractions in a 10-minute period. It should always be qualified by the presence or absence of fetal heart rate abnormalities. The terms *uterine hypertonus*, *hyperstimulation*, and *hypercontractility* are terms no longer defined, and their use is not recommended.

Because uterine tachysystole associated with fetal compromise may develop when prostaglandins are used with preexisting spontaneous labor, such use is not recommended. If tachysystole follows the 10-mg insert, its removal by pulling on the tail of the surrounding net sac will usually reverse this effect. Irrigation to remove the gel preparation has not been shown to be helpful.

The manufacturers recommend caution when these preparations are used in women with ruptured membranes. This concern is also extended to women with glaucoma or asthma. However, in a review of 189 women with asthma, dinoprostone was not associated with asthma worsening or exacerbation

(Towers, 2004). Other contraindications listed by the manufacturers include prior dinoprostone hypersensitivity, suspicion of fetal compromise or cephalopelvic disproportion, unexplained vaginal bleeding, six or more prior term pregnancies, and contraindications to vaginal delivery. Others are women already receiving oxytocin, those with a contraindication to oxytocin, or those who may be endangered by prolonged uterine contractions, for example, those with prior cesarean delivery or uterine surgery.

Administration

PGE_2 preparations should be administered only in or near the delivery suite. Moreover, uterine activity and fetal heart rate should be monitored (American College of Obstetricians and Gynecologists, 2019a). These guidelines stem from the risk of uterine tachysystole. When contractions begin, they are usually apparent in the first hour and show peak activity in the first 4 hours. According to manufacturer guidelines, oxytocin induction that follows prostaglandin use for cervical ripening should be delayed for 6 to 12 hours following PGE_2 gel administration or for at least 30 minutes after removal of the vaginal insert.

■ Prostaglandin E_1

Misoprostol—*Cytotec*—is a synthetic prostaglandin E_1 (PGE_1) that is approved as a 100- or 200-μg tablet for peptic ulcer prevention. These tablets can be split to administer 25- or 50-μg doses. The drug is absorbed from both vaginal, oral, and buccal administration. Randomized trials of labor induction with misoprostol have evaluated various induction regimens with differing primary outcomes (Table 26-4).

Misoprostol is widely used "off label" safely for preinduction cervical ripening (American College of Obstetricians and Gynecologists, 2019a). The tablets are stable at room temperature, and the drug currently is the preferred prostaglandin for cervical ripening at Parkland Hospital.

Vaginal Administration

Compared with intracervical or intravaginal PGE_2, vaginally administered misoprostol tablets offer equivalent or superior efficacy for cervical ripening or labor induction (Hofmeyr, 2010). Compared with oxytocin or with intravaginal or intracervical dinoprostone, vaginal misoprostol increased the vaginal delivery rate within 24 hours. Although the uterine tachysystole rate was higher, this did not affect cesarean delivery rates. Moreover, compared with dinoprostone, misoprostol lowered the need for oxytocin induction, but it raised the frequency of meconium-stained amnionic fluid. Higher doses of misoprostol are associated with a decreased need for oxytocin but with greater rates of uterine tachysystole, with and without fetal heart rate changes. The American College of Obstetricians and Gynecologists (2019a) recommends a 25-μg vaginal dose. The drug is evenly distributed among 100-μg tablets that are quartered.

Oral Administration

PGE_1 tablets are also effective when given orally, but with a faster peak concentration and decline compared with the

TABLE 26-4. Randomized Trials with 200 or More Subjects Designed to Compare Misoprostol (PGE_1) With or Without Foley Bulb

Study	Comparators	Primary Outcome	N	Findings
Kehl (2015)	Double balloon catheter + oral PGE_1 (50 μg) vs oral PGE_1 alone	TTD	326	Longer TTD with Foley + oral PGE_1 (32h) vs oral E_1 alone (22h) ($p = 0.004$)
Ten Eikelder (2016)	PROBAAT-II: Oral PGE_1 (50 μg) vs Foley	Neonatal asphyxia or EBL >1000 mL	1859	No difference in primary outcome: Foley (12%) vs oral PGE_1 (11.5%)
Levine (2016)	FOR MOMI: Vaginal PGE_1 (25 μg) + Foley vs oxytocin + Foley vs vaginal PGE_1 alone vs Foley alone	TTD	492	Shorter TTD with combinations: Foley + PGE_1 (13.1h), oxytocin + Foley (14.5h), PGE_1 alone (17.6h), Foley alone (17.7h) ($p < 0.001$)
Kruit (2016)	Foley vs oral PGE_1 (50–100 μg)	CD and infections	202	No difference in CD or maternal/neonatal infection rates
Mundle (2017)	Foley vs oral PGE_1 (25 μg)	VD within 24h	602	VD within 24h more common in oral PGE_1 (57%) vs Foley (47%) ($p = 0.014$)
Al-Ibraheemi (2018)	Vaginal PGE_1 (25 μg) ± Foley	TTD	200	TTD in combination group (15h) vs vaginal PGE_1 alone (19h) ($p = 0.001$)
Young (2020)	Oral PGE_1 (50 μg) vs vaginal PGE_1 (25–50 μg) vs dinoprostone gel (1 to 2 mg)	TTD	511	TTD differences not significant: oral PGE_1 (22.6h), vaginal PGE_1 (25.5h), vaginal dinoprostone (20.1h) ($p = 0.46$)
Adhikari (2020)	Oral PGE_1 (100 μg) ± Foley	VD	2227	No difference in VD rates: Foley + oral PGE_1 (78%), PGE_1 alone (77%)

CD = cesarean delivery; EBL = estimated blood loss; N = participant number; PGE_1 = prostaglandin E_1; TTD = time to delivery; VD = vaginal delivery.

vaginal route. One Cochrane metaanalysis of 76 trials reported that oral misoprostol compared with placebo significantly increased the rate of vaginal birth within 24 hours, while decreasing the need for oxytocin and lowering the cesarean delivery rate (Alfirevic, 2014). Comparisons of oral misoprostol and oxytocin and of oral misoprostol and dinoprostone also found significantly reduced rates of cesarean delivery with misoprostol. Similar efficacy was noted between oral misoprostol and vaginal administration, although oral administration was associated with significantly higher Apgar scores and less postpartum hemorrhage. Thorbiörnson and associates (2017) also reported lower rates of cesarean delivery with oral misoprostol compared with vaginal dinoprostone.

■ Nitric Oxide Donors

Over the years, agents that stimulate nitric oxide production have been studied for labor induction. Physiologically, nitric oxide is likely a mediator of cervical ripening. Cervical nitric oxide metabolite concentrations are increased at the beginning of uterine contractions.

Both *isosorbide mononitrate* and *glyceryl trinitrate* have been studied but are less effective clinically than prostaglandins for cervical ripening. In one metaanalysis, the rate of cesarean delivery was not reduced in those given nitric oxide donors compared with those given placebo, intravaginal or intracervical prostaglandins, intravaginal misoprostol, or intracervical catheter (Ghosh, 2016). However, nitric oxide donors were associated with significantly more headaches, nausea, and vomiting.

■ Mechanical Techniques

These include transcervical placement of a Foley catheter, with or without extraamnionic saline infusion; hygroscopic cervical dilators; and membrane stripping. In one metaanalysis, mechanical methods reduced the risk of uterine tachysystole compared with prostaglandins, although cesarean delivery rates were unchanged (Jozwiak, 2012). Trials comparing mechanical techniques and oxytocin found a lower rate of cesarean delivery with mechanical methods. Trials comparing mechanical options with dinoprostone found a higher rate of multiparas undelivered at 24 hours with mechanical methods. In another metaanalysis comparing Foley catheter and intravaginal dinoprostone inserts, cesarean delivery rates were similar, but uterine tachysystole was less frequent with catheter use (Jozwiak, 2013).

Transcervical Catheter

Generally, this option is only used with an unfavorable cervix because the catheter comes out as the cervix opens. It is suitable for women with membranes that are intact or ruptured. In most cases, a Foley catheter is placed through the internal cervical os, and downward tension is created by taping the catheter to the thigh (Mei-Dan, 2014). *Extraamnionic saline infusion (EASI)* is one modification. It adds a constant saline infusion through the catheter into the space between the internal os and placental membranes (Fig. 26-2). In one study, chorioamnionitis was significantly less frequent when infusion was added compared with no infusion—6 versus 16 percent (Karjane, 2006). Similarly,

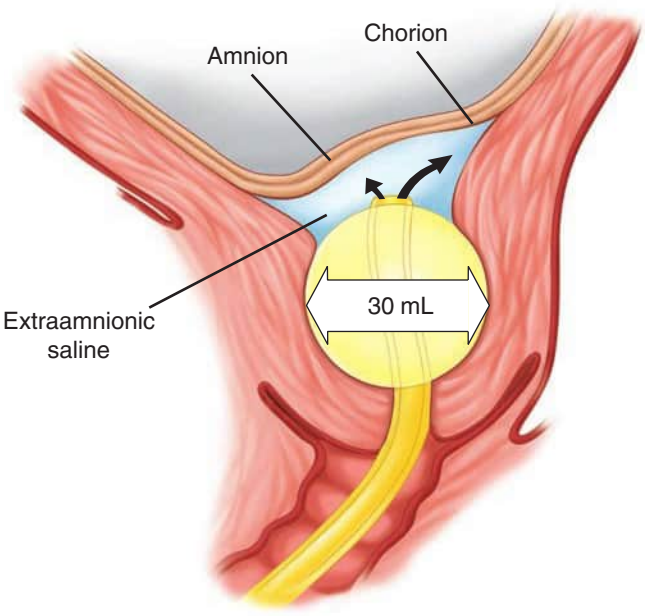

FIGURE 26-2 Extraamnionic saline infusion (EASI) through a 26F Foley catheter that is placed through the cervix. The 30-mL balloon is inflated with saline and pulled snugly against the internal os, and the catheter is taped to the thigh. Room-temperature normal saline is infused through the catheter port of the Foley at 30 or 40 mL/hour by intravenous infusion pump.

in a metaanalysis, transcervical catheters were not associated with higher rates of maternal or fetal infection (McMaster, 2015).

As discussed earlier, transcervical catheters do not reduce the cesarean delivery rate compared with prostaglandins. There were several iterations of the PROBAAT trials—I, P, M, and II—in which cervical ripening with a Foley catheter was compared with vaginal dinoprostone gel, dinoprostone vaginal inserts, and vaginal or oral misoprostol (Jozwiak, 2011, 2013, 2014; Ten Eikelder, 2016). These studies reported similar outcomes between the mechanical methods and the prostaglandin agents. Also, fewer overall cases of cardiotocographic changes were seen in the mechanical technique group.

Similar cesarean delivery rates are found in other comparison studies. Schoen and coworkers (2017) observed that concurrent oxytocin with a transcervical Foley catheter shortened the median time to delivery compared with a Foley catheter followed by oxytocin. However, rates of cesarean delivery were unchanged. Connolly and associates (2016) reported similar findings for women within intact membranes undergoing labor induction. Amorosa and colleagues (2017) found no benefit for transcervical catheter coupled with oxytocin compared with oxytocin alone for women with ruptured membranes. Other studies of concurrent misoprostol reported reduced time to delivery without affecting cesarean delivery rates (Carbone, 2013; Levine, 2016). With catheter induction plus misoprostol, one randomized trial found vaginal misoprostol to be superior to buccal administration (Gomez, 2021). Last, addition of tension does not appear to enhance catheter efficacy (Fruhman, 2017). These investigators randomly assigned 140 women to transcervical Foley catheter placement, with and without tension, and reported similar vaginal delivery rates.

One large trial at Parkland Hospital evaluated the addition of a Foley catheter to oral misoprostol. With catheter addition, investigators found no improvement in the vaginal delivery rate, but the chorioamnionitis rate was 30-percent higher (Adhikari, 2020). The unaltered vaginal delivery rate persisted in a stratified analysis of nulliparas and multiparas. In this study, our standard labor induction protocol with misoprostol alone achieved a 77-percent vaginal delivery rate.

Hygroscopic Cervical Dilators

Cervical dilation can be accomplished using hygroscopic or osmotic cervical dilators, which are illustrated in Chapter 11 (p. 209). Briefly, these include *Laminaria japonicum* or hygroscopic devices (Dilapan-S). Intuitive concerns of ascending infection have not been verified, and their use appears to be safe. Placement generally requires a speculum and positioning of the woman on an examination table. Studies comparing hygroscopic cervical dilators and prostaglandins found few benefits (Maier, 2018).

METHODS OF INDUCTION AND AUGMENTATION

Oxytocin has been used for labor induction for more than 70 years (Theobald, 1948). As discussed, other methods now include prostaglandins, which are used alone or in combination with oxytocin. Prostaglandins include misoprostol and dinoprostone. Mechanical methods encompass membrane stripping, artificial rupture of membranes, extraamnionic saline infusion, transcervical balloons, and hygroscopic cervical dilators. As recommended in *Guidelines for Perinatal Care*, each obstetrical department should have written protocols that describe administration of these methods for labor induction and augmentation (American College of Obstetricians, 2017).

Because preinduction cervical ripening frequently prompts labor, studies to determine induction efficacy for some of these agents have produced confusing results. The use of prostaglandins for labor augmentation has generally been considered experimental due to high rates of uterine tachysystole.

■ Prostaglandin E_1

Both vaginal and oral misoprostol are used for either cervical ripening or labor induction. For labor induction in women at or near term with either prematurely ruptured membranes or a favorable cervix, 100 μg of oral or 25 μg of vaginal misoprostol has similar efficacy compared with intravenous oxytocin. From these studies, evidence supports that oral misoprostol may be superior (Alfirevic, 2014; Hofmeyr, 2010; Lo, 2003). That said, misoprostol is associated with a greater rate of uterine tachysystole, particularly at higher doses. Also, induction with PGE_1 may prove ineffective and require subsequent induction or augmentation with oxytocin.

Thus, although there are trade-offs regarding the risks, costs, and ease of administration of each drug, either is suitable for labor induction. At Parkland Hospital, we administer an initial oral 100-μg dose, which may be repeated for inadequate labor after 6 hours. Four hours after the second dose or in those with tachysystole, an oxytocin infusion is begun, if needed, for hypotonic labor. One study compared oral misoprostol and a newer misoprostol vaginal insert that releases drug up to 24 hours. With the insert, cesarean delivery and adverse neonatal outcome rates were higher, but time to delivery was shorter (Döbert, 2018). Additional studies found these adverse outcomes were mitigated if the insert time was limited to 10 hours (Brandstetter, 2019, 2020).

For *labor augmentation*, results of a randomized controlled trial showed oral misoprostol, 75 μg given at 4-hour intervals for a maximum of two doses, to be safe and effective (Bleich, 2011). Although the uterine tachysystole rate was higher among women with labor augmented with misoprostol, the frequency of nonreassuring fetal status or cesarean delivery did not differ between oxytocin and misoprostol.

■ Oxytocin

As previously emphasized, in many instances, preinduction cervical ripening and labor induction are simply a continuum. In this regard "ripening" can also stimulate labor. If not, induction or augmentation may be continued with solutions of oxytocin given by infusion pump. Its use in augmentation is a key component in the *active management of labor*, described in Chapter 22 (p. 430). With oxytocin use, the American College of Obstetricians and Gynecologists (2019a) recommends fetal heart rate and uterine contraction monitoring. Contractions can be monitored either by palpation or by electronic means.

Intravenous Oxytocin Administration

A 1-mL vial contains 10 units of oxytocin. A typical infusate consists of 10 or 20 units, which is 10,000 or 20,000 mU, respectively, mixed into 1000 mL of crystalloid or dextrose solution. This mixture results in an oxytocin concentration of 10 or 20 mU/mL, respectively, and is administered by infusion pump. To avoid bolus administration, the infusion should be inserted into the main intravenous line close to the venipuncture site.

The goal of induction or augmentation is to effect uterine activity sufficient to produce cervical change and fetal descent, while avoiding development of a nonreassuring fetal status. According to the American College of Obstetricians and Gynecologists (2019a), the latter is a category III fetal heart rate tracing. In general, oxytocin is discontinued if the number of contractions persists with a frequency of more than five in a 10-minute period or more than seven in a 15-minute period or with a persistent nonreassuring fetal heart rate pattern. Oxytocin discontinuation nearly always rapidly lowers contraction frequency. When oxytocin is stopped, its concentration in plasma rapidly falls because the half-life is approximately 3 to 5 minutes.

The uterus contracts within 3 to 5 minutes of beginning an oxytocin infusion, and a plasma steady state is reached in 40 minutes (Seitchik, 1984). Response varies greatly and depends on preexisting uterine activity, cervical status, pregnancy duration, and individual biological differences. Caldeyro-Barcia and Poseiro (1960) reported that the uterine response to oxytocin increases from 20 to 30 weeks' gestation and rises rapidly at term.

TABLE 26-5. Various Low- and High-Dose Oxytocin Regimens Used for Labor Induction

Regimen	Starting Dose (mU/min)	Interval (min)	Incremental Increase (mU/min)
Low-dose	0.5–1.5	15–40	1–2
	2	15	4, 8, 12, 16, 20, 25, 30
High-dose	4	15	4
	4.5	15–30	4.5
	6	20–40[a]	3–6[b]

[a]Uterine tachysystole is more common with shorter intervals.
[b]With uterine tachysystole and after oxytocin infusion is discontinued, it is restarted at one half the previous dose and then increased at 3-mU/min incremental doses.
From American College of Obstetricians and Gynecologists, 2019a; Hauth, 1986; Satin, 1992, 1994; Son, 2021; Tesemma, 2020.

Oxytocin is generally very successful when used to stimulate labor. In one large Cochrane metaanalysis, oxytocin was compared with expectant management, and fewer women—8 versus 54 percent—failed to deliver vaginally within 24 hours with oxytocin (Alfirevic, 2009). This analysis studied different oxytocin dosing regimens.

Oxytocin Regimens

Several evidence-based regimens for labor stimulation are now recommended by the American College of Obstetricians and Gynecologists (2019a). These and others are shown in Table 26-5. Initially, only variations of low-dose protocols were used in the United States. Subsequently, O'Driscoll and colleagues (1984) described their Dublin protocol for the active management of labor that called for oxytocin at a starting dosage of 6 mU/min and advanced in 6-mU/min increments. Subsequent comparative trials during the 1990s studied high-dose (4 to 6 mU/min) versus conventional low-dose (0.5 to 1.5 mU/min) regimens, both for labor induction and for augmentation.

From Parkland Hospital, Satin and associates (1992) evaluated an oxytocin regimen using an initial and incremental dosage of 6 mU/min compared with one using 1 mU/min. Among 1112 women undergoing induction, the 6-mU/min regimen resulted in a shorter mean admission-to-delivery time, fewer failed inductions, and no cases of neonatal sepsis. Among 1676 women who had labor augmentation, those who received the 6-mU/min regimen had a shorter duration-to-delivery time, fewer forceps deliveries, fewer cesarean deliveries for dystocia, and lower rates of intrapartum chorioamnionitis or neonatal sepsis. With this protocol, uterine tachysystole was managed by oxytocin discontinuation followed by resumption when indicated and at half the stopping dosage. Thereafter, the dosage was increased at 3 mU/min when appropriate, instead of the usual 6-mU/min increase used for women without tachysystole. No adverse neonatal effects were observed. More recently, Son and colleagues (2021) confirmed these findings in a randomized clinical trial.

In 1990 at Parkland Hospital, routine use of the 6-mU/min oxytocin beginning and incremental dosage was incorporated and continues through today. In other labor units, a 2-mU/min beginning and incremental oxytocin regimen is preferred and administered. With either regimen, dosages are employed for either labor induction or augmentation.

Interval Between Incremental Dosing

Intervals to increase oxytocin doses vary from 15 to 40 minutes (see Table 26-5). Satin and associates (1994) addressed this aspect with a 6-mU/min regimen providing increases at either 20- or 40-minute intervals. Women assigned to the 20-minute interval regimen for labor augmentation had a significantly reduced cesarean delivery rate for dystocia compared with that for the 40-minute interval regimen—8 versus 12 percent. As perhaps expected, uterine tachysystole was significantly more frequent with the 20-minute escalation regimen.

Other investigators reported even more frequent incremental increases. Frigoletto (1995) and Xenakis (1995) and their coworkers gave oxytocin at 4 mU/min with increases as needed every 15 minutes. Merrill and Zlatnik (1999) started with 4.5-mU/min doses and increased this every 30 minutes. López-Zeno and associates (1992) used 6-mU/min doses and 15-minute intervals.

Maximal Oxytocin Dosage

The *maximal* effective dose of oxytocin to achieve adequate contractions in all women is different. In one study of 1151 consecutive nulliparas, the likelihood of progression to vaginal delivery decreased at and beyond an oxytocin dosage of 36 mU/min (Wen, 2001). Still, at a dosage of 72 mU/min, half of the nulliparas were delivered vaginally. Thus, if contractions are not adequate—less than 200 Montevideo units—and if the fetal status is reassuring and labor has arrested, an oxytocin infusion dose greater than 48 mU/min has no apparent risks (Tesemma, 2020).

■ Risks versus Benefits

Unless the uterus is scarred, uterine rupture associated with oxytocin infusion is rare, even in parous women. Flannelly and associates (1993) reported no cases of uterine rupture, with or without oxytocin, in 27,829 nulliparas. Eight instances of overt uterine rupture during labor were noted in 48,718 parous women. Only one of these was associated with oxytocin use. A population-based retrospective review from Denmark reported a rupture rate of 3.3 per 100,000 women without prior cesarean, with the highest risk among multiparas (Thisted, 2015). Our experience from Parkland Hospital is that oxytocin induction and augmentation are associated with uterine rupture. During an 8-year period in which there were almost 95,000 births, 15 women suffered a primary uterine rupture, and 14 of these cases were associated with oxytocin use. In half of these women, prostaglandins were also given before augmentation with oxytocin.

Oxytocin has amino-acid homology similar to arginine vasopressin (AVP) and has significant antidiuretic action. When infused at doses of 20 mU/min or more, renal free water clearance drops markedly. If aqueous fluids are infused in appreciable amounts along with oxytocin, *water intoxication* can lead to convulsions, coma, and even death. In general, if

oxytocin is to be administered in high doses for a considerable period of time, its concentration should be increased rather than raising the flow rate of a more dilute solution. Consideration also should be given to use of crystalloids—either normal saline or lactated Ringer solution.

Uterine Contraction Pressures

Contraction forces in spontaneously laboring women range from 90 to 390 Montevideo units (Chap. 24, p. 462). Early researchers found that the mean or median spontaneous uterine contraction pattern between 140 and 150 Montevideo units resulted in progression to vaginal delivery (Caldeyro-Barcia, 1950; Seitchik, 1984).

Labor arrest in first-stage labor is described in Chapter 23 (p. 434). In the management of active-phase arrest, and with no contraindication to intravenous oxytocin, decisions must be made with knowledge of the safe upper range of uterine activity. Hauth and colleagues (1986) described an effective and safe protocol for oxytocin augmentation for active-phase arrest. With it, more than 90 percent of women achieved an average of at least 200 to 225 Montevideo units. They later reported that nearly all women in whom active-phase arrest persisted despite oxytocin generated more than 200 Montevideo units (Hauth, 1991). Importantly, despite no labor progression, no adverse maternal or perinatal effects were noted in those ultimately requiring cesarean delivery. Data regarding the safety and efficacy of contraction patterns in women with a prior cesarean delivery, with twins, or with an overdistended uterus are lacking.

Amniotomy for Induction and Augmentation

Elective amniotomy with the intention of accelerating labor is often performed. For labor induction, artificial rupture of the membranes—sometimes called *surgical induction*—can be used and always implies a commitment to delivery. The main disadvantage of amniotomy used alone for labor induction is the unpredictable and occasionally long interval until labor onset. That said, in a randomized trial, Bakos and Bäckström (1987) found that amniotomy alone or combined with oxytocin was superior to oxytocin alone. Mercer and colleagues (1995) randomly assigned 209 women undergoing oxytocin induction to either early amniotomy at 1 to 2 cm or late amniotomy at 5 cm. Early amniotomy was associated with a 4-hour reduction in labor duration. With early amniotomy, however, the incidence of chorioamnionitis was elevated. In a metaanalysis, De Vivo and associates (2020) reported that early amniotomy did not increase the risk of cesarean delivery yet reduced the interval from induction to delivery.

For labor augmentation, amniotomy is commonly performed when labor is abnormally slow. Shown in Table 26-6, amniotomy at approximately 5-cm dilation accelerated spontaneous labor by 1 to 1½ hours. Importantly, neither the need for oxytocin stimulation nor the overall cesarean delivery rate was higher. Although the incidences of mild and moderate cord compression patterns were increased following amniotomy, cesarean delivery rates for fetal distress were not greater. Most importantly, there were no adverse perinatal effects.

Rouse and associates (1994) also found that amniotomy with oxytocin augmentation for arrested active-phase labor shortened the time to delivery by 44 minutes compared with that of oxytocin alone. Although amniotomy did not alter the delivery route, one drawback was that it significantly increased the incidence of chorioamnionitis.

Regardless of the indication, amniotomy is associated with a risk of cord prolapse. To minimize this risk, disengagement of the fetal head during amniotomy is avoided. Toward this goal, fundal or suprapubic pressure or both may be helpful. Some clinicians prefer to rupture membranes during a contraction. If the vertex is not well applied to the lower uterine segment, a gradual egress of amnionic fluid can sometimes be accomplished by several membrane punctures with a 26-gauge needle held with a ring forceps and with direct visualization using a vaginal speculum. Alternatively, the trumpet used for pudendal blockade can sheath the needle and manually guide it through the cervix for amniotomy. In many of these cases, however, membranes tear and fluid is lost rapidly. Because of the risk of cord prolapse, or rarely placental abruption, the fetal heart rate is assessed before and immediately after amniotomy.

Membrane Stripping for Labor Induction

Labor induction by membrane "stripping" or "sweeping" is a frequent practice. Several studies have suggested that membrane stripping is safe and lowers the incidence of postterm pregnancy without consistently raising the incidence of ruptured

TABLE 26-6. Randomized Clinical Trials of Elective Amniotomy in Early Spontaneous Labor at Term

		Effects of Amniotomy					
Study	Number	Mean Dilation at Amniotomy	Mean Shortening of Labor	Need for Oxytocin	Cesarean Delivery Rate	Abnormal Tracing	Neonatal Effects
Fraser (1993)	925	<5 cm	125 min	None	None[a]	None	None
Garite (1993)	459	5.5 cm	81 min	Decreased	None	Increased[b]	None
UK Amniotomy Group (1994)	1463	5.1 cm	60 min	None	None	NA	None

[a]No effect on overall rate; cesarean delivery for fetal distress significantly increased.
[b]Increased mild and moderate umbilical cord compression patterns.
NA = not assessed.

membranes, infection, or bleeding. Randomized trials are limited and a metaanalysis of two of these reported sweeping to be ineffective (Hamidi, 2020). Downsides are discomfort and associated bleeding (Boulvain, 2005).

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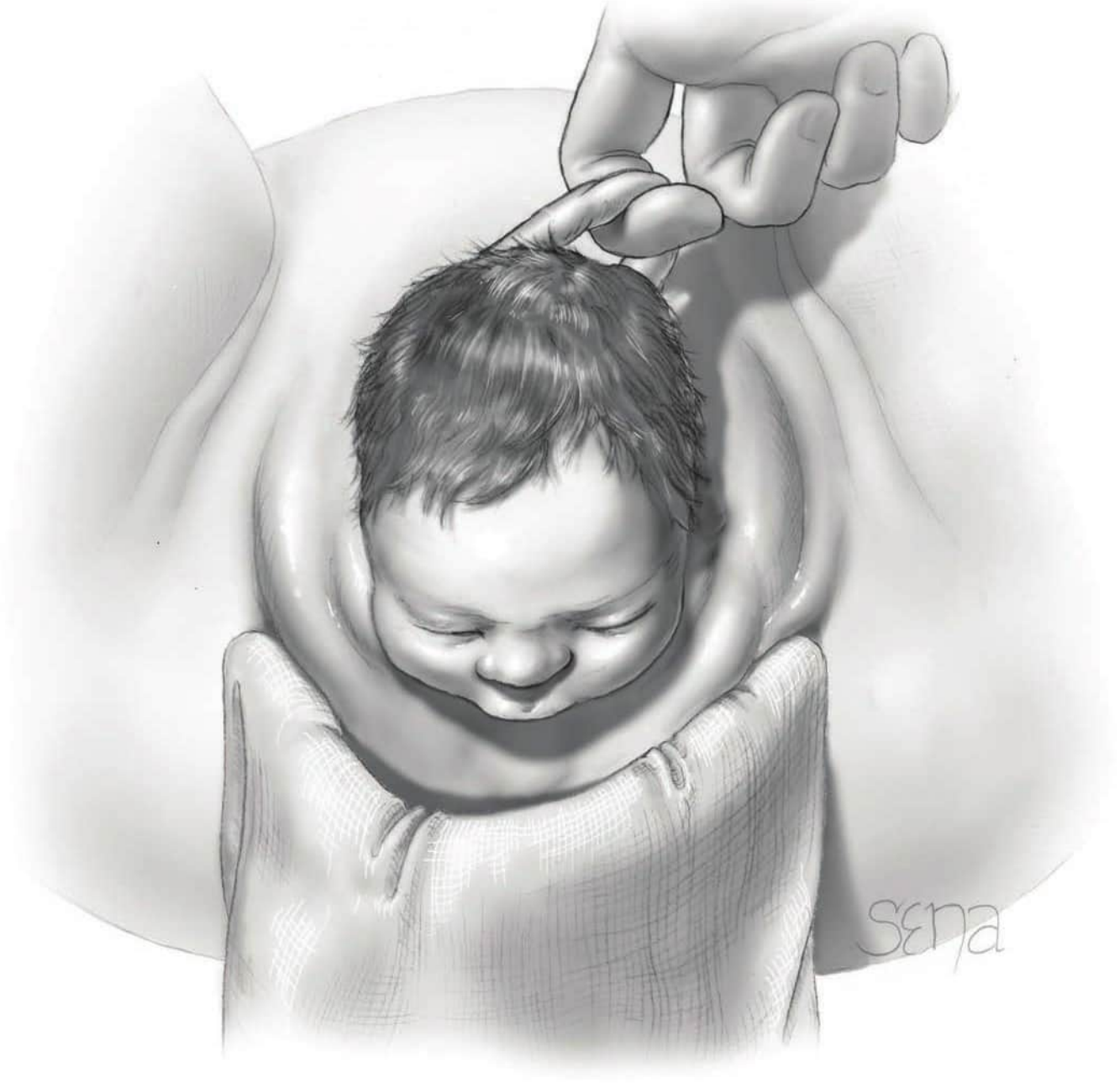
SECTION 8

DELIVERY



CHAPTER 27

Vaginal Delivery

The natural culmination of second-stage labor is controlled vaginal delivery of a healthy neonate with minimal trauma to the mother. Although some clinical settings favor cesarean delivery, for most fetuses, vaginal birth is preferred. For the mother, spontaneous vaginal vertex delivery poses the lowest risk of most maternal comorbidity, and comparisons with cesarean delivery are found in Chapter 30 (p. 548). Delivery is usually spontaneous, although some maternal or fetal complications may warrant operative vaginal delivery, described in Chapter 29 (p. 533). Last, a malpresenting fetus or multifetal gestation in many cases may be delivered vaginally but requires special techniques. These are described in Chapters 28 and 48.

DELIVERY TECHNIQUE

Preparation

The end of second-stage labor is heralded as the perineum begins to bulge, and the fetal scalp is seen through the separating labia. Perineal pressure from the fetal head creates reflexive pushing efforts. At this time, additional staff to attend the neonate and instruments are readied for delivery. Fetal heart rate monitoring continues. As one example, a nuchal cord often tightens with fetal descent and may lead to deepening variable decelerations. If the bladder is distended, catheterization can provide added pelvic space.

During second-stage labor, pushing positions may vary. But for delivery, the dorsal lithotomy position is most common and often the most satisfactory. Leg holders or stirrups are often used to assist. With or without their use, perineal laceration rates were equal in one randomized study of 214 parturients (Corton, 2012). With positioning, legs are not separated too widely or placed one higher than the other. Legs are not strapped into the stirrups. This permits quick flexion of the thighs backward onto the abdomen should shoulder dystocia develop. Legs may cramp during second-stage pushing, and cramping can be relieved by creating gentle muscle stretch, by brief massage, or both.

Preparation for delivery includes vulvar and perineal cleansing. If desired, sterile drapes are placed to cover the legs and abdomen and expose only the perineum. Scrubbing, gowning, gloving, and donning protective mask and eyewear protect both the gravida and accoucheur from infectious agents.

Delivery of the Head

By the end of second-stage labor, the position of the occiput is usually known. In some cases, however, molding and caput formation may have precluded early accurate identification. At this time, careful assessment is again performed as described in Chapter 22 (p. 429). In most cases, position is occiput anterior (OA) or is rotated slightly oblique. But, in perhaps 5 percent, an occiput posterior (OP) position persists.

With each contraction, the vulvovaginal opening is dilated by the fetal head to gradually form an ovoid and finally, an

almost circular opening. This encirclement of the largest head diameter by the vulvar ring is termed *crowning*. The anus becomes greatly stretched, and the anterior wall of the rectum is easily seen through it. The perineum thins and may spontaneously lacerate. Third- and fourth- degree perineal lacerations, which by definition involve the anal sphincter and perineal body, are collectively termed obstetric anal sphincter injuries (OASIS). Because of their associated morbidity (p. 508), one main goal during delivery is OASIS prevention.

To improve perineal elasticity and protect against laceration, some perform daily antepartum perineal massage starting at 34 to 35 weeks' gestation. With a lubricant, the woman or her partner inserts one or two fingers 3 cm into the vagina and applies pressure, first downward for 2 minutes and then laterally to each side of the vaginal entrance for 2 minutes. In one large randomized study, nulliparas benefited mainly by lower rates of episiotomy and of first-degree laceration (Labreque, 1999). Third- and fourth-degree laceration rates are not lowered (Beckmann, 2013). As another tool, antepartum use of the *Epi-No* intravaginal pump balloon similarly aims to stretch the perineum. However, in randomized trials, it did not prevent episiotomy, perineal trauma, or levator injury (Brito, 2015; Kamisan Atan, 2016). Instead of antepartum use, perineal massage can be performed solely intrapartum during second-stage labor. In a large randomized study, the rates of episiotomy, OASIS, and intact perineum were similar to those in a nonmassage group (Stamp, 2001). In subsequent systematic reviews, this practice was noted to lower OASIS rates and raise rates of delivery over an intact perineum (Aasheim, 2017; Aquino, 2020a).

When the head distends the vulva and perineum enough to open the vaginal introitus to a diameter of 5 cm or more, slow delivery of the head and control of accelerative forces may minimize lacerations (Laine, 2008). One of two approaches may be instituted. With the *hands-on method*, the thumb and remaining fingers form a V pressed against the perineum to bolster it. The other hand maintains fetal neck flexion to deliver the smallest head diameter through the introitus and provides gentle pressure against rapid forward movement to avoid expulsive delivery. Instead, with the *hands-poised method*, hands touch neither the head or perineum but are applied only selectively to slow rapid head expulsion. In a large randomized trial with more than 5000 gravidas, rates of intact perineum or OASIS did not differ between groups. In the hands-poised cohort, episiotomy rates were lower (McCandlish, 1998). Subsequent systematic reviews of randomized trials similarly note lower episiotomy rates with a hands-poised approach. However, among these analyses, intact perineum or OASIS rates were not consistently benefitted by this method (Aasheim, 2017; Huang, 2020; Pierce-Williams, 2019).

Alternatively, if expulsive efforts are inadequate or an expedited delivery is needed, the *Ritgen maneuver* may be employed or an episiotomy cut. With the maneuver, gloved fingers grasp the fetal chin just behind or in the anus and exert upward pressure between contractions. As a counter, the other hand presses against the occiput to control forces against the perineum (Fig. 27-1) (Cunningham, 2008). Although expeditious, this maneuver does not alter OASIS rates (Aquino, 2020b).

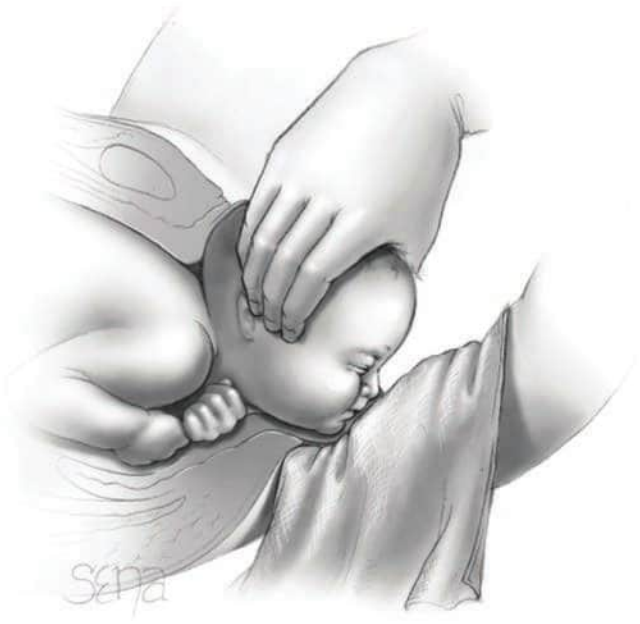


FIGURE 27-1 Modified Ritgen maneuver. Moderate upward pressure is applied to the fetal chin by the posterior hand covered with a sterile towel, while the occiput is held against the symphysis.

Delivery of the Shoulders

Following delivery of the fetal head, a finger is passed across the fetal neck to determine whether it is encircled by one or more umbilical cord loops. The nuchal cord incidence increases with gestational age and is found in nearly 25 percent of deliveries at term (Larson, 1997). If an umbilical cord coil is felt, it is slipped over the head if loose enough. If applied too tightly, the loop is cut between two clamps. Tight nuchal cords complicate approximately 6 percent of all deliveries but are not associated with worse neonatal outcomes than those without a cord loop (Henry, 2013).

Following its delivery, the fetal head falls posteriorly, bringing the face almost into contact with the maternal anus. The occiput promptly turns toward one of the maternal thighs, and the head assumes a transverse position. This external rotation indicates that the *bisacromial diameter*, which is the distance between the shoulders, has rotated into the anteroposterior diameter of the pelvis.

Most often, the shoulders appear at the vulva just after external rotation and are born spontaneously. If delayed, extraction aids controlled delivery. The sides of the head and neck are grasped with two hands, and if needed, *gentle* axial traction may be applied until the anterior shoulder appears under the pubic arch. Axial traction is aligned with the fetal spine, and lateral deviation of the neck does not exceed 25 to 45 degrees (American College of Obstetricians and Gynecologists, 2019c). Next, the posterior shoulder is delivered. During delivery, abrupt or powerful lateral extension of the neck is avoided to avert brachial plexus injury.

The rest of the body almost always follows the shoulders without difficulty. With prolonged delay, however, its birth may be hastened by moderate outward traction on the head and moderate pressure on the uterine fundus. Hooking the fingers

in the axillae is avoided. This can injure upper extremity nerves and produce a transient or possibly permanent paralysis. After the newborn, a gush of amnionic fluid that can be blood-tinged but not grossly bloody usually follows.

Previously, immediate nasopharyngeal bulb suctioning of the newborn was routine to remove secretions. However, suctioning of the nasopharynx may lead to neonatal bradycardia (Gungor, 2006). American Heart Association neonatal resuscitation recommendations eschew most suctioning immediately following birth—even with meconium present (Chap. 32, p. 589). Moreover, with meconium-stained fluid, routine intubation for tracheal suction is not recommended for vigorous or for nonvigorous neonates. Suctioning is reserved for neonates who have obvious obstruction to spontaneous breathing or who require positive-pressure ventilation (Wyckoff, 2015). For suctioning, options are bulb syringe or suction catheter aspiration and may include intubation and suctioning if the airway is obstructed.

Cord Clamping

The umbilical cord is cut between two clamps placed 6 to 8 cm from the fetal abdomen, and later an umbilical cord clamp is applied 2 to 3 cm from its insertion into the fetal abdomen.

For vigorous term neonates, umbilical cord clamping is ideally delayed 30 to 60 seconds to transfer blood to the newborn. Resting the newborn below the level of the uterus allows gravity to aid flow (Yao, 1974). As a result, higher total body iron stores and lower anemia rates for the neonate are sustained (Andersson, 2011; McDonald, 2013). This practice may be particularly valuable in populations in which iron deficiency is prevalent (World Health Organization, 2014). In general, delayed compared with early umbilical cord clamping does not worsen Apgar scores or umbilical cord pH values. For the mother, postpartum hemorrhage rates and puerperal hemoglobin status do not differ between early and delayed clamping groups (Andersson, 2013; Gomersall, 2021; Nudelman, 2020).

Of potential harms, a greater hemoglobin concentration raises risks for hyperbilirubinemia (Chap. 33, p. 606). Data are conflicting but suggest that neonatal phototherapy rates do not differ (Andersson, 2011; Chen, 2018; McDonald, 2013). That said, the American College of Obstetricians and Gynecologists (2020e) recommends that protocols should be in place that identify neonatal jaundice. Other cautions are cases requiring expedited maternal or fetal resuscitation. Others are those having abnormal placentation or compromised placental function, such as with abruption or fetal-growth restriction. Fewer data are available regarding cord "milking," in which the operator pushes blood through the cord toward the newborn. This maneuver appears safe for term newborns and may be advantageous if rapid cord clamping is clinically indicated (Panburana, 2020).

For the preterm neonate, delayed cord clamping for 30 seconds or longer has several benefits. From systematic reviews on the topic, these include decreased rates of blood transfusion and death before hospital discharge (Fogarty, 2018; Rabe, 2019). However, one large randomized study did not show an advantage for its primary outcome, which was a composite of death plus major neonatal morbidity (Tarnow-Mordi, 2017). The American College of Obstetricians and Gynecologists (2020e) recommends delayed cord clamping for vigorous term and preterm neonates not needing immediate resuscitation at birth.

Cord milking in the preterm neonate may pose potential harm. Although conflicting, some data suggest higher associated rates of severe interventricular hemorrhage in those <32 weeks' gestation (Katheria, 2019, 2020; Kumbhat, 2021). Because of rapid blood volume changes, organizations currently recommend against the routine use of cord milking for neonates born <29 weeks' gestation (Seidler, 2021; Wyckoff, 2015).

Occiput Transverse Position

In some cases, pelvic shape leads to a persistent occiput transverse (OT) position that is not easily overcome during second-stage pushing. A platypelloid pelvis is flattened anteroposteriorly and an android pelvis is heart shaped (Fig. 2-16, p. 29). With these, space may be inadequate for occipital rotation to either an anterior or posterior position.

In the absence of a pelvic architectural abnormality or asynclitism, the OT position is usually transitory. Thus, unless contractions are hypotonic, the head usually rotates spontaneously to an OA position. If rotation ceases because of poor expulsive forces, vaginal delivery can be aided. The easiest is manual rotation of the occiput either anteriorly to an OA or, less commonly, posteriorly to an OP position. Kielland forceps also can rotate the occiput anteriorly. Both manual and forceps rotations are described in Chapter 29 (p. 540).

Persistent Occiput Posterior Position

Approximately 2 to 10 percent of singleton, term, cephalic fetuses deliver in an OP position (Cheng, 2010). Many fetuses delivering OP are OA in early labor but malrotate during labor. Predisposing risks include epidural analgesia, nulliparity, greater fetal weight, and prior delivery with OP positioning (Cheng, 2006a; Gardberg, 2004; Lieberman, 2005). Of pelvic shapes, an anthropoid pelvis and narrow subpubic angle can predispose (Barth, 2015; Ghi, 2016).

Women with a persistent OP position have higher associated rates of prolonged second-stage labor, cesarean delivery, and operative vaginal delivery. For women who deliver vaginally, rates of blood loss and of OASIS are increased (Senécal, 2005).

Newborns delivered from an OP position have higher complication rates than those born positioned OA. In one study of neonatal outcomes in 2591 women undergoing delivery from a persistent OP position, rates of acidemic umbilical cord gases, birth trauma, Apgar scores <7, and intensive care nursery admission, among others, were higher compared with an OA position (Cheng, 2006b). Others report similar findings (Fitzpatrick, 2001; Ponkey, 2003).

Fetal head position assessment is essential to management (Chap. 22, p. 429). However, digital examination for identification of fetal head position can be inaccurate, and transabdominal sonography may increase accuracy (Bellussi, 2017). The transducer is placed transversely just cephalad to

the maternal mons pubis. In the sonogram, fetal orbits and nasal bridge lie ventrally, whereas the occiput apposes the lower sacrum. Such information may explain prolonged second-stage labor and identify suitable candidates for rotation. Of other interventions, varying maternal position either antepartum or during labor does not appear to lower rates of persistent OP position (Kariminia, 2004; Le Ray, 2016).

If the bony pelvic outlet is roomy and the perineum is somewhat relaxed from prior deliveries, rapid spontaneous OP delivery can take place. Conversely, if the perineum is resistant to stretch, second-stage labor may be appreciably prolonged. During each maternal push, the head is driven against the perineum to a greater degree than when the head position is OA. This leads to greater rates of OASIS (Groutz, 2011). For these reasons, manual rotation with spontaneous delivery from an OA position has advantages. Lower rates of cesarean delivery, severe perineal laceration, chorioamnionitis, and maternal blood loss follow rotation to OA position (Shaffer, 2011). Alternatively, forceps rotation to an OA position may be attempted for those with suitable skills. Last, forceps or vacuum device also can be applied and delivery completed from an OP position. These operative vaginal techniques are detailed in Chapter 29 (p. 540).

Infrequently, protrusion of fetal scalp through the introitus can be erroneously encouraging. In these cases, findings reflect marked fetal head elongation from molding plus substantive scalp edema and not fetal descent. In some cases, the head may not even be engaged—that is, the biparietal diameter may not have passed through the pelvic inlet. Labor is characteristically long and descent of the head is slow. Careful palpation above the symphysis may disclose the fetal head to be above the pelvic inlet. Prompt cesarean delivery is appropriate.

SHOULDER DYSTOCIA

Following complete emergence of the fetal head during vaginal delivery, the remainder of the body may not rapidly follow. The anterior fetal shoulder can become wedged behind the symphysis pubis and fail to deliver with maternal pushing and gentle axial traction by the provider. One indicator may be retraction of the baby's head against the mother's perineum—the *turtle sign*. Because the umbilical cord is compressed within the birth canal, shoulder dystocia is an emergency. Several maneuvers may be performed to free the shoulder. This requires a team approach, and effective communication and leadership are critical.

Consensus regarding a specific definition of shoulder dystocia is lacking. Some, including the American College of Obstetricians and Gynecologists (2019c), diagnose it if maneuvers are required to free the shoulder. Spong and coworkers (1995) reported that the mean head-to-body delivery time in normal births was 24 seconds compared with 79 seconds in those with shoulder dystocia. These investigators proposed that a head-to-body delivery time >60 seconds be used to define shoulder dystocia. Currently, however, the diagnosis continues to rely on the clinical perception that the normal traction needed for fetal shoulder delivery is ineffective.

Because of these differing definitions, the incidence of shoulder dystocia varies. One review cites a clinically useful average of 1 percent of all deliveries (Ouzounian, 2016). The incidence has risen in recent decades, likely due to increasing fetal birthweight (Øverland, 2014). Greater recognition and documentation also may boost reported incidences (Kim, 2016).

■ Maternal and Neonatal Consequences

In general, shoulder dystocia poses greater risk to the fetus than to the mother. The main maternal risks are serious perineal tears and postpartum hemorrhage, usually from uterine atony but also from lacerations (Hehir, 2020; Rahman, 2009). In contrast, significant neuromusculoskeletal injury and asphyxia are neonatal concerns. These specific injuries are described fully in Chapter 33 (p. 599). In one review of 1177 shoulder dystocia cases, brachial plexus injury was diagnosed in 11 percent and clavicular or humeral fracture in 2 percent (Chauhan, 2014). MacKenzie and associates (2007) reviewed 514 cases. Of the neonates, 7 percent showed evidence of acidosis at delivery, and 1.5 percent required cardiac resuscitation or developed hypoxic ischemic encephalopathy (HIE). In another review of 200 cases, rates of severe fetal acidosis and HIE were each 0.5 percent if delivery was completed within 5 minutes. These rates rose to 6 and 24 percent, respectively, with delivery delays ≥5 minutes (Leung, 2011).

■ Prediction and Prevention

Although several factors are clearly associated with this complication, shoulder dystocia cannot be accurately predicted or prevented (American College of Obstetricians and Gynecologists, 2019c). Associated characteristics include fetal macrosomia, maternal obesity, prolonged second-stage labor, operative vaginal delivery, and a prior shoulder dystocia (Mehta, 2004; Zhang, 2018).

Of these, increasing birthweight creates a corresponding rise in the incidence of shoulder dystocia (Øverland, 2012). With fetal macrosomia, commonly associated maternal characteristics are obesity, postterm pregnancy, multiparity, and diabetes (Koyanagi, 2013). The combination of fetal macrosomia and maternal diabetes mellitus escalates the frequency of shoulder dystocia (Nesbitt, 1998). This predisposition may stem from anthropomorphic differences between comparable-weight fetuses of nondiabetic and diabetic mothers. The latter fetal group has larger shoulder and extremity circumferences and greater shoulder-to-head and chest-to-head size (Modanlou, 1982). However, translating these specific measurements into stand-alone sonographic thresholds shows poor predictive sensitivity (Burkhardt, 2014). Planned cesarean delivery should be considered for the nondiabetic woman with a fetus whose estimated fetal weight is >5000 g or for the diabetic woman whose fetus is estimated to weigh >4500 g (American College of Obstetricians and Gynecologists, 2019c).

As prevention, early labor induction has been evaluated. In one study, approximately 800 women with suspected macrosomic fetuses were randomly assigned to early induction between 37 and 39 weeks' gestation or to expectant care (Boulvain, 2015). Women with insulin-requiring diabetes were excluded. Dystocia rates were lowered by two thirds in the induction group, and neither group suffered brachial plexus injury. Other

neonatal outcomes were similar, except for a higher rate of hyperbilirubinemia and phototherapy in the induction group. A systematic review of four randomized trials again with the same compared groups showed no differences in rates of cesarean delivery, shoulder dystocia, or operative vaginal delivery. Fetal fracture rates were lower in the induction group (Magro-Malosso, 2017). Notably, when assessing the benefits, the poor accuracy of antepartum fetal weight prediction should be considered (Malin, 2016). Moreover, potential benefits of early induction are balanced against potential harms from early delivery. The American College of Obstetricians and Gynecologists (2019a,c) recommends against labor induction before 39 weeks for suspected macrosomia alone.

Of other risks, recurrent shoulder dystocia ranges from 4 to 13 percent in the three largest series (Al-Hawash, 2019). For many women with prior shoulder dystocia, labor may still be a reasonable option. The American College of Obstetricians and Gynecologists (2019c) recommends that estimated fetal weight, gestational age, maternal glucose intolerance, and severity of prior neonatal injury be evaluated. Antepartum, risks and benefits of cesarean delivery are discussed with any woman with a history of shoulder dystocia. After discussion and risk assessment, either mode of delivery is appropriate.

Management

Shoulder dystocia cannot be accurately predicted. Thus, the labor and delivery team, which includes nurses, obstetrical providers, and anesthesia staff, should be well versed in its management. An emergent call for assistance should assemble these members.

Because of ongoing cord compression with this dystocia, one goal is to reduce delivery time. This is balanced against the second goal, which is avoiding fetal and maternal injury from aggressive manipulations. Adequate analgesia assists maneuvers. Episiotomy may be needed to provide sufficient room for essential manipulations but itself does not lower brachial plexus injury rates (Gurewitsch, 2004; Paris, 2011).

Various techniques can be used to free the anterior shoulder from its impacted position behind the symphysis pubis. The *McRoberts maneuver* is often selected first. With it, legs are lifted from stirrups, hips are sharply flexed up onto the abdomen, and knees remain flexed. Gherman and colleagues (2000) analyzed the McRoberts maneuver using x-ray pelvimetry. The procedure causes straightening of the sacrum relative to the lumbar vertebrae, rotation of the symphysis pubis toward the maternal head, and a decrease in the angle of pelvic inclination. This does not increase pelvic dimensions, but pelvic rotation cephalad tends to free the impacted anterior shoulder. Gonik and coworkers (1989) tested the McRoberts position objectively with laboratory models and found that the maneuver reduced the forces needed to free the fetal shoulder. During McRoberts maneuver, an assistant can apply downward and laterally directed *suprapubic pressure* (Fig. 27-2). This abducts the anterior shoulder to create a shorter bisacromial diameter. It also rotates the shoulders into the oblique diameter, which at the pelvic inlet is longer than the anteroposterior diameter. If unsuccessful, most move next to the posterior shoulder or to rotation maneuvers.

FIGURE 27-2 The McRoberts maneuver. The maneuver consists of removing the legs from the stirrups and sharply flexing the thighs up onto the abdomen. Simultaneously, an assistant also provides suprapubic pressure that is directed down and lateral.

With *delivery of the posterior shoulder,* the provider inserts a hand into the posterior pelvis, carefully sweeps the posterior arm of the fetus forward across its chest, and delivers the arm (Fig. 27-3). If possible, the operator's fingers are aligned parallel to the long axis of the fetal humerus to lower fracture risks. With the arm now outside of the pelvis, the bisacromial diameter is diminished. Next, the shoulder girdle is rotated into one of the oblique diameters of the pelvic inlet. These steps resolve the disproportion to free the anterior shoulder.

Of the rotational maneuvers, the method recommended by Rubin (1964) aims to shorten the bisacromial diameter (Fig. 27-4). A pelvic hand reaches the most easily accessible fetal shoulder, often the posterior one, which is then pushed toward the anterior surface of the chest. This maneuver abducts the posterior shoulder and rotates both shoulders into one of the pelvic inlet's oblique diameters. Friction from the vagina also abducts the anterior shoulder to some degree during this rotation. Again, resolution of the disproportion can free the anterior shoulder.

Instead, Woods (1943) reported that by rotating the posterior shoulder progressively in a corkscrew fashion, the impacted anterior shoulder could be released. For performance, one hand

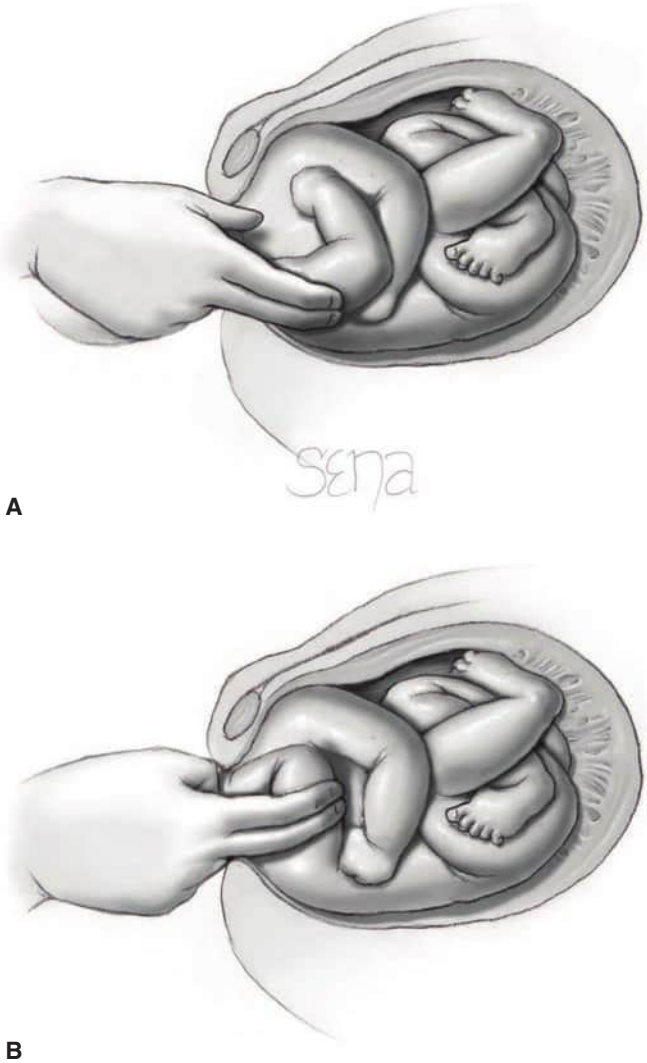


FIGURE 27-3 Delivery of the posterior shoulder for relief of shoulder dystocia. **A.** The operator's hand is introduced into the vagina along the fetal posterior humerus. **B.** The arm is splinted and swept across the chest, keeping the arm flexed at the elbow. **C.** The fetal hand is grasped and the arm extended along the side of the face. The posterior arm is delivered from the vagina.

is pressed against the anterior surface of the posterior shoulder, and pressure is directed toward the fetal back. The posterior shoulder is then rotated 180 degrees, and in doing so, it becomes the anterior-positioned limb. With rotation, this shoulder comes to lie beneath, not behind, the symphysis and can be delivered.

In a review of these four methods, all had similar neonatal injury rates (Spain, 2015). Importantly, delivery duration and the number of maneuvers raises neonatal injury rates.

If the above are initially unsuccessful, they may be repeated, and other methods may be elected. With an *all-fours maneuver*, also called the Gaskin maneuver, the parturient rolls onto her hands and knees. Here, axial traction against the head and neck attempts to free the posterior shoulder (Bruner, 1998). Challenges with this include immobility from regional analgesia and time lost in patient repositioning.

In some cases, the posterior arm is inaccessible for delivery. Cluver and Hofmeyr (2009) described *posterior axilla sling traction* to deliver the posterior arm. With this, suction tubing or a stiff urinary catheter is threaded under the fetal axilla, and both ends are brought together above the shoulder. This forms a loop beneath the axilla. Catheter traction then sweeps upward and outward to deliver the shoulder. Data continue to accrue. In a case series of 119 cases in which this was the first maneuver, the success rate was 96 percent (Ansell, 2019).

For refractory cases despite the above efforts, deliberate *fracture of the anterior clavicle* by using the thumb to press it toward and against the maternal pubic ramus can be attempted to free the shoulder impaction. In practice, however, deliberate fracture of a large neonate's clavicle is difficult. If successful, the fracture will heal rapidly and is usually trivial compared with brachial nerve injury, asphyxia, or death.

Symphysiotomy involves cutting of the intervening symphyseal cartilage and much of its ligamentous support to widen

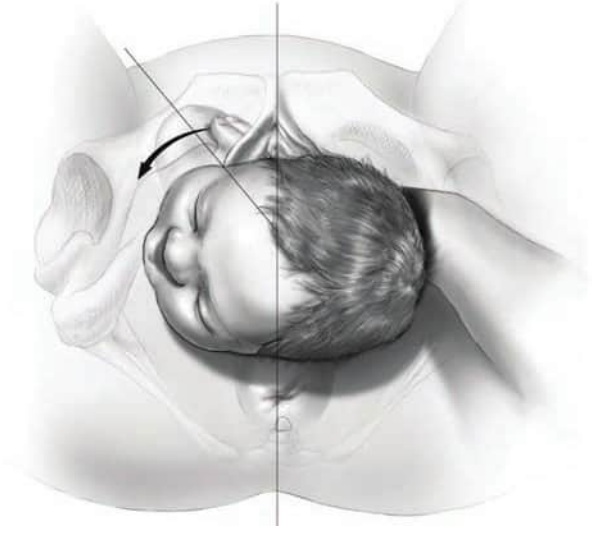


FIGURE 27-4 Rubin maneuver. The bisacromial diameter is aligned vertically. The more easily accessible fetal shoulder (the anterior is shown here) is pushed toward the anterior chest wall of the fetus (*arrow*). Most often, this results in abduction of both shoulders, which reduces the bisacromial diameter and frees the impacted anterior shoulder.

the symphysis pubis. In rare cases, it has been used successfully for shoulder dystocia (Goodwin, 1997). Using local analgesia, symphysiotomy surgically divides the intervening symphyseal cartilage and much of its ligamentous support to widen the symphysis pubis up to 2.5 cm (Basak, 2011). If feasible, a previously inserted urinary catheter is displaced from the midline with the index finger of the left hand, which is inside the vagina. Lack of provider training and potentially serious maternal pelvic or urinary tract injury explain its rare use in the United States.

The *Zavanelli maneuver* involves replacement of the fetal head into the pelvis followed by cesarean delivery (Sandberg, 1985). Terbutaline, 0.25 mg, is given subcutaneously to produce uterine relaxation. The operator first turns the head to an OA or OP position, flexes it, and slowly elevates it back into the vagina. Cesarean delivery is then performed. Sandberg (1999) reviewed 103 reported cases. It was successful in 91 percent of cephalic cases and in all cases of breech head entrapments. Despite successful replacement, fetal injuries were common but may have resulted from the multiple manipulations used before the Zavanelli maneuver (Sandberg, 2007).

Cleidotomy consists of cutting the clavicle with scissors or other sharp instruments. It is usually done for a dead fetus (Schramm, 1983).

In preparation for shoulder dystocia, clinical simulations aim to improve performance, documentation, and retention of drill steps. Their use has translated into improved neonatal outcome in some, but not all, investigations (Crofts, 2016; Fransen, 2017; Gurewitsch Allen, 2017; Walsh, 2011). At our institution, these drills involve resident, faculty, nursing, and anesthesia staff.

SPECIAL POPULATIONS

Home Birth

In 2017, 1.4 percent of deliveries in the United States were planned home births. Unplanned home births constituted 0.2 percent (MacDorman, 2019).

Of *unplanned* home births in a 15-year epoch in Norway, 69 of 6027 or 1.1 percent resulted in fetal or neonatal death. This high rate was attributable to infection, prematurity, and placental abruption (Gunnarsson, 2017). Multiparity and distance from the hospital were ascribed risks (Gunnarsson, 2014). In the United States, youth, lack of prenatal care, minority race, and lower educational attainment are risks (Declercq, 2010).

With *planned* home birth of a low-risk pregnancy, benefits include fewer medical interventions that include labor augmentation, episiotomy, operative vaginal delivery, and cesarean delivery (Bolten, 2016; Cheyney, 2014). Regarding the safety of planned home birth, data from randomized trials are lacking, and large observational studies derive from heterogeneous care systems, whose results may not be generalizable. For example, several developed countries deliver a large volume of carefully screened women at home. Gravidas are attended by midwives with substantial training and in a setting closely integrated with the local health-care system (Comeau, 2018; de Jonge, 2015). The level of such coordination in the United States is less uniform.

Overall, neonatal risks of home births in the United States are small but greater than those of hospital delivery. Midwife-attended home births carry a neonatal mortality risk of 1.3 per 1000 births. This is a nearly fourfold greater rate compared with midwife-attended hospital births (Grünebaum, 2020). The most common underlying causes of death are those attributed to labor and delivery events, to congenital anomalies, and to infection. Of neonatal injuries, rates of neonatal seizure and serious neurological dysfunction also are elevated in home-birth groups (Grünebaum, 2013, 2014, 2017; Snowden, 2015). Importantly, substantial risks attend home birth for those with preeclampsia, with multifetal gestation, with prior cesarean delivery, or with breech presentation (Caughey, 2019). The American College of Obstetricians and Gynecologists (2020b) specifically considers the last three to be absolute contraindications. Further, the College considers accredited hospitals and birthing centers to be the safest site for birth but recognizes the autonomy of the well-counseled patient.

Water Birth

As one option for pain relief, some women choose to spend part of first-stage labor in a large water tub. With this practice, one Cochrane review found lower rates of regional analgesia use and no greater adverse neonatal or maternal effects compared with traditional labor (Cluett, 2018).

For second-stage labor, water birth similarly aims to relieve pain, but it can pose neonatal risks. The rate of cord avulsion during water birth approximates 3 per 1000 births and stems primary from abruptly bringing the newborn out of the water (Schafer, 2014). Fresh-water drowning and pneumonia with sepsis are reported causes of neonatal death (Byard, 2010). The latter emphasizes the need for rigorous sanitizing protocols. Systematic reviews comment on the paucity of high-quality data but do not identify overall greater neonatal or maternal harms or benefits from water birth in low-risk, term, singleton gestations (Cluett, 2018; Taylor, 2016). Given the lack of robust data and potential for serious complications, the American College of Obstetricians and Gynecologists (2016) currently recommends that "birth occur on land, not in water."

Female Genital Mutilation

This practice refers to medically unnecessary vulvar and perineal surgical modification. In the United States, it is a federal crime to perform unnecessary genital surgery on a girl younger than 18 years and is condemned by major health organizations that include the American College of Obstetricians and Gynecologists (2019b). Despite this, forms of female genital mutilation are practiced in countries throughout Africa, the Middle East, and Asia (UNICEF, 2020).

The World Health Organization (WHO) (2018a) classifies female genital mutilation (FGM) into four types (Table 27-1). Some long-term risks include propensity for urogenital infection, chronic vulvar pain, and dyspareunia (Berg, 2014b). Thus, early in care, new gravidas are asked about these problems or prior obstetrical complications. The psychiatric consequences also can be profound, and referral for psychological assessment can be offered (Low-Beer, 2018).

TABLE 27-1. World Health Organization Classification of Female Genital Mutilation

Type I	Partial or total removal of the clitoris and/or prepuce
Type II	Partial or total removal of the clitoris and the labia minora, with or without labia majora excision
Type III	Partial or total labial minora and/or majora excision, followed by fusion of the wound, termed infibulation, to cover and narrow the vagina. With or without clitoridectomy
Type IV	Pricking, piercing, incising, scraping, cautery, or other injury to female genitalia

With physical examination, a finger or cotton swab assesses elasticity and caliber of the vaginal opening. Parturients with types I, II, and IV typically require only routine obstetrical care. Those with type III FGM or with extensive scarring have higher delivery risks. If an obstruction to childbirth is recognized, the advantages of surgical release are ideally discussed early antenatally. Division of midline scar tissue to reopen the vulva is termed *defibulation* but also called *deinfibulation* or *anterior episiotomy* (Kalis, 2012).

FGM is associated with some adverse maternal and neonatal complications. Moreover, vaginal obstruction can delay diagnosis of other pregnancy conditions. From a prospective study, the WHO (2006) estimated that FGM raised perinatal morbidity rates by 1 to 2 percent. For mothers with FGM, rates for prolonged labor, perineal lacerations and episiotomy, and postpartum hemorrhage were higher than those without prior FGM (Berg, 2014a; Chibber, 2011). Evidence supports that gravidas with type III FGM who undergo defibulation benefit from lower rates of cesarean delivery and OASIS (Berg, 2018; Rodriguez, 2016). To prevent obstetrical complications, the WHO (2016) recommends defibulation, which can be completed antepartum or intrapartum (Fig. 27-5). In our and other's experiences, intrapartum defibulation allows successful vaginal delivery without major complications (Rouzi, 2012).

In discussing defibulation, cultural sensitivity is essential, and some women may be offended by the suggestion that they have been assaulted or mutilated (American College of Obstetricians and Gynecologists, 2014). Preoperative counseling ideally discusses expected anatomic and physiologic changes. *Partial defibulation* uncovers the vagina and urethra, and *total defibulation* extends the incision to reveal the clitoris, if present. Women with infibulation often have a slow urine stream, and they perceive menses and urine to originate from the same opening. Both will change after scar incision. Affected women may be unfamiliar with normal vaginal anatomy, which will be visible following surgery. One excellent review is provided by Abdulcadir and associates (2018). Wound complications such as hematoma, cellulitis, or incisional dehiscence are rare but are discussed during counseling. Postoperative dyspareunia is uncommon, and in most studies, female sexual functioning scores improve (Berg, 2018; Nour, 2006).

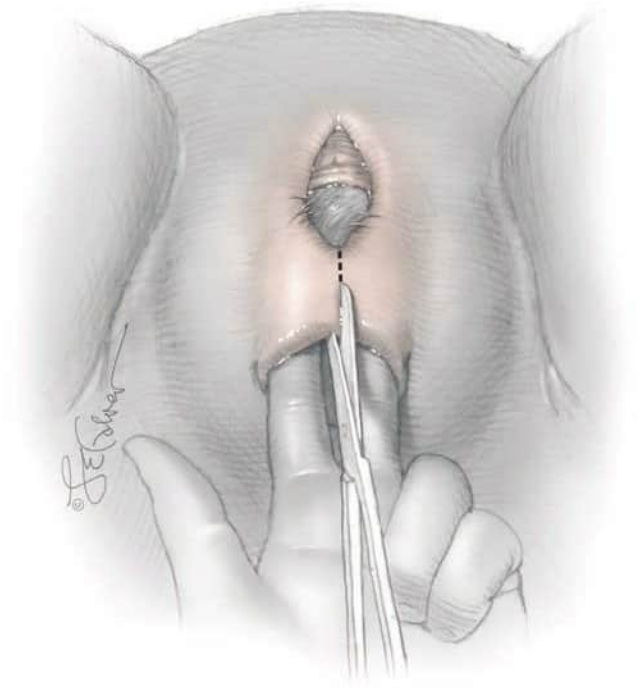


FIGURE 27-5 Deinfibulation. Although not shown here, lidocaine is first infiltrated along the planned incision if regional analgesia is not in place already. To protect underlying structures, two fingers or the tips of a narrow clamp are insinuated behind the shelf created by fused labia but in front of the urethra and crowning head. The shelf is then incised in the midline. After delivery, the raw edges are sutured with rapidly absorbable material to secure hemostasis. (Reproduced with permission from Hawkins JS: Lower genital tract procedures. In Yeomans ER, Hoffman BL, Gilstrap LC III, et al (eds): Cunningham and Gilstrap's Operative Obstetrics, 3rd ed. New York, NY: McGraw Hill; 2017.)

Prior Pelvic Reconstructive Surgery

These surgeries are performed with increasing frequency in reproductive-aged women, and thus pregnancy following them is not uncommon. Major concerns are the degradation of repair by pregnancy and by vaginal birth.

After midurethral sling surgery and then a subsequent pregnancy, continence is preserved for most. Multiple pregnancies, however, may raise recurrence risk. Evidence does not favor a delivery route, and vaginal delivery is suitable (Adams-Piper, 2016; Cavkaytar, 2014; Dyrkorn, 2020).

Sacral neuromodulation units are recommended to be turned off because of unknown pregnancy effects from chronic electrical stimulation. From small reviews, lowered device efficacy and displaced or broken device leads can follow both vaginal and cesarean delivery (Mahran, 2017; Roulette, 2018). Data do not proscribe vaginal birth.

Hysteropexy aims to correct prolapse of the vaginal apex yet preserve the uterus. Available case series are few and small and do not allow estimates of recurrence rate or delivery route recommendations (Wieslander, 2020). Most undergo elective cesarean delivery.

Anomalous Fetuses

Rarely, delivery can be obstructed by extreme hydrocephaly, body stalk anomaly, conjoined twins, or massive fetal abdominal

enlargement from a greatly distended bladder, ascites, or organomegaly. Specifically, with milder forms of hydrocephaly, if the biparietal diameter is <10 cm or if the head circumference is <36 cm, vaginal delivery may be permitted (Anteby, 2003).

In rare cases in which neonatal death has occurred or is certain due to associated anomalies, vaginal delivery may be reasonable, but the head or abdomen must be reduced in size for delivery. Removal of fluid by cephalocentesis or paracentesis with sonographic guidance can be performed intrapartum. As described earlier, cleidotomy can shorten the bisacromial diameter. For hydrocephalic fetuses that are breech, cephalocentesis can be accomplished suprapubically when the aftercoming head enters the pelvis. Currently, these practices are more germane in developing countries.

THIRD STAGE OF LABOR

■ Delivery of the Placenta

Third-stage labor begins immediately after fetal birth and ends with placental delivery. Goals include delivering an intact placenta and avoiding uterine inversion or postpartum hemorrhage. The latter two, described in Chapter 42 (p. 731), are intrapartum emergencies.

Immediately after newborn birth, uterine fundal size and consistency are examined. If the uterus remains firm and bleeding is minimal, watchful waiting until the placenta separates is the usual practice. Neither massage nor downward fundal pressure is employed, but the fundus is frequently palpated to ensure that it does not become atonic and filled with blood from placental separation. *To prevent uterine inversion, umbilical cord traction must not be used to pull the placenta from the uterus.* Signs of separation include a sudden gush of blood into the vagina, a globular and firmer fundus, outward movement of the umbilical cord as the placenta descends into the vagina, and elevation of the uterus into the abdomen. With the last, the placenta, having separated, passes down into the vagina. Here, its bulk pushes the uterine body upward.

These signs appear within minutes after newborn delivery, and the median time ranges from 4 to 12 minutes (Frolova, 2016; Shinar, 2016b). Once the placenta has detached from the uterine wall, the mother can bear down, and intraabdominal pressure often expels the placenta into the vagina. These efforts may fail or may not be possible because of analgesia. After ensuring that the uterus is contracted firmly, the umbilical cord is kept slightly taut but is not pulled. Pressure is exerted by a hand wrapped around the fundus to propel the detached placenta into the vagina (Fig. 27-6). Concurrently, the heel of the same hand exerts pressure between the symphysis pubis and the uterine fundus and directs it toward the sacrum. This aims to prevent inversion. Once the placenta passes through the introitus, pressure on the uterus is relieved. The placenta is then gently lifted away. Care is taken to prevent placental membranes from being torn off and left behind. If the membranes begin to tear, they are grasped with a clamp and removed by gentle teasing (Fig. 27-7).

■ Management of the Third Stage

Practices within this stage of labor may be broadly considered as either expectant or active. Expectant management involves waiting for placental separation signs and allowing the placenta to deliver either spontaneously or aided by nipple stimulation or gravity (World Health Organization, 2012).

In contrast, active management of third-stage labor includes earlier cord clamping, controlled cord traction during placental delivery, and immediate prophylactic administration of a uterotonic agent. The goal of this triad is to limit postpartum hemorrhage. However, the value of this bundled approach is questioned (Begley, 2019). For example and as noted previously (p. 500),

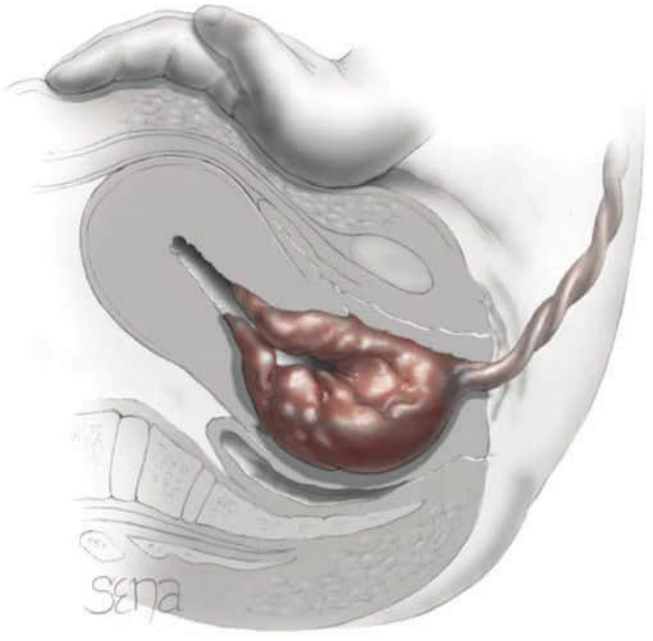


FIGURE 27-6 Expression of the detached placenta. Note that the hand is *not* trying to push the fundus through the birth canal! As the placenta leaves the uterus and enters the vagina, the uterus is pushed cephalad by the heel of the hand on the abdomen while the cord is held in position. The mother can aid in the delivery of the placenta by bearing down. As the placenta reaches the perineum, the cord is lifted, which in turn lifts the placenta out of the vagina.

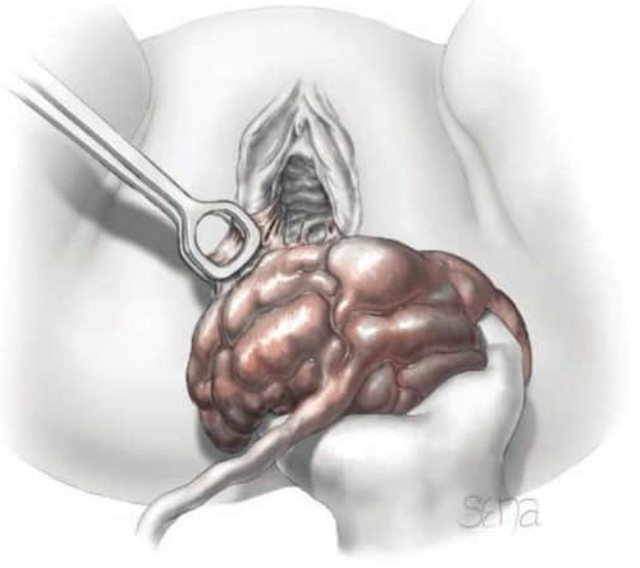


FIGURE 27-7 Membranes that were somewhat adhered to the uterine lining are separated by gentle traction with ring forceps.

delayed cord clamping does not raise postpartum hemorrhage rates, and thus early clamping is a less important component of this trio. Similarly, cord traction fails to prevent hemorrhage. Traction does lower manual placenta removal rates and shortens third-stage labor (Deneux-Tharaux, 2013; Hofmeyr, 2015). Following placental delivery, we support uterine massage to prompt uterine firming but recognize that evidence for its benefits to avoid postpartum hemorrhage is not strong (Saccone, 2018).

Therefore, uterotonic drugs play an essential preemptive role to decrease postpartum blood loss (Salati, 2019). A single agent is given either before or after placental expulsion, and timing does not affect rates of postpartum hemorrhage, placental retention, or third-stage labor length (Soltani, 2010). Choices for hemorrhage *prophylaxis* include oxytocin (Pitocin), misoprostol (Cytotec), and the ergots, namely ergonovine (Ergotrate) and methylergonovine (Methergine). In addition, a combination agent of oxytocin plus ergonovine (Syntometrine) is used outside the United States. Also in other countries, carbetocin (Duratocin), a long-acting oxytocin analogue, is available and effective for hemorrhage prevention (Kalafat, 2021). Prescribing information for carbetocin cites its use for cesarean delivery, but randomized trials reflect similar use for vaginal birth. Of agents, the WHO (2018) recommends oxytocin for first-line use.

High-dose Oxytocin

Synthetic oxytocin is identical to that produced by the posterior pituitary. Its action is noted at approximately 1 minute, and it has a mean half-life of 3 to 5 minutes. Recommended storage temperature is ≤25C°, which may pose problems in some low-resource countries. When given as a bolus, oxytocin can cause profound hypotension (Svanström, 2008). This hemodynamic change may be dangerous to women with hemorrhage-related hypovolemia or with certain cardiac conditions. Thus, oxytocin should be given as a dilute solution by continuous intravenous infusion or as an intramuscular injection.

Despite the routine use of oxytocin, no standard prophylactic dose has been established for its use following either vaginal or cesarean delivery. Water intoxication can result from the antidiuretic action of high-dose oxytocin if administered in a large volume of electrolyte-free dextrose solution (Whalley, 1963). Our practice is to add 20 units (2 mL) of oxytocin per liter of crystalloid solution. This is administered after delivery of the placenta at a rate of 10 to 20 mL/min—200 to 400 mU/min—for a few minutes until the uterus remains firmly contracted and bleeding is controlled. The infusion rate then is reduced to 1 to 2 mL/min until the mother is ready for transfer to the postpartum unit. The infusion is usually then discontinued. For women without intravenous access, 10 units of intramuscular oxytocin are injected.

Other Agents

Ergonovine and methylergonovine have similar activity in myometrium, but only methylergonovine is currently manufactured in the United States. These ergot alkaloid agents lower the rates of postpartum hemorrhage and the need for additional uterotonic drugs. However, blood pressure elevation is a concerning side effect (Liabsuetrakul, 2018). Methylergonovine is contraindicated in hypertensive women. If selected, a 200-μg dose of methylergonovine is given intramuscularly or is slowly injected intravenously in a period not less than 60 seconds to avoid sudden hypertension.

Misoprostol is a prostaglandin E_1 analogue, which has proved inferior to oxytocin for postpartum hemorrhage prevention (Tunçalp, 2012). However, in resource-poor settings that lack oxytocin, misoprostol is suitable for hemorrhage prophylaxis and is given orally as a single 400- or 600-μg dose (World Health Organization, 2018c). Side effects include fever and diarrhea.

From systematic reviews, carbetocin and oxytocin show equivalent efficacy for postpartum hemorrhage prevention after vaginal birth (van der Nelson, 2021; Widmer, 2018). Carbetocin is more expensive. A heat-stable form may have benefit in low-resource settings that may have inconsistent temperatures during supply distribution (Malm, 2018).

Tranexamic acid (TXA) is an antifibrinolytic agent and has been evaluated to *prevent* postpartum hemorrhage (Ahmadzia, 2018). In one metaanalysis, a 1-g intravenous TXA dose following delivery in addition to oxytocin was reported to lower the hemorrhage rate from 11.4 to 8.7 percent (Saccone, 2020). In a randomized trial of 3891 women, however, TXA plus oxytocin did not decrease the postpartum hemorrhage incidence compared with oxytocin alone (Sentilhes, 2018). Currently, TXA use is not recommended prophylactically (American College of Obstetricians and Gynecologists, 2019c). To *treat* hemorrhage, TXA use is described in Chapters 42 (p. 736) and 44 (p. 773).

■ Manual Removal of Placenta

In approximately 2 percent of singleton births, the placenta may not deliver promptly (Cheung, 2011). This may represent: (1) *placenta adherens*, in which uterine contractions are insufficient to detach the placenta; (2) lower uterine segment constriction and a detached but trapped placenta; or (3) placenta accreta spectrum. Consistent risks for retained placenta include stillbirth, prior cesarean delivery, prior retention, and preterm delivery (Belachew, 2014; Coviello, 2015; Endler, 2014). For the last, in one study with nearly 46,000 deliveries, analysis predicted that 90 percent of placentas would spontaneously deliver by 180 minutes for gestations at 20 weeks; 21 minutes at 30 weeks; and 14 minutes at 40 weeks (Dombrowski, 1995).

Postpartum hemorrhage can complicate a retained placenta, and bleeding risk accrues with the length of third-stage labor. In the absence of bleeding, evidence supports 15 to 20 minutes (Frolova, 2016; Shinar, 2016a; van Ast, 2019). The WHO (2012) cites a 60-minute threshold. Notably, if brisk bleeding ensues and the placenta cannot be delivered by standard technique, manual removal of the placenta is indicated (Fig. 27-8). When performed, some administer a single dose of intravenous antibiotics, however, one systematic review of observational studies found no benefits (Chibueze, 2015). The American College of Obstetricians and Gynecologists (2020d) concluded that data neither support nor refute this practice, but the WHO (2012) recommends prophylaxis. At our institution, we administer a single dose of cefazolin to women not already receiving antibiotics and not penicillin allergic.

IMMEDIATE POSTPARTUM CARE

The hour immediately following delivery of the placenta is critical. During this time, lacerations are repaired. Although uterotonic agents are administered, postpartum hemorrhage as the

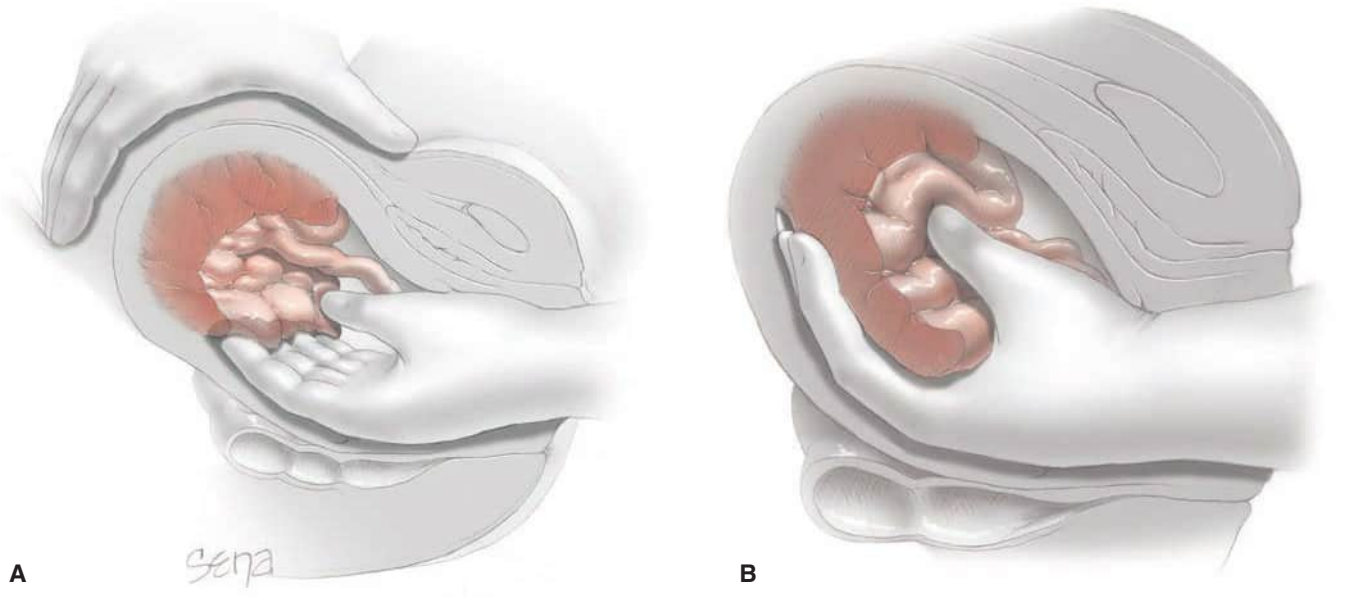


FIGURE 27-8 Manual removal of placenta. **A.** One hand grasps the fundus and the other hand is inserted into the uterine cavity and the fingers are swept from side to side as they are advanced. **B.** When the placenta detaches, it is grasped and removed.

result of uterine atony is most likely at this time. Hematomas may expand. Consequently, uterine tone and the perineum are frequently evaluated. The mother's blood pressure and pulse are recorded immediately after delivery and every 15 minutes for the first 2 hours. Her temperature is recorded every 4 hours during the first 8 hours and then every 8 hours thereafter. Vital signs may be obtained more frequently in patients at higher risk of postpartum complications (American Academy of Pediatrics, 2017). The placenta, membranes, and umbilical cord are examined for completeness and anomalies, as described in Chapter 6 (p. 107).

Skin-to-skin Contact

This practice aims to connect the mother and newborn dyad early to promote breastfeeding (American College of Obstetricians and Gynecologists, 2020a; Moore, 2016; World Health Organization, 2018b). Ideally, the mother lies in a semireclined position. After the newborn is dried to prevent cooling, its chest is placed against the mother's breast with access to her nipple. Its legs are flexed, and the mother's arm steadies its body. Covered with warm blankets and often a cap, the neonate's head is uncovered, turned to the side, and placed in a sniffing position. Mouth and nares should remain unobstructed (Widström, 2019). The dyad is continually monitored for physiologic stability, somnolence, unobstructed breathing, and safe positioning to avoid smothering or falls (Feldman-Winter, 2016).

Lower Genital Tract Lacerations

These lacerations may involve the cervix, vagina, or perineum. Those of the cervix and vagina are described in Chapter 42 (p. 739). In general, those of the perineum follow vaginal delivery, and most are first- and second-degree lacerations. Lacerations are classified by depth and involved anatomy, and complete definitions and visual examples are given in Figure 27-9. Of these, third-degree lacerations involve the anal sphincter and are subcategorized as:

(3a) <50 percent external anal sphincter (EAS) tear;
(3b) >50 percent EAS tear; and
(3c) EAS plus internal anal sphincter (IAS) tears.

Third- and fourth-degree perineal lacerations are considered obstetric anal sphincter injuries (OASIS), and their combined incidence is 0.1 to 5 percent (Blondel, 2016; Friedman, 2015). Risk factors for these more complex lacerations include nulliparity, midline episiotomy, persistent OP position, Asian race, increasing fetal birthweight, and operative vaginal delivery (Gurol-Urganci, 2013; Landy, 2011).

Morbidity rates rise as laceration severity increases. Compared with simpler lacerations, OASIS are associated with greater blood loss and puerperal pain. Wound disruption and infection rates are other risks (Goldaber, 1993; Lewicky-Gaupp, 2015). Stock and coworkers (2013) reported that approximately 7 percent of 909 OASIS had complications. Long term, OASIS are linked with approximately doubled rates of anal incontinence compared with vaginal delivery without OASIS (Evers, 2012; Schei, 2019). Fourth-degree lacerations pose greater anal incontinence risk than third-degree ones (Gommesen, 2020; Jangö, 2018). Evidence implicating OASIS in subsequent long-term dyspareunia are conflicting (Mous, 2008; O'Shea, 2018).

To ensure appropriate repair, identification and correct categorization is essential. Intrapartum endoanal ultrasound has been used to unmask clinically occult tears (Faltin, 2005). Few data currently support this imaging intrapartum, and the American College of Obstetricians and Gynecologists (2020c) does not recommended it.

For women with a prior OASIS, questions may arise as to subsequent pregnancy. In those without anal incontinence after OASIS repair, the rate of developing this incontinence is not increased by a subsequent vaginal birth (Jangö, 2016;

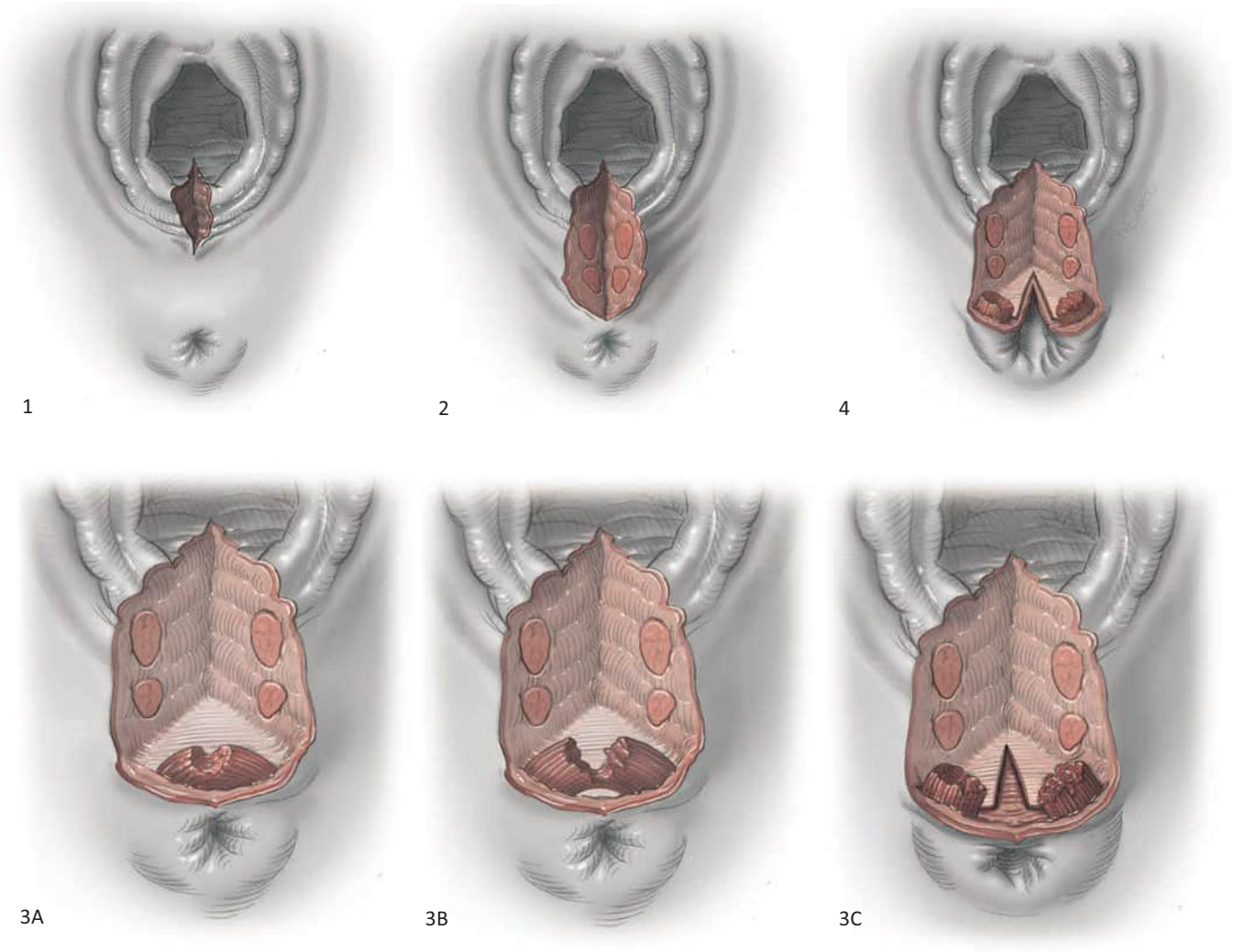


FIGURE 27-9 1. First-degree perineal laceration: injury to only the vaginal epithelium or perineal skin. **2.** Second-degree laceration: injury to perineum that spares the anal sphincter complex but involves the perineal muscles, which are the bulbospongiosus and superficial transverse perineal muscles. **3a.** Third-degree laceration: <50 percent of the external anal sphincter (EAS) is torn. **3b.** Third-degree laceration: >50 percent of the EAS is torn, but the internal anal sphincter (IAS) remains intact. **3c.** Third-degree laceration: EAS and IAS are torn. **4.** Fourth-degree laceration: the perineal body, entire anal sphincter complex, and anorectal mucosa are lacerated. (Reproduced with permission from Kenton K, Mueller M: Episiotomy and obstetric anal sphincter lacerations. In Yeomans ER, Hoffman BL, Gilstrap LC III, et al (eds): Cunningham and Gilstrap's Operative Obstetrics, 3rd ed. New York, NY: McGraw Hill; 2017.)

Webb, 2017). Thus, a vaginal route is reasonable. However, women with a prior OASIS do have a higher recurrence rate with a subsequent delivery compared with multiparas without a prior OASIS (Edozien, 2014; Elfaghi, 2004). The risk mirrors that of primiparas in the general population and is low (Basham, 2013; Boggs, 2014). But, in those who experience a recurrent OASIS, the risk of anal incontinence can be substantial (Jangö, 2017). Fetal macrosomia and operative vaginal delivery are factors for OASIS recurrence and can influence counseling in future pregnancies. Specifically, patients may choose cesarean delivery to avoid repeat OASIS. This consideration may be most pertinent for those with prior postpartum anal incontinence, with OASIS complications that required a second repair, or with psychological trauma (American College of Obstetricians and Gynecologists, 2020c). Planned cesarean delivery is balanced against its associated operative risks (Chap. 30, p. 548).

■ Episiotomy

In contrast to spontaneous perineal tears, *episiotomy* is intended incision of the perineum. Its goal is enlargement of vaginal opening for birth. Textbooks and organizational guidelines often differ in their description. Kalis and colleagues (2012) presents one classification, and we agree with the need for terminology standardization.

Midline and mediolateral episiotomies are the two main types and vary by the angle of perineal incision. Involved structures mirror those found with second-degree laceration, and their repairs are analogous. The *midline episiotomy* begins at the fourchette, incises the perineal body in the midline, and ends well before the EAS is reached. The chosen incision length varies from 2 to 3 cm depending on perineal length, degree of tissue thinning, and outlet diameter needs for delivery. The *mediolateral episiotomy* begins at the midline of the fourchette

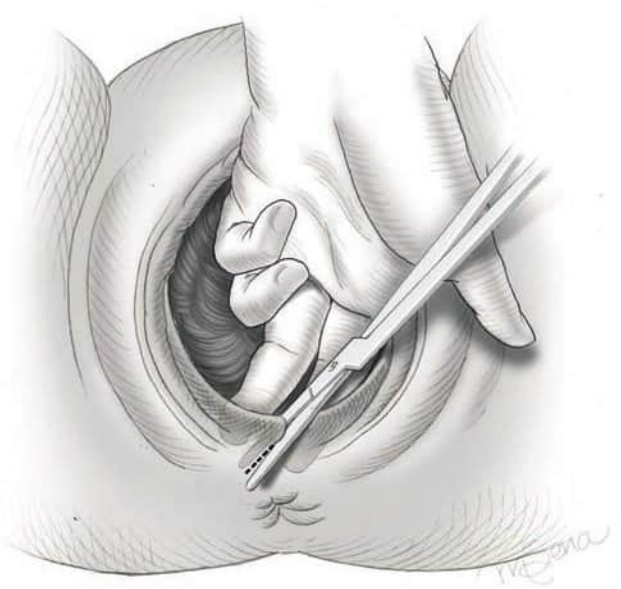


FIGURE 27-10 A mediolateral episiotomy is cut as the baby's head crowns. Fingers are insinuated between the perineum and head. The incision begins in the midline and is directed toward the ipsilateral ischial tuberosity at an angle 60 degrees off the midline. (Reproduced with permission from Kenton K, Mueller M: Episiotomy and obstetric anal sphincter lacerations. In Yeomans ER, Hoffman BL, Gilstrap LC III, et al (eds): Cunningham and Gilstrap's Operative Obstetrics, 3rd ed. New York, NY: McGraw Hill; 2017.)

and is directed to the right or left at an angle 60 degrees off the midline (Fig. 27-10). This angle accounts for stretch distortion of perineal anatomy during crowning. After delivery and distortion resolution, it ultimately yields an incision 45-degrees from the midline for suturing (Kalis, 2011). Used less often, the *lateral episiotomy* begins at point 1 to 2 cm lateral from the midline of the fourchette. It too is angled toward either the right or the left ischial tuberosity.

The American College of Obstetricians and Gynecologists (2020c) recommends selective use of episiotomy rather than routine use. Evidence shows lower rates of severe perineal trauma in women undergoing spontaneous birth with a restrictive use of episiotomy (Dillon, 2019; Jiang, 2017). One potential indication is fetal jeopardy, and the quickly enlarged vaginal opening can speed delivery. Others are shoulder dystocia, breech delivery, fetal macrosomia, operative vaginal delivery, persistent OP position, and other instances in which failure to perform an episiotomy will result in significant perineal rupture. Surgical judgment and common sense should guide selection.

As a result of selective use, episiotomy rates have dropped. Oliphant and coworkers (2010) analyzed rates between 1979 and 2006 in the United States and noted a 75-percent decline. In the United States in 2012, episiotomy was performed in approximately 12 percent of vaginal births (Friedman, 2015).

Before episiotomy, analgesia is provided by existing labor regional analgesia, by bilateral pudendal nerve blockade, or by local infiltration of 1-percent lidocaine. Some instead advocate 2.5-percent lidocaine-prilocaine cream (EMLA cream). However, for efficacy, it requires application an hour before expected delivery, which may be logistically difficult (Abbas, 2020).

If episiotomy is performed unnecessarily early, incisional bleeding may be considerable before delivery. If it is performed too late, lacerations will not be prevented. Typically, episiotomy is completed when the head is visible during a contraction to a diameter of 4 to 5 cm.

Few data directly compare midline and mediolateral types. As noted, midline episiotomy has a greater likelihood of associated OASIS (Coats, 1980; de Leeuw, 2001). Short-term rates of pain and dyspareunia are similar or increased with mediolateral episiotomy (Fodstad, 2013, 2014; Sartore, 2004).

Even fewer studies compare lateral episiotomy to either mediolateral or midline. One randomized trial compared lateral and mediolateral types in nulliparas. Groups did not differ in pain scores, in sexual quality of life, or in vaginal or perineal trauma, including OASIS (Karbanova, 2014a,b; Necesalova, 2016). The authors also reported that mediolateral episiotomies required less time and suture for the repair. Thus, among the three, mediolateral episiotomy may be the preferred incision to reduce OASIS rates.

Laceration and Episiotomy Repairs

Typically, perineal repairs are deferred until the placenta has been delivered. This policy permits undivided attention to the signs of placental separation and delivery. A further advantage is that repair is not interrupted or disrupted by placenta delivery. This is especially true if manual placenta removal must be performed. The major disadvantage is continuing blood loss until the repair is completed. Direct pressure from an applied gauze sponge will help to limit this volume.

For suitable repair, an understanding of perineal anatomy is necessary (Chap. 2, p. 14). Adequate analgesia is imperative. Locally injected lidocaine can be used solely or as a supplement to bilateral pudendal nerve blockade. In those with epidural analgesia, additional doses can be given. Following any repair, needle and sponge counts are reconciled and recorded in the delivery note (Steelman, 2018).

First-degree lacerations do not always require repair, and sutures are placed to control bleeding or restore anatomy. Here, few data guide suture selection. A fine-gauge, absorbable suture such as chromic gut or a delayed-absorbable type such as polyglactin 910 (Vicryl) or poliglecaprone (Monocryl) are suitable. If a site is hemostatic, skin glue is another option (Feingenberg, 2014).

Second-degree laceration is shown in Figures 27-11. Midline and mediolateral episiotomy repairs use similar steps. Namely, these close the vaginal epithelium and reapproximate the bulbospongiosus and superficial transverse perineal muscles during restoration of the perineal body. Compared with placing interrupted sutures, a continuous suturing method closes the defect faster, and has lower short-term pain scores, but wound complications and long-term pain rates are comparable and low (Kettle, 2012; Kindberg, 2008; Valenzuela, 2009). Selected less often, blunt needles are suitable and aim to decrease the incidence of needle-stick injuries (Mornar, 2008). Commonly used suture materials are chromic catgut or 2–0 Vicryl. Compared with chromic catgut, Vicryl is associated with less short-term discomfort, but long-term pain rates are

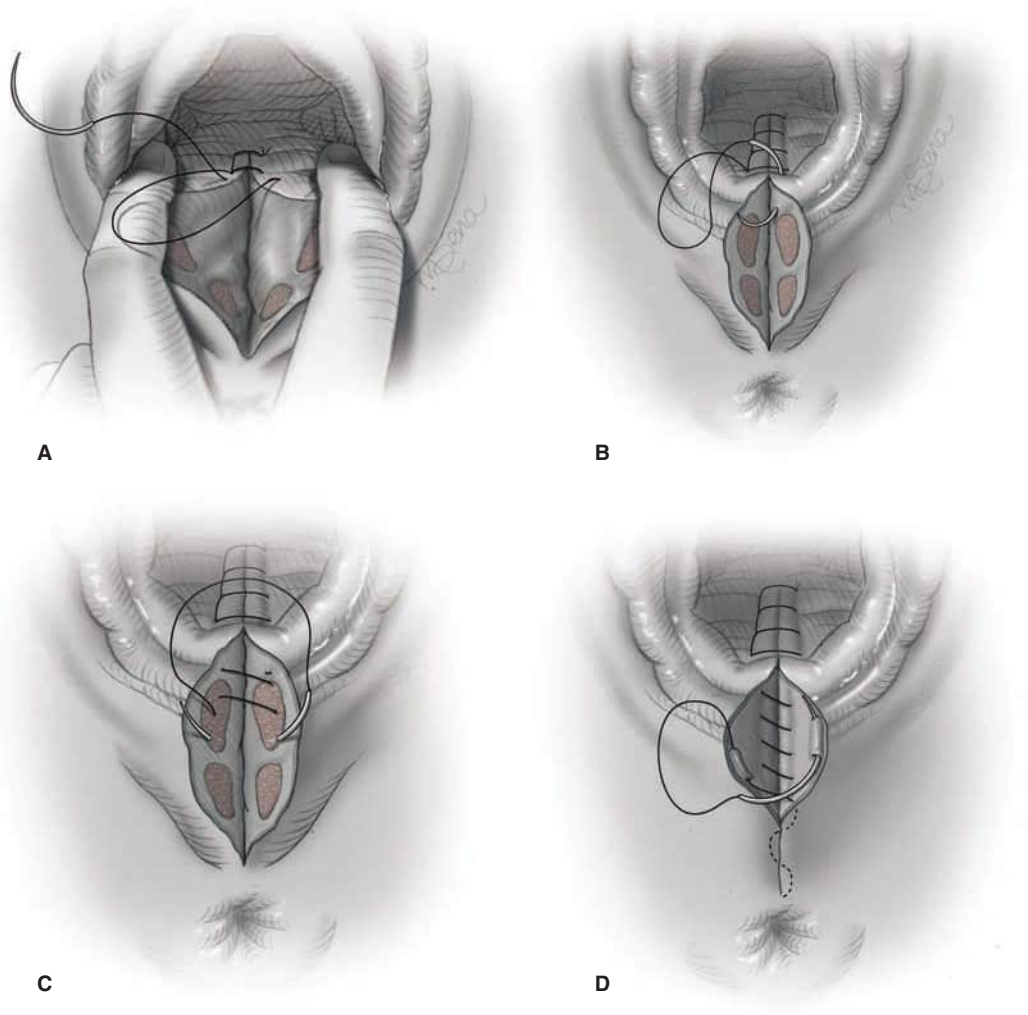


FIGURE 27-11 Midline episiotomy repair. **A.** An anchor stitch is placed above the wound apex to begin a running, locking closure with 2–0 suture to close the vaginal epithelium and deeper tissues and reapproximate the hymeneal ring. **B.** A transition stitch redirects suturing from the vagina to the perineum. **C.** The superficial transverse perineal and bulbospongiosus muscles are reapproximated using a continuous, nonlocking technique with the same length of suture. This aids restoration of the perineal body for long-term support. **D.** The continuous suture is then carried upward as a subcuticular stitch. The final knot is tied proximal to the hymeneal ring. (Reproduced with permission from Kenton K, Mueller M: Episiotomy and obstetric anal sphincter lacerations. In Yeomans ER, Hoffman BL, Gilstrap LC III, et al (eds): Cunningham and Gilstrap's Operative Obstetrics, 3rd ed. New York, NY: McGraw Hill; 2017.)

comparable (Kettle, 2010). However, traditional Vicryl occasionally requires removal of residual suture from the repair site because of pain. This disadvantage may be reduced by selecting a rapidly absorbed polyglactin 910 suture (Vicryl Rapide) (Greenberg, 2004; Kettle, 2002). Other delayed absorbable options include Monocryl or polydioxanone (PDS II). The perineal skin is closed by a running subcuticular stitch with the same suture type used to close the perineal defect.

For third-degree laceration repair, two methods are available to repair the EAS. The first is an *end-to-end technique*, which we prefer, and is shown in Figure 27-12. Initially, the torn ends of the EAS, which often retract, are isolated. The EAS and its surrounding connective tissue are brought to the midline. As a misnomer, this connective tissue is often called a *capsule* (Maldonado, 2020). The strength of this closure is derived from the connective tissue surrounding the sphincter and less so from the striated muscle. Thus, serial interrupted sutures incorporate sphincter fibers and a substantial portion of the perisphincter connective tissue to bring EAS ends together. If the IAS is torn, a running, nonlocking closure is completed with 3-0 or 4-0 suture (see Fig. 27-13B). Few data guide suture selection for sphincter repair, but delayed-absorbable material can provide sustained tensile strength during healing (Williams, 2006). This theory is supported by the study by Jallad and coworkers (2016), which showed a higher perineal breakdown rate following OASIS repair with chromic catgut.

With the *overlapping technique,* the ends of the EAS are brought to the midline, lie atop one another, and are sutured in this position. This method is suitable only for type 3c lacerations—those with complete EAS rupture. Two rows of mattress sutures travel through both overlapping EAS ends to recreate the anal ring. In comparing the two methods, neither yields superior long-term anatomical or functional results (Farrell, 2012; Fernando, 2013; Fitzpatrick, 2000). Also with type 3c lacerations, the IAS is repaired before the EAS and is described next.

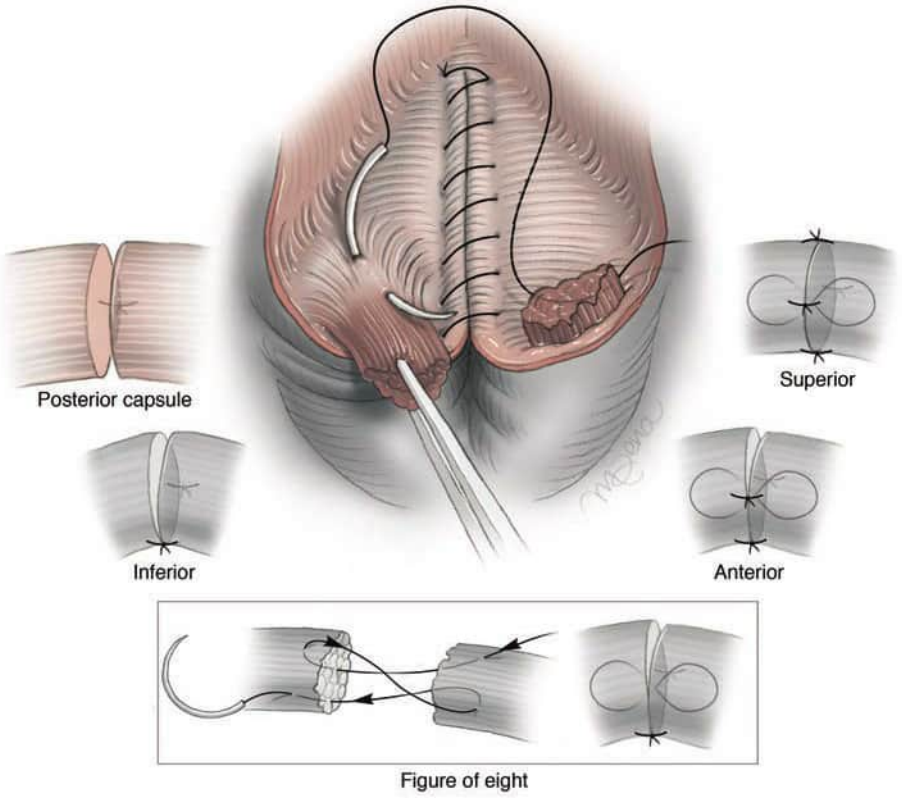


FIGURE 27-12 In overview, with end-to-end approximation of the external anal sphincter (EAS), a suture is placed through the EAS muscle, and four to six simple interrupted 2–0 or 3–0 sutures of polyglactin 910 are placed at the 3, 6, 9, and 12 o'clock positions through the perisphincter connective tissue. To begin, disrupted ends of the striated EAS muscle and capsule are identified and grasped. The first suture is placed posteriorly to maintain clear exposure. Another suture is then placed inferiorly at the 6 o'clock position. The sphincter muscle fibers are next reapposed by a figure-of-eight stitch. Last, the remainder of the fascia is closed with a stitch placed anterior to the sphincter cylinder and again with one placed superior to it. (Reproduced with permission from Kenton K, Mueller M: Episiotomy and obstetric anal sphincter lacerations. In Yeomans ER, Hoffman BL, Gilstrap LC III, et al (eds): Cunningham and Gilstrap's Operative Obstetrics, 3rd ed. New York, NY: McGraw Hill; 2017.)

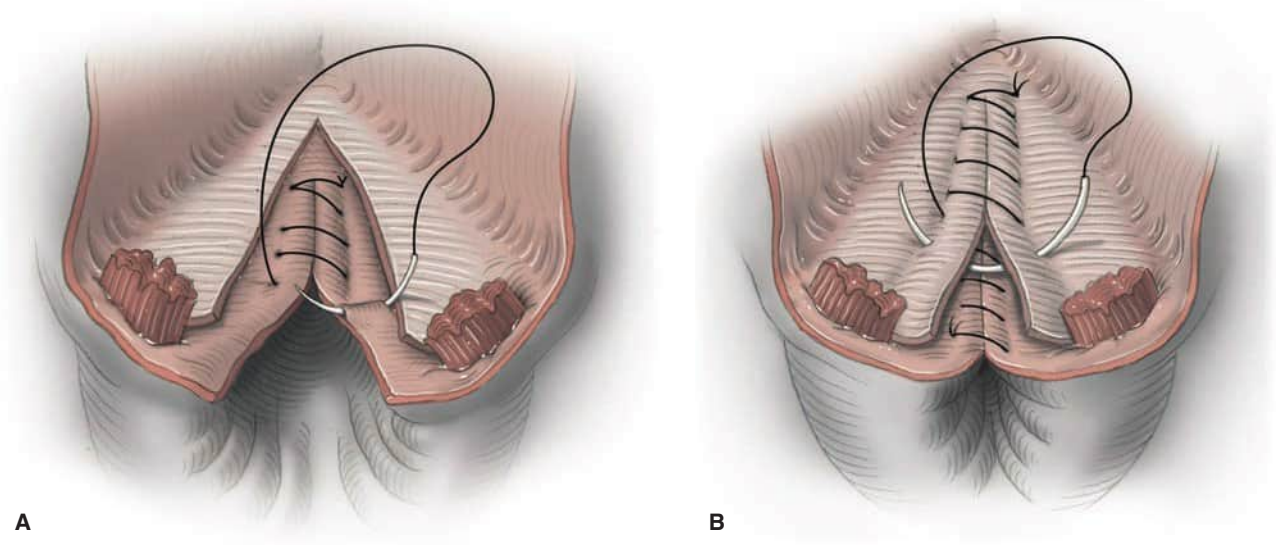


FIGURE 27-13 **A.** Suturing of the anorectal mucosa begins above the laceration apex using a continuous, nonlocking method with fine-gauge absorbable suture such as 3–0 or 4–0 chromic gut or polyglactin 910. Sutures are placed through the anorectal submucosa approximately 0.5 cm apart down to the anal verge. **B.** A second reinforcing layer uses 3–0 delayed-absorbable suture in a continuous, nonlocking fashion. This incorporates the torn ends of the internal anal sphincter (IAS), which can be identified as the glistening white fibrous structure lying between the anal canal submucosa and the fibers of the external anal sphincter. In many cases, the IAS retracts laterally and must be sought and retrieved for repair. (Reproduced with permission from Kenton K, Mueller M: Episiotomy and obstetric anal sphincter lacerations. In Yeomans ER, Hoffman BL, Gilstrap LC III, et al (eds): Cunningham and Gilstrap's Operative Obstetrics, 3rd ed. New York, NY: McGraw Hill; 2017.)

With fourth-degree laceration repairs, both torn edges of the rectal mucosa are reapproximated first (see Fig. 27-13). Starting at a point 1 cm proximal to the wound apex, sutures are placed approximately 0.5 cm apart in the rectal muscularis and do not enter the anorectal lumen. Clinicians often use 4–0 delayed-absorbable suture or chromic gut for this running suture line. Some recommend a second reinforcing layer above this (Hale, 2007). The next layer to cover the anorectal mucosa is formed by reapproximation of the IAS.

For reduction of infectious morbidity associated with OASIS, a single dose of antibiotic at the time of repair may be considered (Buppasiri, 2014; Duggal, 2008; Lewicky-Gaupp, 2015; Stock, 2013). A single dose of a second-generation cephalosporin is suitable, or clindamycin for penicillin-allergic women. With OASIS, postoperatively, stool softeners are prescribed for a week, and enemas and suppositories are avoided.

■ Perineal Laceration Care

Initially, locally applied ice packs help reduce swelling and allay discomfort (de Souza Bosco Paiva, 2016). In subsequent days, warm sitz baths aid comfort and hygiene. Additionally, a small squirt bottle of warm water can cleanse the site after voiding or stooling. Analgesics containing codeine provide considerable relief. For lesser degrees of discomfort, nonsteroidal antiinflammatory drugs can be given.

Because pain may instead signal a large vulvar, paravaginal, or ischiorectal fossa hematoma or perineal cellulitis, these sites should be examined carefully if pain is severe or persistent. Management of these complications is discussed in Chapters 37 and 42 (pp. 657 and 740). In addition to pain, urinary retention may complicate episiotomy recovery, and management is described in Chapter 36 (p. 643).

For those with second-degree lacerations or OASIS, intercourse is usually proscribed until after the first puerperal visit. Compared with women with intact perineum, those with perineal trauma show higher rates of delayed intercourse at 3 and 6 months, but not at 1 year (McDonald, 2015; Rådestad, 2008; Signorello, 2001).

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CHAPTER 28

Singleton Breech Delivery

CLASSIFICATION

Near term, the typical fetus spontaneously assumes a cephalic presentation. However, if the fetal buttocks or legs enter the pelvis before the head, the presentation is *breech*. At term, breech presentation persists in 2 to 5 percent of singleton deliveries (Bin, 2016; Cammu, 2014; Toijonen, 2019). Breech delivery of a second twin is discussed in Chapter 48 (p. 856).

The categories of frank, complete, and incomplete breech presentations differ in their varying relations between the lower extremities and buttocks. With a *frank breech*, lower extremities are flexed at the hips and extended at the knees, and thus the feet lie close to the head (Fig. 28-1). With a complete breech, both hips are flexed, and one or both knees are also flexed (Fig. 28-2). With an incomplete breech, one or both hips are extended. As a result, one or both feet or knees lie below the breech, and thus a foot or knee is lowermost in the birth canal. A footling breech is an incomplete breech with one or both feet below the breech.

Of singleton term breech fetuses, the neck may be extremely hyperextended in perhaps 5 percent, and the term *stargazing fetus* is used (Cimmino, 1975). With transverse lie and similar hyperextension of the fetal neck, the term *flying fetus* is applied. With these, fetal or uterine anomalies may be more prevalent and are sought if not previously identified (Phelan, 1983; Shipp, 2000). With hyperextension, vaginal delivery can injure the cervical spinal cord. Thus, if identified at term, cesarean delivery is indicated (Westgren, 1981). However, cases of spinal cord injury have been reported following uneventful

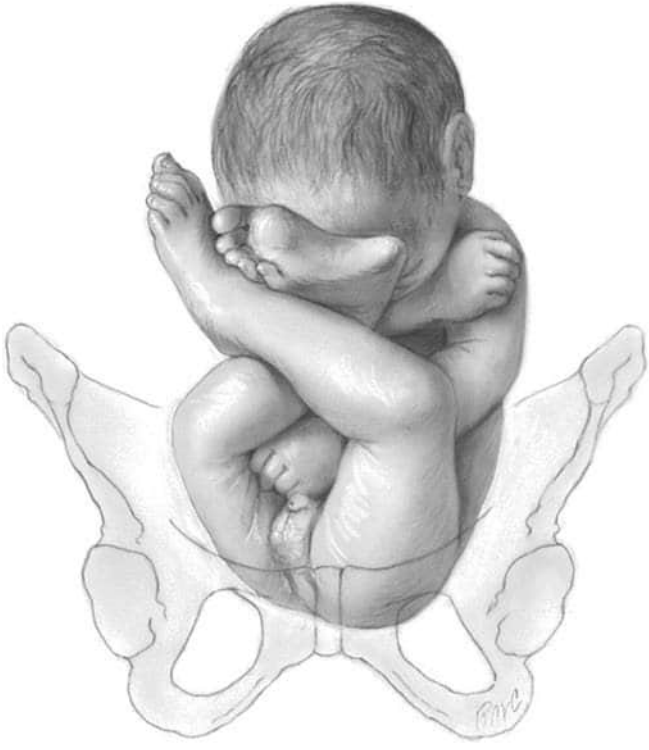

FIGURE 28-1 Frank breech presentation.

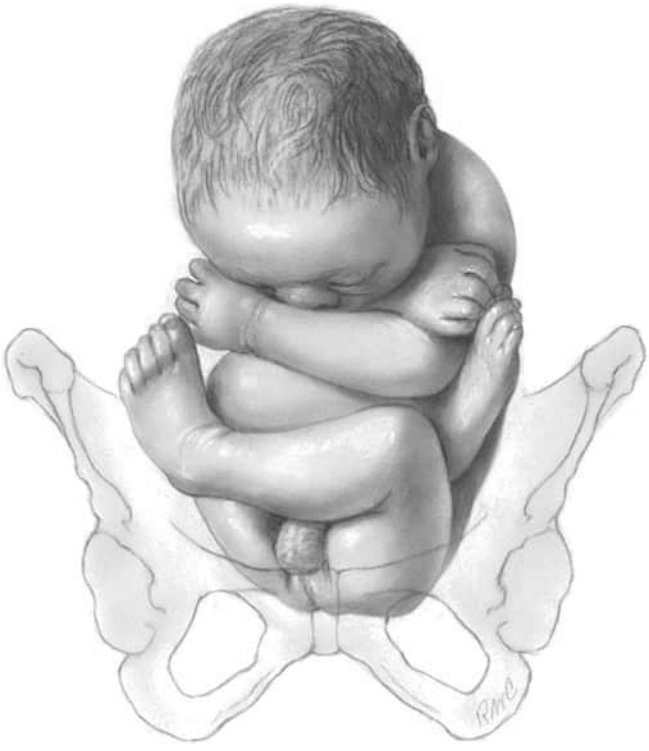

FIGURE 28-2 Complete breech presentation.

cesarean delivery of breech fetuses. Here, the flexion itself may be implicated (Hernandez-Marti, 1984; Weinstein, 1983).

DIAGNOSIS

Risk Factors

Understanding the clinical settings that predispose to breech presentation can aid early recognition. This fetal lie is more common remote from term, as earlier in pregnancy each fetal pole has similar bulk (Toijonen, 2019). Multifetal gestation is another (Chap. 48, p. 856). With singletons, other factors include extremes of amnionic fluid volume, fetal anomalies, structural uterine abnormalities, placenta previa, nulliparity, increased maternal age, female fetal gender, prior breech delivery, and size that is small for gestational age (Bin, 2016; Cammu, 2014; Noli, 2019; Roberts, 1999). One study found that following one breech delivery, the recurrence rate for a second breech presentation was 10 percent, and for a subsequent third breech it was 28 percent (Ford, 2010).

Examination

Leopold maneuvers to ascertain fetal presentation are discussed in Chapter 22 (p. 419). With the first maneuver, the hard, round fetal head occupies the fundus. The second maneuver identifies the hard, broad back to be on one side of the abdomen and the knobby small parts on the other. With the third maneuver, if not engaged, the softer breech is movable above the pelvic inlet. After engagement, the fourth maneuver shows the breech to be beneath the symphysis. The accuracy of this palpation varies (Lydon-Rochelle, 1993; Nassar, 2006). Thus, with unclear presentation, sonographic examination is indicated.

During cervical examination with a frank breech, no feet are appreciated, but the fetal ischial tuberosities, sacrum, and anus are usually palpable. After further fetal descent, the external genitalia also may be distinguished. When labor is prolonged, the fetal buttocks may become markedly swollen, rendering digital differentiation of a face and breech difficult. In some cases, the anus may be mistaken for the mouth and the ischial tuberosities for the malar eminences. With careful examination, however, the finger encounters muscular resistance with the anus, whereas the bony, less yielding jaws and palate are felt through the mouth. The finger, upon removal from the anus, may be stained with meconium. The mouth and malar eminences form a triangular shape, whereas the ischial tuberosities and anus lie in a straight line. With a complete breech, the feet may be felt alongside the buttocks. In footling presentations, one or both feet are inferior to the buttocks.

The fetal sacrum is palpated to establish position. As with cephalic presentations, fetal position is designated to reflect the relations of the fetal sacrum to the maternal pelvis. Thus, with left sacrum anterior (LSA), the fetus's back is up and its sacrum occupies the left upper (ventral) quadrant of the mother's pelvis. Other positions are right sacrum anterior (RSA), right or left sacrum posterior (RSP or LSP), and right or left sacrum transverse (RST or LST).

DELIVERY ROUTE

Multiple factors aid determination of the best delivery route. These include maternal parity and pelvic dimensions; coexistent pregnancy complications; provider experience; patient preference; hospital capabilities; and fetal size, anatomy, and gestational age (Table 28-1).

TABLE 28-1. Factors Favoring Cesarean Delivery of the Breech Fetus

Clinical characteristics
Lack of operator experience
Patient request for cesarean delivery
Prior perinatal death or neonatal birth trauma
Sonographic fetal characteristics
Large fetus: >3800 to 4000 g
Severe fetal-growth restriction; term weight <2500 to 2800 g
Oligohydramnios
Fetal anomaly incompatible with vaginal delivery
Incomplete breech presentation
Hyperextended neck
Apparently healthy, viable preterm fetus either with active labor or with indicated delivery
Maternal characteristics
Pelvic contraction or unfavorable pelvic shape determined clinically or with pelvimetry
Prior cesarean delivery

Compiled from text references.

Compared with their term counterparts, preterm breech fetuses have distinct complications related to their small size and immaturity. Accordingly, a separate discussion of term and preterm breech fetuses is presented.

Term Breech Fetus

Current obstetrical thinking regarding vaginal delivery of the term breech fetus was tremendously influenced by results of the Term Breech Trial (Hannah, 2000). This trial included 1041 women randomly assigned to planned cesarean and 1042 to planned vaginal delivery. These comparator groups reflect actual risks, and the planned vaginal delivery group included those who required intrapartum cesarean delivery. In the planned vaginal delivery group, 57 percent were actually delivered vaginally. Planned cesarean delivery was associated with a lower risk of perinatal mortality compared with planned vaginal delivery—3 per 1000 versus 13 per 1000. Cesarean delivery was also associated with a lower risk of "serious" neonatal morbidity—1.4 versus 3.8 percent. Short-term maternal morbidity was similar between groups.

Critics of the Term Breech Trial emphasize that fewer than 10 percent of candidates underwent radiological assessment of pelvic capacity. In addition, most of the outcomes included in the "serious" neonatal morbidity composite did not actually portend long-term infant disability (Whyte, 2004).

Since that trial, however, additional data favoring cesarean delivery has come from the World Health Organization (Lumbiganon, 2010). In more than 100,000 deliveries from nine participating Asian countries, planned cesarean delivery offered improved perinatal outcomes for the term breech fetus compared with planned vaginal delivery. Other studies also have found lowered neonatal morbidity and mortality rates with cesarean delivery (Lyons, 2015; Rietberg, 2005; Vistad, 2015). From one metaanalysis, the calculated absolute risk of perinatal mortality was 0.3 percent, and risk of fetal birth trauma or neurological morbidity was 0.7 percent (Berhan, 2016).

In contrast, other studies support vaginal delivery as a suitable option at term (Hofmeyr, 2015a). The *Presentation et Mode d'Accouchement (PREMODA)* study—which translates as presentation and mode of delivery—showed no differences in corrected neonatal mortality rates and neonatal outcomes according to delivery mode (Goffinet, 2006). Severe acute maternal morbidity scores were similar (Korb, 2019). This French prospective observational study involved more than 8000 women with term breech singletons. Strict criteria were used to select 2526 of these for planned vaginal delivery, and 71 percent of that group were delivered vaginally. Data from the Lille Breech Study Group in France also showed no excessive morbidity in term breech singletons delivered vaginally provided that strict fetal biometric and maternal pelvimetry parameters were applied (Michel, 2011). Other smaller studies support these findings as long as guidelines are part of the selection process (Alarab, 2004; Giuliani, 2002; Toivonen, 2012).

Long-term evidence supporting vaginal breech delivery comes from Eide and associates (2005). These investigators analyzed intelligence testing scores of more than 8000 men delivered breech, and delivery route did not affect later intellectual performance. Moreover, a 2-year follow-up from the Term Breech trial showed similar risks for death and for neurodevelopmental delay between delivery groups (Whyte, 2004). Other studies support these findings (Bin, 2017; Macharey, 2018).

Despite evidence for this debate, at least in the United States, rates of planned vaginal delivery attempts continue to decline (Grunebaum, 2016). Thus, as predicted, the number of skilled providers able to safely select and vaginally deliver breech fetuses steadily dwindles (Dotters-Katz, 2020). Moreover, obvious medicolegal concerns make physician training in such deliveries difficult. In response, some institutions have developed birth simulators to improve resident competence in vaginal breech delivery (Deering, 2006; Maslovitz, 2007).

In selecting suitable term breech vaginal delivery candidates, factors outlined in Table 28-1 are weighed. Of these, various national organizations recommend that the estimated term fetal weight lies between >2500 to 2800 g and <3800 to 4000 g (American College of Obstetricians and Gynecologists, 2018b; Impey, 2017b; Kotaska, 2019). Fetal-growth restriction and oligohydramnios are other contraindications, because of their inherent association with poor neonatal outcome (Chaps. 14 and 47, pp. 260 and 831). Data support this concern for the term breech fetus (Hinnenberg, 2019; Macharey, 2017a). Of uterine factors, prior hysterotomy carries an inherent risk for rupture in labor. The PREMODA, Term Breech Trial, and other studies allowed a trial of labor after cesarean for vaginal breech delivery, but in each, these constituted a small percentage of participants. Other studies have considered prior cesarean as a contraindication. Very limited data suggest a possible link with adverse perinatal outcome (Azria, 2012; Macharey, 2017a). Moreover, a prior cesarean delivery performed for arrested labor may suggest a relatively contracted pelvis and a greater labor risk. In contrast, parity and prior vaginal birth are positive factors and likely reflect sufficient pelvic capacity. Last, those with spontaneous labor and normal labor curves have higher successful vaginal birth rates.

Preterm Breech Fetus

In contrast to the term breech fetus, no randomized trials guide delivery selection for the preterm breech fetus. Comparison of the available observational studies is often hampered by their combining, splitting, or overlapping of gestational age groups. Other study biases include differing gestational age thresholds for planned neonatal resuscitation, assigning mortality causation to delivery rather than immaturity, and tendency to favor vaginal delivery for fetuses with a poor prognosis. In addition, the effects of precipitous vaginal delivery and associated incomplete antenatal prophylaxis with corticosteroids and antibiotics is difficult to evaluate.

Despite these limitations, for preterm breech fetuses as whole, data support that planned cesarean delivery confers a survival advantage compared with planned vaginal delivery. Reddy and associates (2012) reported data from deliveries between 24 and 32 weeks' gestation. For breech fetuses within these gestational ages, attempting vaginal delivery yielded a low success rate, and this group was associated with higher neonatal mortality rates compared with planned cesarean delivery.

From a metaanalysis incorporating data from more than 3500 parturients, similar mortality associations were reported (Bergenhenegouwen, 2014). In contrast, in their smaller cohort with gestational ages of 26 to 34 weeks, Lorthe and coworkers (2019) found similar rates of survival or of survival at discharge without severe morbidity.

For less mature subgroups—23 to 28 weeks—the data are more conflicting as to whether survival rates are improved with planned cesarean delivery (Bergenhenegouwen, 2015; Grabovac, 2018; Kayem, 2015; Thomas, 2016; Tucker Edmonds, 2015). In the balance, cesarean delivery is proposed to avoid fetal injury from vaginal birth that may include anoxia, trauma, and head entrapment. This is measured against maternal morbidity from a classical uterine incision, which is often needed in this early preterm group due to a poorly developed lower uterine segment. This incision typically poses a risk of greater blood loss, higher infection rate, and increased risk of uterine rupture in future pregnancies (Patterson, 2002; Reddy, 2015; Sciscione, 2008). The high-level skills needed for safe vaginal delivery of the very preterm fetus and the ultimate prognosis of the neonate are other directing factors. For *periviable fetuses*, defined by them as 20 to $25^{6/7}$ weeks, a consensus workshop of perinatal organizations concluded that "available data do not consistently support routine cesarean delivery to improve perinatal mortality or neurological outcomes for early preterm infants" (Raju, 2014). A subsequent joint statement by the American College of Obstetricians and Gynecologists and the Society for Maternal-Fetal Medicine (2017) suggested *consideration* for cesarean delivery for periviable fetuses beginning at $23^{0/7}$ weeks, with a recommendation for cesarean delivery at $25^{0/7}$ weeks.

For more mature preterm breech fetuses, that is, between 32 and 37 weeks, again limited data guide delivery route selection. Bergenhenegouwen and coworkers (2015) studied more than 6800 breech deliveries in a subgroup between 32 and 37 weeks. With planned cesarean delivery or planned vaginal birth, they found similar perinatal mortality and morbidity rates.

All these findings shape practice. Thus, individualized decision-making is needed for the preterm breech fetus for whom resuscitation is planned. Provider skill, gestational age, parity, labor curve, and facility capability weigh heavily in this process. For the fetus in which resuscitation is not planned, vaginal delivery is likely preferable.

Delivery Complications

Compared with cephalic-presenting fetuses, higher rates of maternal and perinatal morbidity can be anticipated with breech presentations. For the mother, with either cesarean or vaginal delivery, genital tract laceration can be problematic. With cesarean delivery, added stretching of the lower uterine segment by forceps or by a poorly molded fetal head can extend hysterotomy incisions. With vaginal delivery, especially with a thinned lower uterine segment, delivery of the aftercoming head through an incompletely dilated cervix or application of forceps may cause vaginal wall or cervical lacerations, and even uterine rupture. Manipulations may also extend an episiotomy, create deep perineal tears, require cervical incision, and raise infection risks. If needed in select cases, inhalant anesthesia sufficient to induce appreciable uterine relaxation during vaginal delivery may cause uterine atony and postpartum hemorrhage. Maternal death is rare, but rates appear higher in those with planned cesarean delivery for breech presentation—a case-fatality rate of 0.47 maternal deaths per 1000 births (Schutte, 2007). Other general short-term and long-term risks of cesarean delivery are listed in Chapter 30 (p. 548).

For the fetus, prematurity and its complications are frequently comorbid with breech presentation. Rates of congenital anomalies also are greater (Mostello, 2014). Compared with cephalic presentation, umbilical cord prolapse is more frequent with breech fetuses and with breech vaginal delivery (Behbehani, 2016; Critchlow, 1994). Collea (1980) reported that the incidence of prolapse approximated 0.5 percent with frank breech presentation, 5 percent with complete breech, and up to 15 percent with footling presentation.

Rare fetal morbidity includes humeral or clavicular fracture, brachial plexus injury, and sternocleidomastoid muscle trauma (Chap. 33, p. 609. These may occur with either route but more frequently complicate vaginal birth. However, cesarean birth does not appear to afford greater protection against femur or skull fractures (Ekéus, 2019; Goffinet, 2006; Hannah, 2000). Rarely, traction may separate scapular, humeral, or femoral epiphyses (Lamrani, 2011). The spinal cord may be injured or vertebrae fractured, especially if great force is employed (Vialle, 2007). Last, genitals may be injured with breech delivery (Saroha, 2015).

Some perinatal outcomes are inherent to the breech position rather than delivery. For example, development of hip dysplasia is more common in breech compared with cephalic presentation and is unaffected by delivery mode (de Hundt, 2012; Hinderaker, 1994).

Imaging

As noted, limited sonographic evaluation near term is reasonable to confirm presentation. Transabdominal sonography of the lower uterine segment in the sagittal plane shows the presenting fetal part. Prior to this and as part of prenatal care, sonographic fetal survey will have been performed in most cases. If not, gross fetal abnormalities, such as hydrocephaly or anencephaly, can be rapidly ascertained with sonography. This will identify many fetuses not suitable for vaginal delivery. It will also help to ensure that a cesarean delivery is not performed under emergency conditions for an anomalous fetus with no chance of survival.

In many fetuses—especially those that are preterm or growth restricted—the breech is smaller than the aftercoming head. Moreover, unlike cephalic presentations, the head of a breech-presenting fetus does not undergo appreciable molding during labor. Thus, if vaginal delivery is considered, fetal size, breech type, and degree of neck flexion are evaluated (Fontenot, 1997; Rojansky, 1994). If needed, simple two-view radiography of the maternal abdomen also can define fetal head inclination. Sonographic identification of a nuchal arm or nuchal cord loops may warrant cesarean delivery to avoid neonatal harm (Sherer, 1989).

The accuracy of fetal weight estimation by sonography is not altered by breech presentation (McNamara, 2012). For planned vaginal delivery at term, thresholds in Table 28-1 guide care. Moreover, a biparietal diameter (BPD) >90 to 100 mm is often considered exclusionary for vaginal delivery (Giuliani, 2002; Roman, 2008).

Pelvimetry

In addition to these requisite fetal parameters, some institutional protocols recommend pelvimetry to assess the maternal bony pelvis prior to planned vaginal term breech birth. Others, including our practice at Parkland Hospital, instead monitor the steady progression of fetal descent and cervical dilation to reflect adequate pelvic capacity.

For pelvimetry, one-view computed tomography (CT), magnetic resonance (MR) imaging, or plain film radiography is suitable. Comparative data among these modalities for pelvimetry are lacking, but CT is favored due to its accuracy, low radiation dose, and widespread availability (Thomas, 1998). Although variable, some suggest specific measurements to permit a planned vaginal delivery: inlet anteroposterior diameter ≥10.5 cm; inlet transverse diameter ≥12.0 cm; and midpelvic interspinous distance ≥10.0 cm (Azria, 2012; Vendittelli, 2006). Some have recommended maternal-fetal biometry correlation. Appropriate values include: the sum of the inlet obstetrical conjugate minus the fetal BPD is ≥15 mm; the inlet transverse diameter minus the BPD is ≥25 mm; and the midpelvis interspinous distance minus the BPD is ≥0 mm (Michel, 2011). From small studies of MR imaging, vaginal delivery success rates approximating 75 percent were noted if the interspinous distance was >11 cm and true obstetrical conjugate was >12 cm (Hoffmann, 2016; Klemt, 2019).

LABOR AND DELIVERY

Labor Management

On arrival to the labor unit, surveillance of fetal heart rate and uterine contractions begins, and immediate recruitment of necessary staff includes: (1) a provider skilled in the art of breech extraction, (2) an associate to assist with the delivery, (3) anesthesia personnel who can ensure adequate analgesia or anesthesia when needed, and (4) an individual trained in newborn resuscitation. For the mother, intravenous access is obtained. This allows, if required, emergency induction of anesthesia or maternal resuscitation following hemorrhage from lacerations or from uterine atony.

Assessing cervical dilation, membranes status, and presenting part station is essential for management. If labor is too far advanced, pelvimetry may be unsafe if fetal expulsion in the radiology department is a possibility. This alone, however, should not force the decision for cesarean delivery. Commonly, stepwise labor progression itself is a good indicator of pelvic adequacy (Biswas, 1993). Sonographic assessment, described earlier, is completed. Ultimately, the choice of abdominal or vaginal delivery is guided by factors listed in Table 28-1.

During labor, one-on-one nursing is ideal because of increased cord prolapse risks, and physicians must be readily available for such emergencies. Guidelines for monitoring the high-risk fetus are applied (Chap. 24, p. 461). For first-stage labor, most clinicians prefer continuous electronic monitoring. At minimum, the fetal heart rate is recorded every 15 minutes. A scalp electrode can be safely affixed to the buttock, but genitalia are avoided.

When membranes rupture, either spontaneously or artificially, the cord prolapse risk rises appreciably. A small or preterm fetus or a non-frank breech presentation raises this risk. Therefore, vaginal examination is performed immediately following rupture, and special attention is directed to the fetal heart rate for the first 5 to 10 minutes thereafter.

Continuous epidural analgesia is advocated by some. This may increase the need for labor augmentation and prolong second-stage labor (Chadha, 1992; Confino, 1985). These potential disadvantages are weighed against the advantages of better pain relief and increased pelvic relaxation should extensive fetal manipulation be required. Analgesia must be sufficient for episiotomy, for breech extraction, and for Piper forceps application. Nitrous oxide plus oxygen inhalation provides further relief from pain. If general anesthesia is required, it must be induced quickly.

Normal second-stage labor should show progressive fetal descent. An initial passive second stage allows the breech to advance to the perineum and is recommended. In the PREMODA study, this stage lasted <30 min for 60 percent of parturients and >60 min for only 20 percent (Goffinet, 2006). For this passive phase, some recommend cesarean if the breech is not visible after 1½ to 2 hours (Impey, 2017b; Kotaska, 2019).

Once the breech is visible, active pushing is encouraged. A hands-off approach in which hands are poised merely to support delivering parts is preferred to allow spontaneous delivery. In the PREMODA study, this active phase was <30 min for 95 percent of those with successful vaginal births (Goffinet, 2006). In their subanalysis of adverse neonatal outcome factors, an active second stage >20 min increased the risk (Azria, 2012). In the Term Breech Trial, the lowest risk for maternal and neonatal adverse outcomes was seen in the group with active second stages lasting <30 min (Su, 2003, 2007). In one small observational study, fetal adverse risks rose if this phase was >40 minutes (Macharey, 2017b). Canadian guidelines recommend cesarean if completed or imminent delivery is not accomplished after 60 min of pushing (Kotaska, 2019).

Labor Induction or Augmentation

Induction or augmentation of labor is controversial for term breech pregnancies. Here again, data are limited and mostly retrospective. With labor induction, Burgos and coworkers (2017) reported equivalent vaginal delivery rates compared with spontaneous labor. With induction, however, they reported higher rates of neonatal intensive care unit (NICU) admission. But, Marzouk and associates (2011) found perinatal outcomes and cesarean delivery rates not to differ. Last, others described greater cesarean delivery rates with induction but similar neonatal outcomes (Macharey, 2016). In a metaanalysis of studies, the NICU admission rate was 3 percent with labor induction and was double that of those delivered from spontaneous labor.

The cesarean delivery rate with induction was higher and was 33 percent (Sun, 2018).

Compared with cephalic presentations, breech labor in general proceeds more slowly, but steady cervical progress is a positive indicator of adequate pelvic capacity (Lennox, 1998). Thus, some protocols avoid augmentation for the breech-presenting fetus, whereas others recommend it only for hypotonic contractions (Alarab, 2004; Kotaska, 2019). In women with a viable fetus, at Parkland Hospital, we use amniotomy to promote contractions but prefer cesarean delivery instead of pharmacological labor induction or augmentation.

Vaginal Delivery Methods

Vaginal breech delivery is accomplished by one of three methods. With *spontaneous breech delivery*, the fetus is expelled entirely without any traction or manipulation other than support of the newborn. With *partial breech extraction*, the fetus is delivered spontaneously as far as the umbilicus, but the remainder of the body is delivered by provider traction and assisted maneuvers, with or without maternal expulsive efforts. With *total breech extraction*, the entire fetal body is extracted by the provider.

Spontaneous Breech Delivery

Similar to vertex delivery, spontaneous expulsion of a breech fetus entails sequential cardinal movements (Chap. 22, p. 421). First, engagement and descent of the breech usually take place with the bitrochanteric diameter in one of the oblique pelvic diameters. The anterior hip usually descends more rapidly than the posterior hip, and when the resistance of the pelvic floor is met, internal rotation of 45 degrees usually follows, bringing the anterior hip toward the pubic arch and allowing the bitrochanteric diameter to occupy the anteroposterior diameter of the pelvic outlet.

After rotation, descent continues until the perineum is distended by the advancing breech, and the anterior hip appears at the vulva. By lateral flexion of the fetal body, the posterior hip then is forced over the perineum, which retracts over the fetal buttocks, thus allowing the fetus to straighten out when the anterior hip is born. The legs and feet follow the breech and may be born spontaneously or require aid.

After the birth of the breech, there is slight external rotation, with the back turning anteriorly as the shoulders are brought into relation with one of the oblique diameters of the pelvis. The shoulders then descend rapidly and undergo internal rotation, with the bisacromial diameter occupying the anteroposterior plane. Immediately following the shoulders, the head, which is normally sharply flexed on the thorax, enters the pelvis in one of the oblique diameters and then rotates to bring the posterior portion of the neck under the symphysis pubis. The head is then born in flexion.

Infrequently, rotation renders the fetal back to lie posteriorly instead of anteriorly. Such rotation is prevented if possible. Although the head can be delivered by allowing the chin and face to pass beneath the symphysis, the slightest traction on the body may cause extension of the head. With this, a longer diameter of the head must pass through the pelvis.

Partial Breech Extraction

With breech delivery, successively larger and less compressible parts are born. Thus, spontaneous expulsion is the exception, and vaginal delivery typically requires skilled provider participation for the fetus to navigate the birth canal. Noteworthy clinical pearls are provided by Yeomans (2017) in *Cunningham and Gilstrap's Operative Obstetrics*, 3rd edition.

First, with all breech deliveries, unless the perineum is considerably lax, an episiotomy is made and is an important adjunct to delivery. As discussed in Chapter 27 (p. 510), mediolateral episiotomy may be preferred for its lower associated risk of anal sphincter lacerations. Ideally, the breech is allowed to deliver spontaneously to the umbilicus. Delivery of the breech draws the umbilicus and attached cord into the pelvis. Therefore, once the breech has passed beyond the vaginal introitus, the abdomen, thorax, arms, and head must be delivered promptly either spontaneously or assisted.

The posterior hip will deliver, usually from the 6 o'clock position, and often with sufficient pressure to evoke passage of thick meconium. The anterior hip then delivers, followed by external rotation to a sacrum anterior position. The mother is encouraged to continue to push as the fetus descends until the legs are accessible. The legs are sequentially delivered by splinting the femur with the operator's fingers positioned parallel to the long axis of the femur. This helps avoid femoral fracture. Pressure is exerted upward and laterally to sweep each leg away from the midline (Fig. 28-3).

Following delivery of the legs, the fetal bony pelvis is grasped with both hands. The fingers should rest on the anterior superior iliac crests and the thumbs on the sacrum. This minimizes

FIGURE 28-3 To deliver the left leg, two fingers of the provider's left hand are placed beneath and parallel to the femur. The thigh is then slightly abducted and pressure from the fingertips in the popliteal fossa should induce knee flexion and bring the foot within reach. The foot is then grasped to gently deliver the entire leg outside the vagina. A similar procedure is followed on the right. (Reproduced with permission from Yeomans ER: Vaginal breech delivery. In Yeomans ER, Hoffman BL, Gilstrap LC III, et al [eds]: Cunningham and Gilstrap's Operative Obstetrics, 3rd ed. New York, NY: McGraw Hill; 2017.)

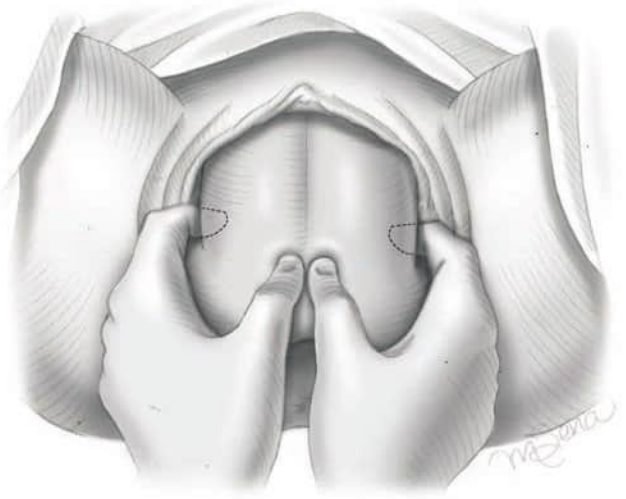

FIGURE 28-4 To deliver the body, thumbs are placed over the sacrum, and each index finger wraps over the top of the corresponding fetal iliac crest. Gentle downward traction is applied until the scapulas are clearly visible. (Reproduced with permission from Yeomans ER: Vaginal breech delivery. In Yeomans ER, Hoffman BL, Gilstrap LC III, et al [eds]: Cunningham and Gilstrap's Operative Obstetrics, 3rd ed. New York, NY: McGraw Hill; 2017.)

the chance of fetal abdominal soft-tissue injury (Fig. 28-4). Maternal expulsive efforts are again used in conjunction with downward traction to affect delivery.

A cardinal rule in successful breech extraction is to employ steady, gentle, downward traction until the lower halves of the scapulas are delivered. Subsequent delivery of the shoulders and arms is not attempted until one axilla becomes visible. It makes little difference which shoulder is delivered first, and two methods are suitable for their delivery. In the first method, with the scapulas visible, the trunk is rotated either clockwise or counterclockwise to bring the anterior shoulder and arm into view (Fig. 28-5). During delivery of the arm, fingers and hand are aligned parallel to the humerus and act as a splint. Perpendicular force risks humeral fracture. The body of the fetus is then rotated 180 degrees in the reverse direction to bring the other shoulder and arm into position for delivery.

The second method is employed if trunk rotation is unsuccessful. With this maneuver, the posterior shoulder is delivered first. For this, the feet are grasped in one hand and drawn upward over the inner thigh of the mother (Fig. 28-6). The operator's hand enters over the fetal shoulder, fingers are aligned parallel to the long axis of the fetal humerus, and the fetal arm is swept upward. The posterior shoulder slides out over the perineal margin and is usually followed by the arm and hand. Then, by depressing the body of the fetus, the anterior shoulder emerges beneath the pubic arch, and the arm and hand usually follow spontaneously. After both shoulders are delivered, the back of the fetus tends to rotate spontaneously to the symphysis. Delivery of the head may then be accomplished.

Nuchal Arm

During delivery, one or both fetal arms occasionally may lie across the back of the neck and become trapped at the pelvic inlet. With such a nuchal arm, delivery is more difficult and can be aided by rotating the fetus through a half circle in such a direction that the friction exerted by the birth canal will draw the elbow toward the face (Fig. 28-7). With a right nuchal arm, the body should be rotated counterclockwise, which rotates the fetal back toward the maternal right. With a left nuchal arm, the rotation is clockwise, which rotates the fetal back toward the maternal left. If rotation fails to free the nuchal arm, it may be necessary to push the fetus upward to a roomier part of the pelvis. If the rotation is still unsuccessful, still in this roomier part of the pelvic, the nuchal arm can be

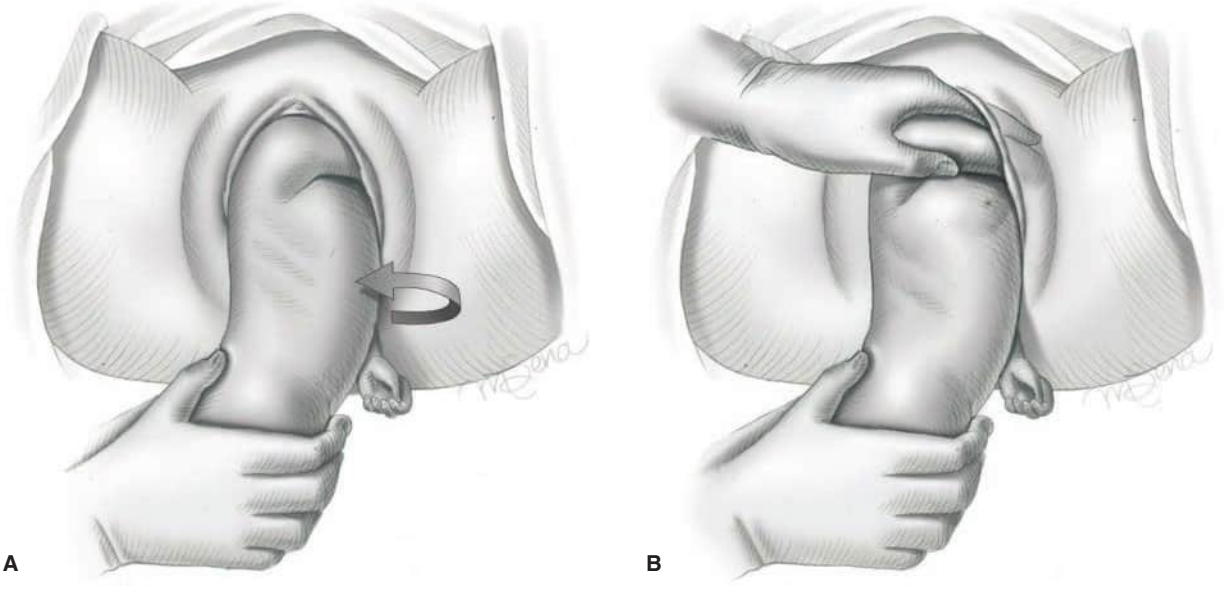

FIGURE 28-5 **A.** After delivery of the first arm, 180-degree rotation of the fetal body brings the sacrum to a right sacrum transverse (RST) position. **B.** Fingers of the provider's hand extended over the right shoulder and parallel to the humerus. These sweep the arm downward across the chest and out. (Reproduced with permission from Yeomans ER: Vaginal breech delivery. In Yeomans ER, Hoffman BL, Gilstrap LC III, et al [eds]: Cunningham and Gilstrap's Operative Obstetrics, 3rd ed. New York, NY: McGraw Hill; 2017.)

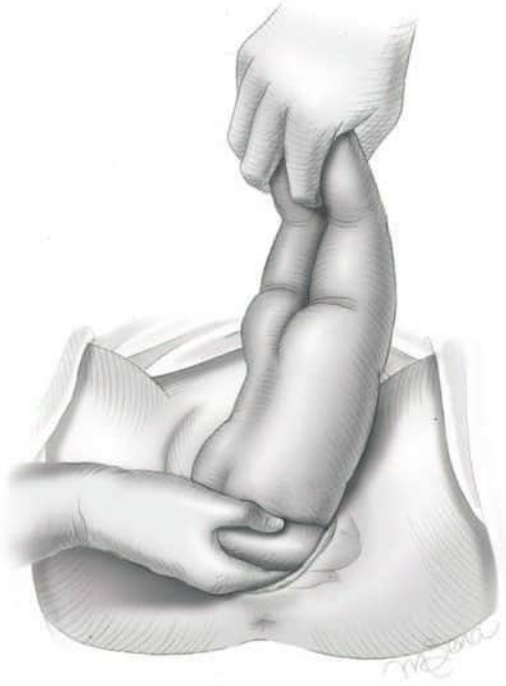

FIGURE 28-6 Infrequently, the posterior arm must be delivered first. For this, the lower half of the fetal body is raised up and over the maternal groin. The provider's fingers are inserted under the posterior shoulder and aligned with the humerus. (Reproduced with permission from Yeomans ER: Vaginal breech delivery. In Yeomans ER, Hoffman BL, Gilstrap LC III, et al [eds]: Cunningham and Gilstrap's Operative Obstetrics, 3rd ed. New York, NY: McGraw Hill; 2017.)

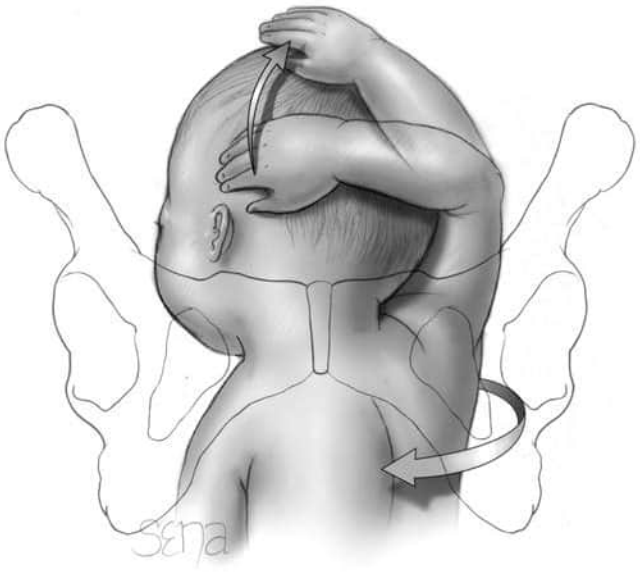

FIGURE 28-7 Reduction of a right nuchal arm is accomplished by rotating the fetal body 180 degrees counterclockwise, which directs the fetal back to the maternal right. Friction exerted by the birth canal will draw the elbow toward the face.

extracted. For this, the operator's hand enters over the fetal shoulder, and fingers are aligned parallel to the long axis of the fetal humerus. Downward pressure flexes the elbow, and the fetal arm is then swept forward and down the ventral body surface for delivery. In this event, fracture of the humerus or clavicle is common.

Delivery of the Aftercoming Head

The head of the fetus is normally extracted with one of the three maneuvers. With any of these, hyperextension of the fetal neck is avoided.

First, with the *Mauriceau maneuver*, the index and middle finger of one hand are applied over the maxilla, to flex the head, while the fetal body rests on the palm of the same hand and forearm (Fig. 28-8). Fetal legs straddle the forearm. Two fingers of the other hand hook over and grasp the shoulders. Downward traction is concurrently applied until the suboccipital region appears under the symphysis. Gentle suprapubic pressure simultaneously applied by an assistant helps keep the head flexed. The body is slightly elevated toward the maternal abdomen, and the mouth, nose, brow, and eventually the occiput emerge successively over the perineum. With this maneuver, the provider uses both hands simultaneously to exert continuous downward gentle traction while balancing forces between the fetal neck and maxilla to avoid neck hyperextension.

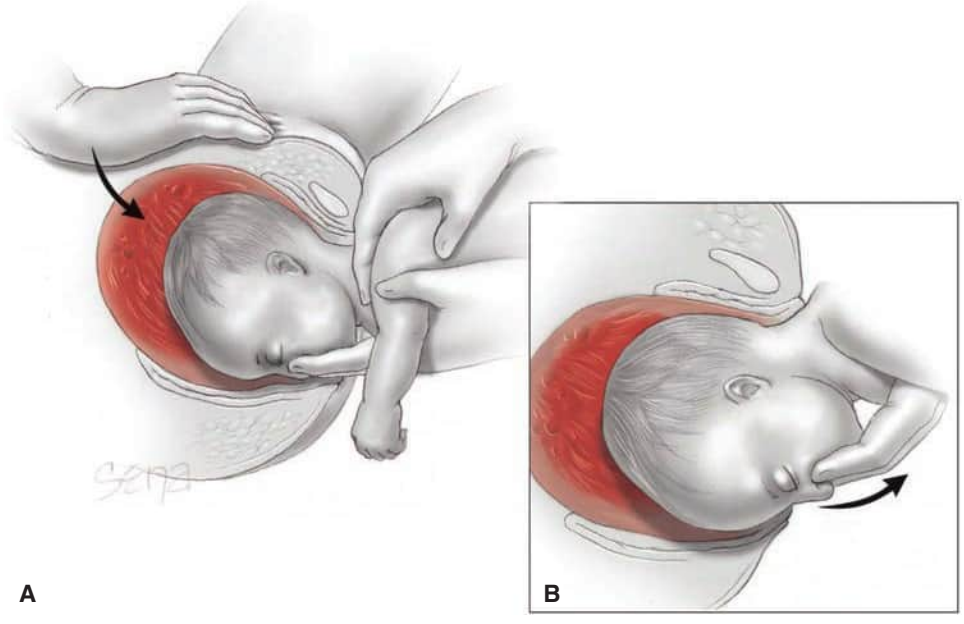

FIGURE 28-8 A. Delivery of the aftercoming head using the Mauriceau maneuver. Note that as the fetal head is being delivered, flexion of the head is maintained by suprapubic pressure provided by an assistant. **B.** Pressure on the maxilla is applied simultaneously by the operator as upward and outward traction is exerted.

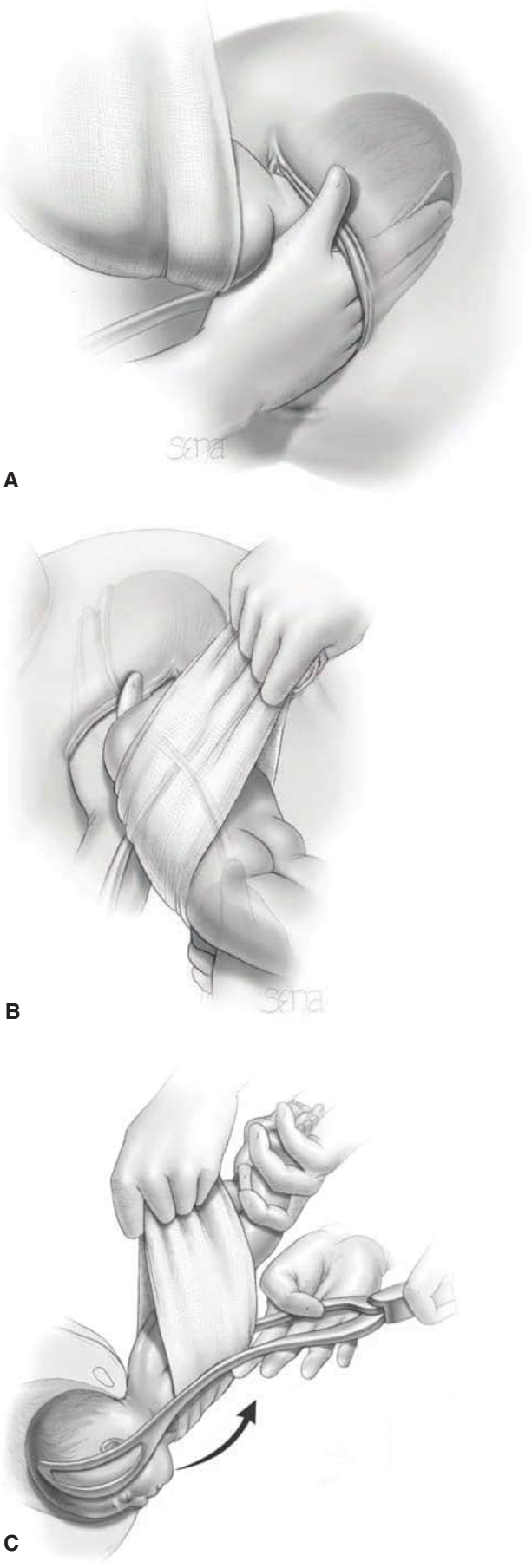

FIGURE 28-9 Piper forceps for delivery of the aftercoming head.

Second, specialized forceps can be used to deliver the aftercoming head. *Piper forceps*, shown in Figure 28-9, or *Laufe-Piper forceps* may be applied electively or when the Mauriceau maneuver cannot be accomplished easily. The blades of the forceps are not applied to the aftercoming head until it has been brought into the pelvis by gentle traction, combined with suprapubic pressure, and is engaged. Suspension of the body of the fetus in a towel effectively holds the fetus up and helps keep the arms and cord out of the way as the forceps blades are applied.

Because the forceps blades are directed upward from the level of the perineum, some choose to apply them from a one-knee kneeling position. Piper forceps have a downward arch in the shank to accommodate the fetal body and lack a pelvic curve. This shape permits direct application of the cephalic curve of the blade along the length of the maternal vagina and fetal parietal bone. The blade to be placed on the maternal left is held in the provider's left hand. The right hand slides between the fetal head and left maternal vaginal sidewall to guide the blade inward and around the parietal bone. The opposite blade mirrors this application.

Once in place, the blades are articulated, and the fetal body rests across the shanks. The head is delivered by pulling gently outward and slightly raising the handle simultaneously. This rolls the face over the perineum, while the occiput remains beneath the symphysis until after the brow delivers. Ideally, the head and body move in unison to minimize neck extension.

Last, in some cases, the back of the fetus fails to rotate to the symphysis. The fetus still may be delivered using the modified *Prague maneuver*. With this, two fingers of one hand grasp the shoulders of the back-down fetus from below while the other hand draws the feet up and over the maternal abdomen (Fig. 28-10).

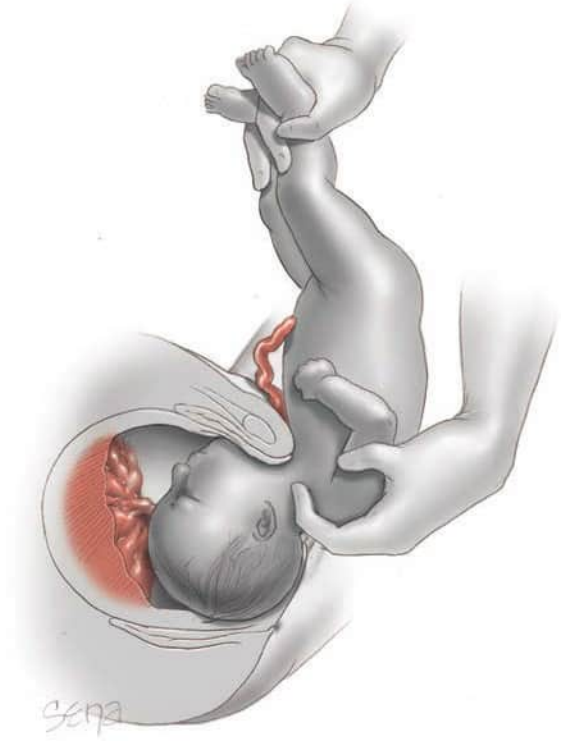

FIGURE 28-10 Delivery of the aftercoming head using the modified Prague maneuver necessitated by failure of the fetal trunk to rotate anteriorly.

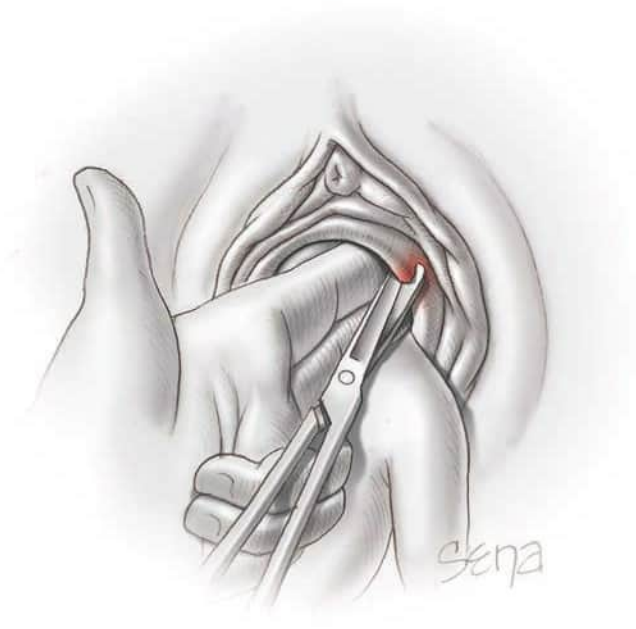

FIGURE 28-11 Dührssen incision being cut at 2 o'clock, which is followed by a second incision if needed at 10 o'clock. Infrequently, an additional incision is required at 6 o'clock. The incisions are so placed as to minimize bleeding from the laterally located cervical branches of the uterine artery. After delivery, the incisions are repaired as described in Chapter 42 (p. 740).

Head Entrapment

Either an incompletely dilated cervix or cephalopelvic disproportion can entrap the head. At this point, a true emergency exists because significant cord compression must be assumed.

First, an incompletely dilated cervix can constrict around the neck, especially with a small preterm fetus. With gentle traction on the fetal body, the cervix at times may be manually slipped over the occiput. If unsuccessful, Dührssen incisions may be needed (Fig. 28-11). General anesthesia with halogenated agents is another option to aid lower uterine segment relaxation. As an extreme measure, replacement of the fetus higher into the vagina and uterus, followed by cesarean delivery, can rescue an entrapped breech fetus. This *Zavanelli maneuver* is classically performed to relieve intractable shoulder dystocia (Sandberg, 1988). However, case reports have also described its use for an entrapped aftercoming head (Sandberg, 1999; Steyn, 1994).

Second, in cases with cephalopelvic disproportion and arrest of aftercoming head, the Zavanelli maneuver or symphysiotomy are options (Sunday-Adeoye, 2004; Wery, 2013). These are described in Chapter 27 (p. 504).

■ Total Breech Extraction

Frank Breech

During complete extraction of a frank breech, moderate traction is exerted by a finger in each groin and aided by a generous episiotomy. Once the breech is pulled through the introitus, the steps just described for partial breech extraction are completed.

Rarely during vaginal delivery, a frank breech will require decomposition inside the uterine cavity. Attributed to Pinard (1889), this procedure converts a frank breech into a footling breech. It is accomplished more readily if the membranes have ruptured only recently. It becomes extremely difficult if amniotic fluid is scant and the uterus is tightly contracted around the fetus. Pharmacological relaxation by general anesthesia or intravenous magnesium sulfate, nitroglycerin, or a betamimetic agent may be required. To begin, two fingers are carried up along one leg to externally rotate the hip by pressing on the medial side of the thigh parallel to the femur. Simultaneously, pressure in the popliteal fossa should prompt spontaneous knee flexion which brings the corresponding foot into contact with the back of the provider's hand. The fetal foot then may be grasped and brought down. Delivery is then accomplished as for incomplete breech, described next.

Incomplete or Complete Breech

If rapid labor progress prohibits cesarean delivery, total extraction of an incomplete or complete breech may be required. A hand is introduced through the vagina, and both fetal feet are grasped. The ankles are held with the middle finger lying between them. With gentle traction, the feet are brought through the introitus (Fig. 28-12). As the legs begin to emerge through the vulva, downward gentle traction is continued. As the legs emerge, successively higher portions are grasped. When the breech appears at the vaginal outlet, gentle traction is applied until the hips are delivered. The thumbs are then placed over the sacrum and the fingers over the iliac crests. Breech extraction is then completed, as described for partial breech extraction.

If only one foot can be grasped, it can be brought down into the vagina and held with the appropriate hand, right hand for right foot and left hand for left foot (Yeomans, 2017). With the first foot secure, the opposite hand is introduced, passed upward along the leg, and guided to locate the other foot. If the remaining hip is extended, the second foot is usually easily grasped and

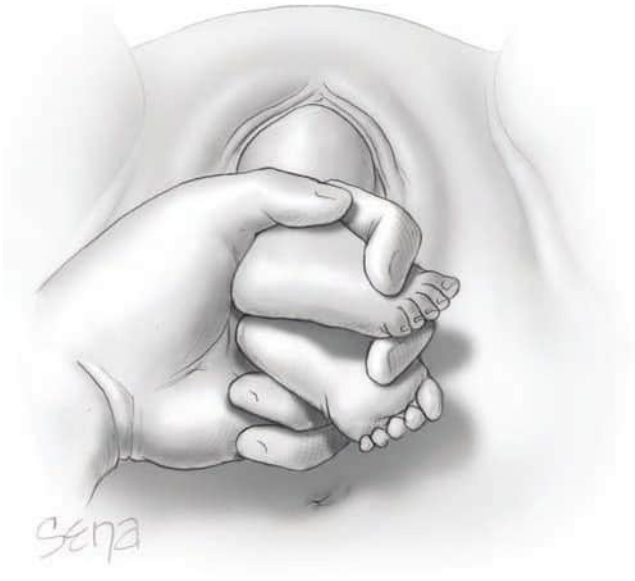

FIGURE 28-12 Complete breech extraction begins with traction on the feet and ankles.

brought down. If the hip is flexed and knee extended, a finger is hooked into that groin, and traction will bring the lower half of the fetus down until the leg can be reached.

For cesarean delivery, these same total breech extraction maneuvers can be used. These steps can aid delivery of a frank, complete, or incomplete breech through the hysterotomy incision.

EXTERNAL CEPHALIC VERSION

With *version*, fetal presentation is altered by physically substituting one pole of a longitudinal presentation for the other, or converting an oblique or transverse lie into a longitudinal presentation. Manipulations performed through the abdominal wall that yield a cephalic presentation are termed *external cephalic version*. Manipulations accomplished inside the uterine cavity that yield a breech presentation are designated *internal podalic version*. This latter procedure is reserved for delivery of a second twin and described in Chapter 48 (p. 856).

Indications

External cephalic version (ECV) reduces the rate of noncephalic presentation at birth, and its success rate is 50 to 60 percent (Hofmeyr, 2015b; Melo, 2019). For women with a transverse lie, the overall success rate is significantly higher.

In general, ECV is attempted before labor in a woman who has reached $37^{0/7}$ weeks' gestation (American College of Obstetricians and Gynecologists, 2020; Impey, 2017a). This threshold aims to balance risks of fetal immaturity and the greater amnionic fluid volume seen in early-term pregnancies, which aids turning. In support of this, one systematic review found that ECV done before $37^{0/7}$ weeks raised ECV success rates but did not lower the ultimate cesarean delivery rate and increased the risk of late-preterm birth (Hutton, 2015). Before this time, breech presentation also still has a high likelihood of correcting spontaneously. And, if ECV is performed too early, time may allow a reversion back to breech (Bogner, 2012). Last, if attempts at version cause a need for immediate delivery, complications of iatrogenic early-term delivery generally are not severe.

Absolute contraindications to ECV are few. It is contraindicated if vaginal delivery is not an option, such as with placenta previa. Relative contraindications are early labor, oligohydramnios or ruptured membranes, known nuchal cord, structural uterine abnormalities, fetal-growth restriction, multifetal gestation, and prior abruption or its risk factors (Rosman, 2013). Little data guide the decision for ECV for women with a prior cesarean delivery. In one pooled series of small studies that contained more than 100 attempts, no uterine ruptures were reported (Impey, 2018). At Parkland Hospital, we do not attempt ECV in these women.

Several factors can improve the chances of an ECV attempt. These are multiparity, unengaged presenting part, nonanterior placenta, nonobese patient, and abundant amnionic fluid (Lauterbach, 2021; Kok, 2008, 2009). To augment the last parameter, neither a preprocedural 2-L intravenous fluid bolus nor amnioinfusion raised ECV success rates (Burgos, 2014; Diguisto, 2018). Dedicated breech teams may increase these rates (Hickland, 2018; Thissen, 2019).

Complications

Patient counseling includes a discussion regarding small but real risks for placental abruption, preterm labor, and fetal compromise. Bradycardia is common during or following ECV, but emergent cesarean rates are ≤0.5 percent. Uterine rupture, fetomaternal hemorrhage, alloimmunization, amnionic fluid embolism, and maternal or fetal deaths are rare (Grootscholten, 2008; Rodgers, 2017). Overall, compared with expectant management, perinatal morbidity and mortality rates are not greater with ECV (Krueger, 2018; Son, 2018).

Even after successful ECV, several reports suggest that the cesarean delivery rate does not completely revert to the baseline for vertex presentations. Specifically, dystocia, malpresentation, and nonreassuring fetal heart patterns may be more common in these fetuses who have undergone successful ECV (Chan, 2004; de Hundt, 2014; Vézina, 2004).

Technique

ECV should be carried out in an area that has ready access to a facility equipped to perform emergency cesarean delivery. Because of the risk for surgical intervention, intravenous access is obtained. Patients also abstain from eating for 6 hours, but clear liquids can be consumed up to 2 hours prior. Sonographic examination is performed to confirm nonvertex presentation, document amnionic fluid volume adequacy, exclude obvious fetal anomalies if not done previously, and identify placental location and fetal spine orientation. Preprocedural external monitoring is performed to document fetal heart rate reactivity. Anti-D immune globulin is given to Rh D–negative women. Tocolysis and regional analgesia may be elected, and rationale for these is provided in subsequent sections.

The woman is placed in left lateral tilt to aid uteroplacental perfusion, and Trendelenburg positioning helps during elevation of the breech. During the procedure, we prefer to monitor fetal heart motion sonographically. An abundant abdominal coating of ultrasound gel permits this and also minimizes painful skin friction (Vallikkannu, 2014).

A forward roll of the fetus usually is attempted first. One or two providers may participate, and one hand grasps the head. The fetal buttocks are then elevated from the maternal pelvis and displaced laterally (Fig. 28-13). These are then gently guided toward the fundus, while the head is simultaneously directed toward the pelvis. If the forward roll is unsuccessful, a backward flip is attempted. ECV attempts are discontinued for excessive discomfort, for persistently abnormal fetal heart rate, or after multiple failed attempts. Failure is not always absolute. Ben-Meir and colleagues (2007) reported a spontaneous version rate of 7 percent among 226 failed versions—2 percent among nulliparas and 13 percent among multiparas.

If ECV is successful, a nonstress test is repeated until a normal test result is obtained. A transient abnormal fetal heart rate tracing during or after ECV complicates 6 to 9 percent of cases. This should prompt a traditional resuscitative response with intravenous fluids, oxygen, and lateral tilt. Rates of abnormal tracings prompting immediate cesarean delivery range from only 0.2 to 0.4 percent (Collaris, 2004; Grootscholten, 2008).

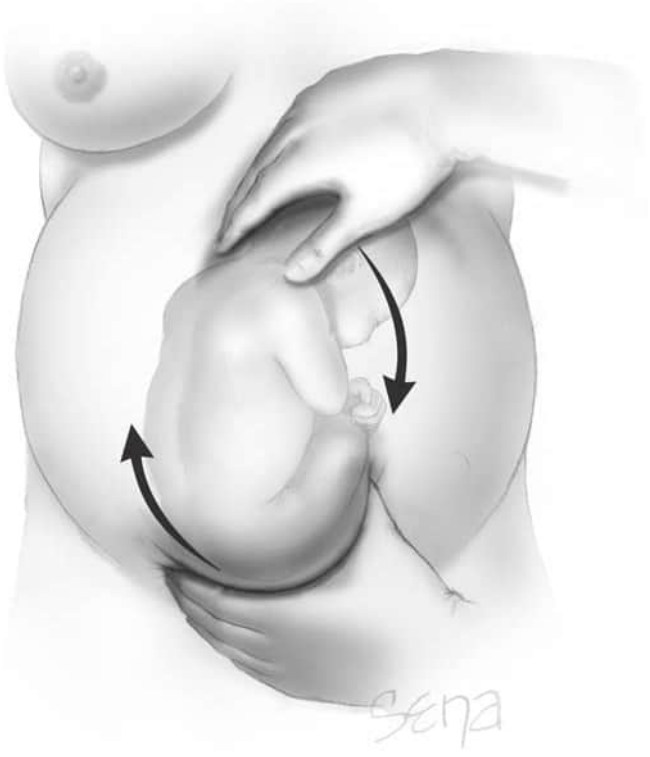

FIGURE 28-13 External cephalic version. With an attempted forward roll, clockwise pressure is exerted against the fetal poles.

Once resolved, Kuppens and coworkers (2017) found that a transient abnormal tracing did not predict later fetal distress in subsequent labor.

If ECV is completed before 39 weeks' gestation, awaiting spontaneous labor and fetal maturity is preferred. In some studies, immediate labor induction is linked to higher cesarean delivery rates (Burgos, 2015; Kuppens, 2013).

Tocolysis

By relaxing the uterus prior to an ECV attempt, tocolysis raises success rates. Most data support the use of the betamimetics terbutaline and ritodrine for this (Cluver, 2015). In one such trial, Fernandez and coworkers (1996) reported that the success rate with subcutaneous terbutaline—52 percent—was significantly higher than without—27 percent. Our policy at Parkland Hospital is to administer 250 μg of terbutaline subcutaneously to most women before attempted ECV. When maternal tachycardia—a known side effect of terbutaline—is noted, the attempt is begun. Terbutaline readily crosses the placenta, and mild elevation of fetal heart rate baseline also is possible (Ingemarsson, 1981; Roth, 1990). Data are limited and in some cases are nonsupportive for other agents that include calcium-channel blockers, such as nifedipine; nitric oxide donors, such as nitroglycerin; the oxytocin-receptor antagonist atosiban; and another betamimetic salbutamol (Burgos, 2010; Cluver, 2015; Hilton, 2009; Levin, 2019; Vani, 2009; Wilcox, 2011).

Conduction Analgesia

Epidural analgesia coupled with tocolysis has been reported to raise ECV success rates compared with tocolysis alone (Goetzinger, 2011; Magro-Malosso, 2016). Moreover, rates of complications that include fetal heart rate aberrations, emergency cesarean delivery, or placental abruption are not greater with regional analgesia. In trials, spinal and epidural have both shown success and are reasonable options (Khaw, 2015; Weiniger, 2010). Although uncommon, risks specific to regional analgesia, such as spinal headache, are possible. Currently, the superior technique and best drugs to administer are unclear. In contrast, from limited data, intravenous sedation or nitrous oxide does not appear to improve ECV success (Burgos, 2016; Dochez, 2019; Khaw, 2015; Straube, 2021).

■ Moxibustion

This is a traditional Chinese medicine technique that burns a cigarette-shaped stick of ground *Artemisia vulgaris*—which is also known as mugwort or in Japanese as *moxa.* At the BL 67 acupuncture point, the stick is directly placed against the skin or indirectly heats an acupuncture needle at the site to increase fetal movement and promote spontaneous breech version (Ewies, 2002). It is performed usually between 33 and 36 weeks' gestation to permit a trial of ECV if not successful. Results from randomized controlled studies are conflicting (Bue, 2016; Coulon, 2014; Coyle, 2012; Sananes, 2016; Vas, 2013).

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CHAPTER 29

Operative Vaginal Delivery

Operative vaginal delivery (OVD) is birth accomplished with assistance from forceps or a vacuum-cup device. Once these are applied to the fetal head, outward traction generates forces that augment maternal pushing to deliver the fetus.

INCIDENCE AND INDICATIONS

From national data, forceps or vacuum-assisted vaginal delivery aided 3.1 percent of births in the United States in 2015. This is a decline from 9 percent in 1990 (Martin, 2017). For these procedures, a vacuum is disproportionately selected, and the vacuum-to-forceps delivery ratio approximates 4:1 (Yeomans, 2010). Most of these procedures are successful in effecting vaginal birth. From 2006 United States data, only 0.4 percent of forceps trials and 0.8 percent of vacuum extraction attempts failed to result in vaginal birth (Osterman, 2009). In the specific group of nulliparas with term gestations, higher failure rates of 4.4 and 6.4 percent, respectively, were found in a study of 25 academic hospitals (Bailit, 2016).

If technically safe, termination of second-stage labor by OVD is considered for any condition that threatens the mother or fetus and that is likely to be relieved by delivery. Of maternal indications, the most common are maternal exhaustion and prolonged second-stage labor. However, a specific, maximum second-stage length beyond which all women should be considered for OVD has not been defined (American College of Obstetricians and Gynecologists, 2019). Other maternal reasons are preexisting or intrapartum conditions that limit effective pushing or warrant expedited delivery. Severe or acute pulmonary compromise, decompensation from intrapartum infection, neurological disease, and serious cardiac disorders are examples. Frequent fetal indications include nonreassuring fetal heart rate and premature placental separation (Schuit, 2012).

CLASSIFICATION AND PREREQUISITES

Classification of OVD is summarized in Table 29-1. It emphasizes that station and rotation are the two most important discriminators of risk for both mother and neonate. Station is measured by the number of centimeters, either above or below, an anatomical zero station, which is a line drawn between the ischial spines. Stations range from −5 to 0 to +5. Procedures are categorized as outlet, low, and midpelvic, and most are low or outlet deliveries. *High forceps, in which instruments are applied above 0 station, have no place in current obstetrics*.

To aid patient selection, the Society for Maternal–Fetal Medicine (2020) published a preprocedural checklist and documentation template. Once station and rotation are determined, the prerequisites listed in Table 29-1 are assessed. For vacuum extraction, fetuses ideally are not younger than 34 weeks' gestation because of cranial hemorrhage vulnerability at earlier ages (Åberg, 2014). Also prior to vacuum use, although infrequently used in the United States, fetal scalp blood sampling should not have been recently performed. Of requisites, ascertaining

TABLE 29-1. Operative Vaginal Delivery Prerequisites and Classification According to Station and Rotation[a]

Procedure	Criteria
Outlet forceps	Scalp is visible at the introitus without separating the labia Fetal skull has reached pelvic floor Fetal head is at or on perineum Head is OA or OP ***or*** Head is right or left OA or OP position but rotation ≤45 degrees
Low forceps (2 types)	Fetal station is ≥+2 cm but not on the pelvic floor, and: (a) Rotation ≤45 degrees is required ***or*** (b) Rotation >45 degrees is required
Midforceps	Fetal station is between 0 and +2 cm

Prerequisites		
Engaged head	Experienced operator	No fetal coagulopathy
Vertex presentation[b,c]	Ruptured membranes	No fetal demineralization disorder
Known fetal head position	Completely dilated cervix	Informed consent completed
CPD not suspected	Adequate anesthesia	Willingness to abandon OVD
Fetal weight estimated	Emptied maternal bladder	

[a]Classification for the vacuum delivery is the same as for forceps except that vacuum is used for traction but not rotation.
[b]Forceps, but not vacuum extractor, may be used for delivery of a mentum anterior face presentation.
[c]Piper forceps may be used to deliver the head during breech delivery.
CPD = cephalopelvic disproportion; OA = occiput anterior; OP = occiput posterior; OVD = operative vaginal delivery.

correct head position is essential, and Figure 29-1 shows fetal skull anatomy. In unclear cases, sonography can help identify fetal orbits and nasal bridge to aid orientation (Ghi, 2018).

Regional analgesia is preferable for low or midpelvic procedures. Pudendal blockade may prove adequate for outlet deliveries. As a causative factor, newer epidural methods or placement during early labor do not raise OVD rates (Anim-Somuahm, 2018; Liu, 2004).

The bladder is emptied to provide additional pelvic space and minimize bladder trauma. Urinary retention and bladder dysfunction are frequent short-term effects of OVD (Mulder, 2012; Pifarotti, 2014). Notably, episiotomy and epidural analgesia, both common associates of OVD, also are risks for urinary retention. Retention usually resolves after 24 to 48 hours of passive catheter bladder drainage (Chap. 36, p. 643).

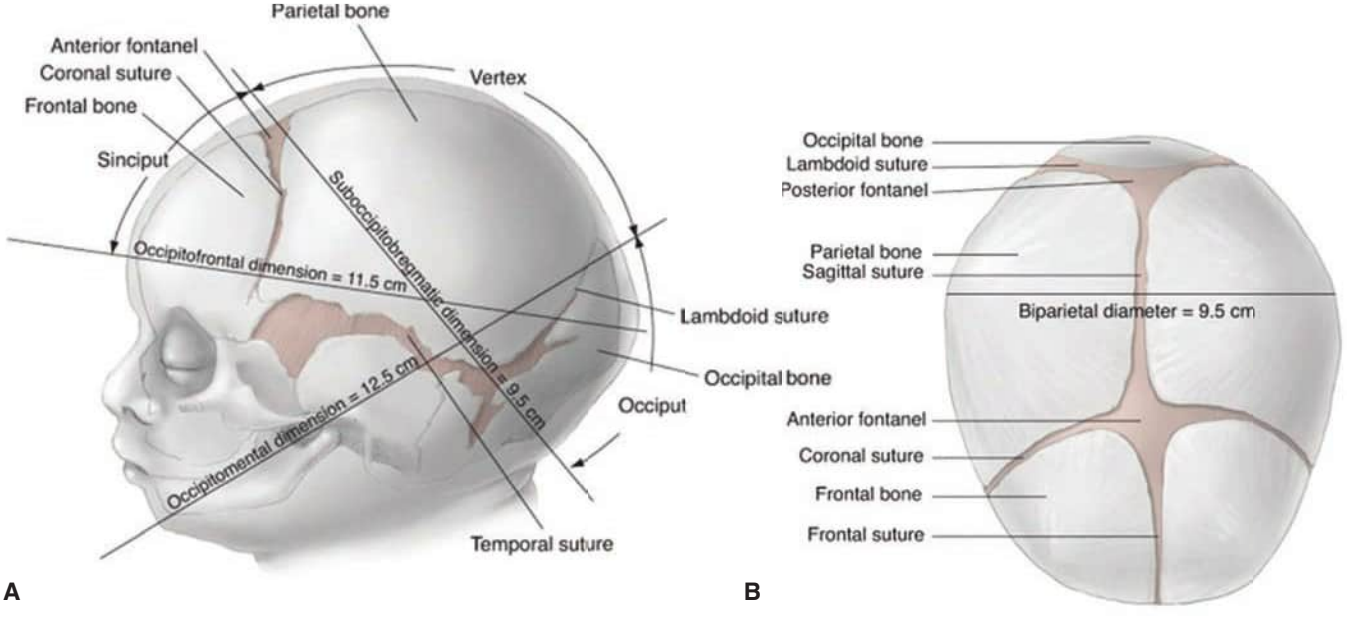

FIGURE 29-1 Fetal head **(A–B)** at term showing fontanels, sutures, and various dimensions.

MORBIDITY

Maternal Morbidity

OVD carries increased risk of certain morbidities for both mother and fetus. In general, a higher station and greater degrees of rotation raise procedure difficulty and the chance of injury. Morbidity is most properly compared with morbidity from cesarean delivery and not with that from spontaneous birth. This is the most appropriate comparator because the alternative to indicated OVD is cesarean delivery.

Lacerations

The very indications that prompt OVD are among those that also increase the need for episiotomy and the likelihood of lacerations (de Leeuw, 2008). That said, higher rates of third- and fourth-degree perineal lacerations, vaginal wall lacerations, and less often cervical tears do complicate OVD compared with spontaneous birth (Friedman, 2015; Gurol-Urganci, 2013; Landy, 2011). These rates with OVD are also substantially higher than with cesarean delivery. Third- and fourth-degree perineal lacerations are grouped as *obstetrical anal sphincter injuries (OASIS)*. In general, these tears more frequently attend forceps delivery compared with vacuum extraction, and especially if an episiotomy is midline (Kudish, 2006; O'Mahony, 2010).

With OVD, *indicated* episiotomy rather than *routine* use is recommended. If required, a mediolateral episiotomy affords greater protection against OASIS than midline incision (Gurol-Urganci, 2013; Jangö, 2014; van Bavel, 2018). But, short-term rates of pain and dyspareunia are similar or increased with mediolateral episiotomy (Chap. 27, p. 510). As another OASIS protection, early forceps disarticulation and removal can avoid the full perineal distention created by the blades and crowning head. Moreover, cessation of maternal pushing during disarticulation or as the head begins to crown allows the clinician sole control of outward forces against the perineum. Similarly, adding a dedicated assistant to bolster the perineum can lower OASIS rates, and this is our practice (Wan, 2020). Last, OASIS are more common with an occiput posterior (OP) position (Damron, 2004). Thus, manual or forceps rotation to an occiput anterior (OA) position may lower rates of lower reproductive tract injury (Bradley, 2013).

Infection and Subsequent-pregnancy Morbidity

As detailed in Chapter 30 (p. 548), cesarean delivery carries greater maternal morbidity compared with spontaneous birth. For OVD, in one study of more than 1 million births, cesarean delivery, but not OVD, was a risk for peripartum hysterectomy (Spiliopoulos, 2011). Further, avoiding cesarean delivery can minimize rates of subsequent pregnancy complications, such as placenta previa, placenta accreta spectrum, uterine rupture, and adhesion-related surgical organ injury.

In addition, postpartum wound or uterine infection is more frequent in women following cesarean compared with OVD (Bailit, 2016; Halscott, 2015). Still, to address peripartum infection, investigators in the ANODE trial randomly assigned nearly 3500 gravidas undergoing OVD to receive either placebo or a single intravenous dose of amoxicillin plus clavulanic acid (Knight, 2019). The puerperal infection rate was 11 percent after antibiotic prophylaxis compared with 19 percent in those given placebo. Notably, these infections often coincide with long labors and multiple cervical examinations, both of which are common with women requiring OVD. Thus, we believe that provision of antibiotics to those undergoing OVD without other infection-related risks warrants further study. Indeed, the American College of Obstetricians and Gynecologists (2020a) notes that this prophylaxis is *reasonable* but recommends against routine antibiotic prophylaxis for all women undergoing OVD. However, the College (2020b) does note that a single antibiotic dose with third- and fourth-degree perineal laceration is reasonable. Several studies support this practice (Duggal, 2008; Lewicky-Gaupp, 2015; Stock, 2013a).

Pelvic Floor Disorders

This term encompasses urinary incontinence, anal incontinence, and pelvic organ prolapse (POP). OVD has been implicated as a possible risk for each. Proposed mechanisms include structural compromise or pelvic floor denervation secondary to forces exerted during delivery.

For urinary incontinence, parity and specifically vaginal delivery are risk factors (Gyhagen, 2013; Rortveit, 2003). But, many studies do not support a higher risk from OVD compared with the risk from vaginal birth alone (Gartland, 2016; Leijonhufvud, 2011; MacArthur, 2016).

Evidence linking anal incontinence with OVD is conflicting. Some studies show that OASIS, but not delivery mode, is the main etiological link (Bols, 2010; Evers, 2012; Nygaard, 1997). In contrast, others directly associate OVD with anal incontinence (Dolan, 2010; MacArthur, 2013). But, these studies may not be incongruous—recall that OVD is associated with increased rates of OASIS. Importantly, several studies and reviews have not found cesarean delivery to be protective long term against anal incontinence (Nelson, 2010).

Similarly for POP, evidence linking it to OVD is mixed (Gyhagen, 2013; Volløyhaug, 2015). First, pelvic floor mechanisms leading to POP are complex and incompletely defined (Gordon, 2019). Despite this, obstetrical avulsion of the levator ani muscle from the pelvic sidewall has been implicated, and OVD, especially forceps delivery, is one risk for this injury (DeLancey, 2007; Dietz, 2008; Friedman, 2019). Again, the pelvic floor injury rather OVD itself may be the causative agent, as those with OVD but no avulsion did not suffer greater POP rates in one recent analysis (Handa, 2019).

Perinatal Morbidity

Acute Perinatal Injury

OVD carries higher risk for fetal injury than cesarean delivery or spontaneous birth. Both OVD methods are implicated, and factors can include delivery duration and the number of pulls or cup pop-offs (Åberg, 2019; Levin, 2019; Miller, 2020). Injuries are more frequent with vacuum extraction, and injuries with this device include cephalohematoma, subgaleal hemorrhage, retinal hemorrhage, neonatal jaundice secondary to these hemorrhages, clavicular fracture, and scalp lacerations. Cephalohematoma and subgaleal hemorrhage are both extracranial

lesions illustrated in Figure 33-2 (p. 608). Shoulder dystocia has been linked to both methods (Dall'Asta, 2016). Forceps delivery has higher rates of facial nerve injury, brachial plexus injury, depressed skull fracture, and corneal abrasion (American College of Obstetricians and Gynecologists, 2020a; Demissie, 2004; Dupuis, 2005). With intracranial hemorrhage, some studies have associated vacuum extraction with higher rates, whereas others show similar rates with either OVD method (Towner, 1999; Wen, 2001; Werner, 2011).

Compared with cesarean delivery, OVD carries higher risk of extracranial hematomas, fractures, nerve injuries, retinal hemorrhage, and head lacerations. However, rates of fetal acidemia or hypoxic encephalopathy are not higher with OVD compared with second-stage cesarean delivery (Bailit, 2016; Contag, 2010; Walsh, 2013). Intracranial hemorrhage rates are similar among newborns delivered by vacuum extraction, forceps, or cesarean delivery during labor (Towner, 1999). But, intracranial hemorrhage rates are higher than among those delivered spontaneously or by cesarean delivery before labor. These authors suggest that the common risk factor for intracranial hemorrhage is abnormal labor. Werner and associates (2011), in their evaluation of more than 150,000 singleton deliveries, reported that forceps delivery was associated with fewer total neurological complications that included seizures, intraventricular hemorrhage, and subdural hemorrhage compared with vacuum-assisted birth or any cesarean delivery.

Compared with rotational OVD, second-stage cesarean delivery has similar maternal and neonatal morbidity rates (Aiken, 2015; Bahl, 2013; Stock, 2013b). For example, in their large series, Tempest and associates (2013) found similar morbidity rates among malpositioned fetuses during second-stage labor that underwent Kielland rotation, rotational vacuum extraction, or emergency cesarean delivery.

Midforceps by definition are performed from a higher station. The bulk of data are from older studies, and most show comparable neonatal morbidity between low and midforceps procedures (Dierker, 1985; Gilstrap, 1984). In a recent report also comparing these two, Ducarme and coworkers (2015) found comparable neonatal and maternal composite morbidity scores.

Comparing midpelvic OVD and second-stage cesarean delivery, most studies support neonatal safety (Bashore, 1990; Cibils, 1990; Hagadorn-Freathy, 1991). But, others have found increased rates of trauma and umbilical cord blood acidemia with midforceps delivery (Robertson, 1990). More recently, Muraca and associates (2018) compared midpelvic OVD methods against second-stage cesarean delivery. For the indication of dystocia, fetal and maternal morbidity composite scores were higher with OVD. With distress as the indication, the neonatal morbidity score was greater only with midpelvic vacuum-assisted OVD, whereas the maternal morbidity score was higher only with midforceps. In another study comparing both midpelvic OVD methods, maternal morbidity was greater with forceps, and neonatal morbidity differed only in a higher cephalohematoma rate with vacuum-assisted delivery (Baerthlein, 1986).

Mechanisms of Acute Injury

The types of fetal injury with OVD can usually be explained by the forces exerted. In cases of cephalohematoma or subgaleal hemorrhage, suction and perhaps rotation during vacuum extraction may lead to a primary vessel shearing. Intracranial hemorrhage may result from skull fracture that lacerates vessels or from vessel rupture alone due to exerted forces. With facial nerve palsy, one of the forceps blades compresses the nerve against the facial bones. To explain brachial plexus injury, Towner and Ciotti (2007) proposed that as the fetal head descends down the birth canal, the shoulders may stay above the pelvic inlet. Thus, similar to shoulder dystocia at the symphysis, this "shoulder dystocia at the pelvic inlet" is overcome by traction forces but with concomitant stretch on the brachial plexus.

Long-term Infant Morbidity

Evidence regarding long-term neurodevelopmental outcomes in children born by OVD is reassuring (Seidman, 1991; Wesley, 1992). Moreover, no association between forceps delivery and later epilepsy was found in a cohort study of more than 21,000 births (Murphy, 2004). In their review, O'Callaghan and colleagues (2011) reported no link between cerebral palsy and OVD. Last, the incidence of neurodevelopmental morbidity was similar in those undergoing successful forceps delivery, failed forceps with cesarean delivery, or cesarean delivery without forceps in one study (Bahl, 2007). Similarly, with midpelvic OVD, long-term neurodevelopment is not harmed in most analyses (Dierker, 1986; Friedman, 1984; Nilsen, 1984; Wesley, 1993).

Trial of Operative Vaginal Delivery

If an attempt to perform OVD is expected to be difficult, it should be considered a trial. Moving the woman to an operating room for this attempt, which could be followed by immediate cesarean delivery if OVD fails, has merit. If forceps cannot be satisfactorily applied, the procedure is stopped. Either a trial of vacuum-assisted delivery or cesarean delivery is then performed. With the former, if the fetus does not descend with traction, the trial should be abandoned and cesarean delivery performed.

With such caveats, cesarean delivery after an OVD attempt was not associated with adverse neonatal outcomes if the fetal heart rate was concurrently reassuring (Alexander, 2009). A similar study evaluated 122 women who had a trial of midpelvic OVD in a setting with full preparations for cesarean delivery (Lowe, 1987). Investigators found no significant difference in immediate neonatal or maternal morbidity compared with that of 42 women delivered for similar indications by cesarean but without such a trial. Conversely, in 61 women who had "unexpected" vacuum or forceps failure in which there was no prior preparation for immediate cesarean delivery, neonatal morbidity was higher.

Some factors associated with OVD failure are persistent OP positions and birthweight >4000 g (Ben-Haroush, 2007; Verhoeven, 2016). However, Palatnik and coworkers (2016) found that risk factors poorly predicted success. In general, to avert morbidity with failed OVD, the American College of Obstetricians and Gynecologists (2020a) cautions that these trials should be attempted only if the clinical assessment suggests a successful outcome. We also emphasize proper training.

Sequential instrumentation most often involves an attempt at vacuum-assisted OVD followed by one with forceps. This sequence likely reflects the overall higher completion rate with forceps. However, this practice significantly raises fetal trauma risks (Dupuis, 2005; Gardella, 2001; Murphy, 2011). The American College of Obstetricians and Gynecologists (2020a) recommends against the sequential use of instruments unless there is a "compelling and justifiable reason."

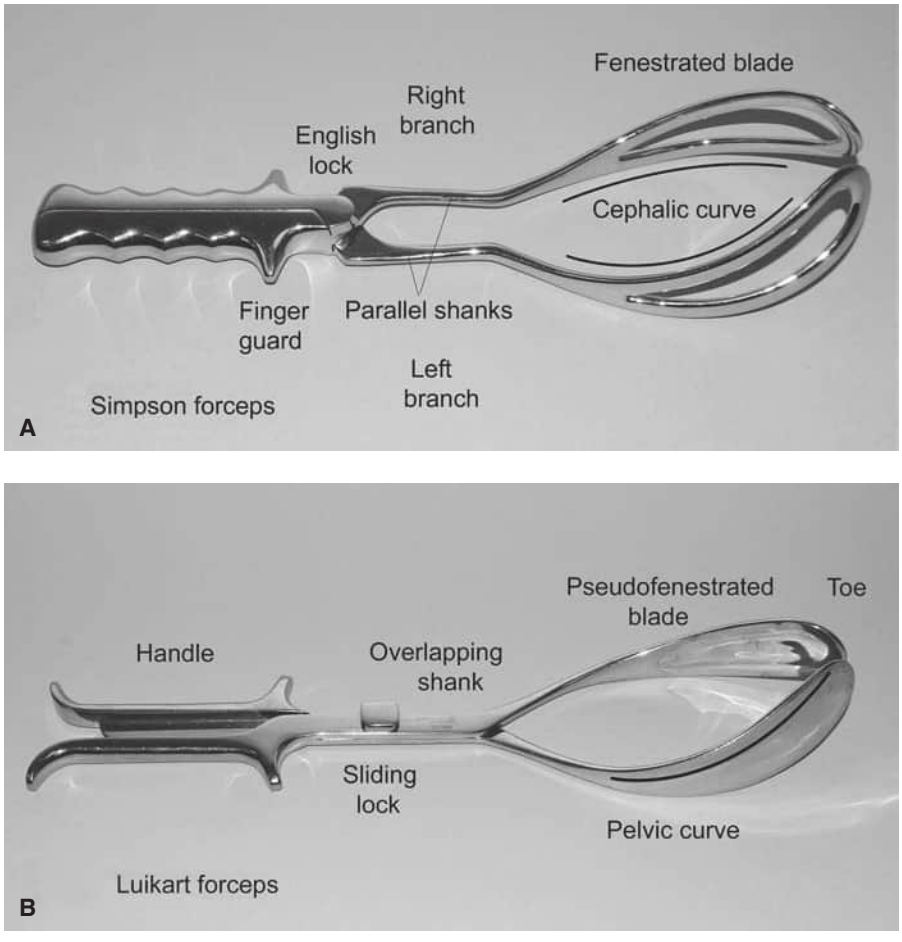

FIGURE 29-2 A. Simpson forceps have fenestrated blades, parallel shanks, and English lock. The cephalic curve accommodates the fetal head. **B.** Luikart forceps have pseudofenestrated blades, overlapping shanks, a sliding lock, and tongue-in-groove handles. The pelvic curve (*black curve*) is marked in this example.

FORCEPS DELIVERY

Design

Forceps refers to the paired instrument, and each member of this pair is called a branch. Branches are designated left or right according to the side of the maternal pelvis to which they are applied (Fig. 29-2A). Each branch has four components: blade, shank, lock, and handle (see Fig. 29-2B). Each blade has a toe, a heel, and two curves. Of these, the outward cephalic curve conforms to the round fetal head, whereas the upward pelvic curve corresponds to the curve of the birth canal. Some blades are *solid*, meaning smooth on both surfaces. Others have an opening within or a depression along the blade surface and are termed *fenestrated* or *pseudofenestrated*, respectively. A true window in the blade reduces the degree of head slippage within the blades during forceps rotation. Disadvantageously, it can increase blade thickness and friction against the vaginal wall. With pseudofenestration, the forceps blade is smooth on the outer maternal side but indented on the inner fetal surface. The goal is to reduce head slipping yet improve the ease and safety of application and removal of forceps. In most situations, however, despite these subtle differences, any are appropriate.

The blades are connected to shanks, which may be parallel or overlapping. *Parallel shanks* limit compression of blades against the fetal head and may be helpful with deliveries employing greater forces. These shanks, however, add width against the introitus. In comparison, overlapping shanks raise compression forces but distend the perineum less. This may offer greatest advantage for outlet deliveries.

Locks are found on all forceps and help to connect the right and left branches and stabilize the instrument. They can be located at the end of the shank nearest to the handles (English lock), at the ends of the handles (pivot lock), or along the shank (sliding lock). Although varied in design, handles, when squeezed, raise compression forces against the fetal head. Thus, forces to consider include traction and compression.

Blade Application and Delivery

Forceps blades grasp the head and are applied according to fetal head position. If the head is in an OA position, two or more fingers of the right hand are introduced inside the left posterior portion of the vulva and advanced into the vagina beside the fetal head. The handle of the left branch is grasped between the thumb and two fingers of the left hand (Fig. 29-3). The blade tip is then gently introduced along the posterior left vaginal wall. It is swept upward and inward between the fetal head and the palmar surface of the fingers (Fig. 29-4). This blade can be held in position by an assistant. For application of the right blade, two or more fingers of the left hand are introduced into the right posterior portion of the vagina to serve as a guide for the right blade. This blade is held in the right hand and introduced into the vagina. With each blade, the thumb is positioned behind the heel, and most of the insertion force comes from this thumb (Fig. 29-5). If the head is positioned in a left OA (LOA) or right OA (ROA) position, then the lower of the two blades is typically placed first.

The blades are constructed so that their cephalic curve is closely adapted to the sides of the fetal head (Fig. 29-6). The fetal head is perfectly grasped only when the long axis of the blades corresponds to the occipitomental diameter (see Fig. 29-1). As a result, most of the blade lies over the lateral face.

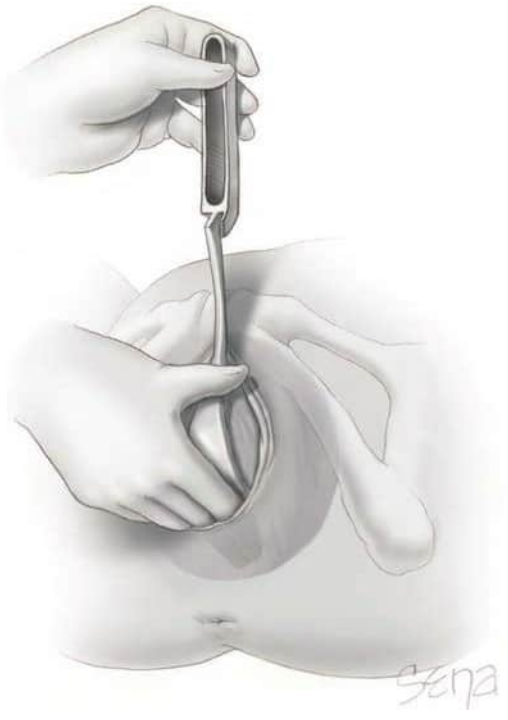

FIGURE 29-3 For OA or LOA positions, the left handle of the forceps is held in the left hand. The blade is introduced into the left side of the pelvis between the fetal head and the fingers of the operator's right hand.

Suboptimal blade placement can increase morbidity (Ramphul, 2015). For OA positions, appropriately applied blades are equidistant from the sagittal suture, and each blade is equidistant from its adjacent lambdoid suture. In OP positions, blades are symmetrically placed relative to the sagittal suture and to each coronal suture. After correct positioning, the branches can be articulated. If branches do not articulate, the blade's relationships to the sutures are reassessed. Applied in this way, forceps should not slip, and traction may be applied most advantageously. With most forceps, if one blade is applied over the brow and the other

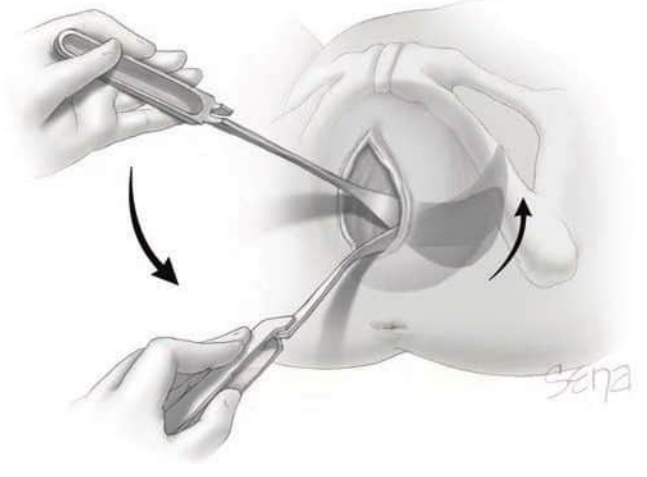

FIGURE 29-4 Insertion arc of the blade. Importantly, the thumb of the right hand, not shown here, guides the blade during placement.

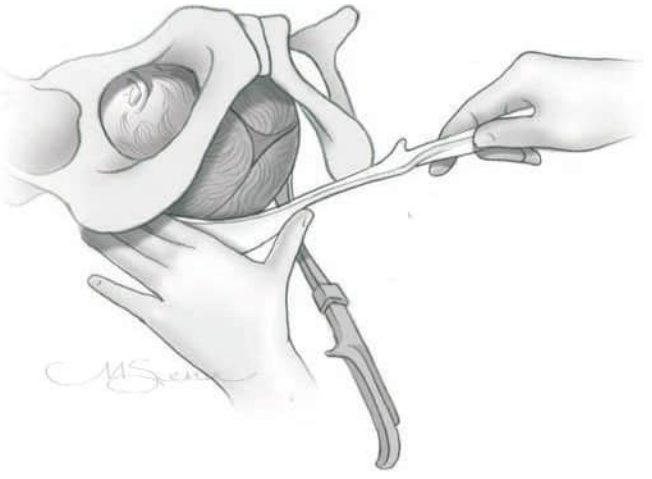

FIGURE 29-5 In applying the second blade, insertional force is generated mainly by the thumb. (Reproduced with permission from Yeomans ER: Operative vaginal delivery. In Yeomans ER, Hoffman BL, Gilstrap LC III, et al (eds): Cunningham and Gilstrap's Operative Obstetrics, 3rd ed. New York, NY: McGraw Hill; 2017.)

over the occiput, the instrument cannot be locked, or if locked, the blades will slip off when traction is applied.

With both branches in place, slow articulation of the handles will also typically correct mild asynclitism. For greater asynclitism, Luikart forceps can be placed and once positioned, one handle will extend further than the other along their long axis. Asynclitism is resolved by pulling and/or pushing each respective branch within the sliding lock along the instrument's long axis until the finger guards align.

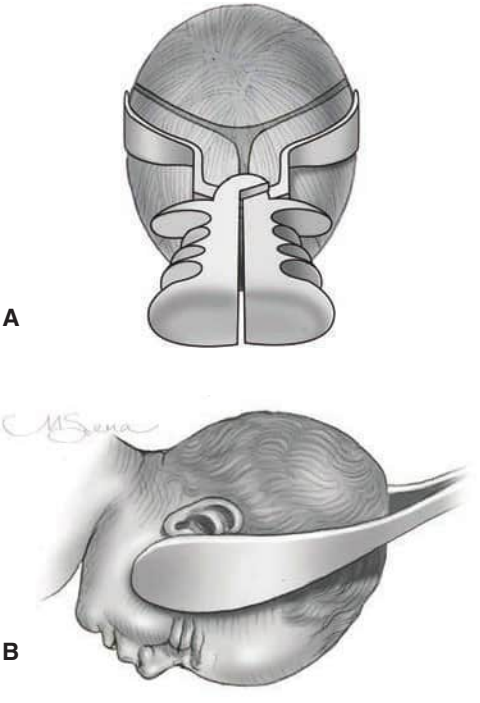

FIGURE 29-6 A. The forceps are symmetrically placed and articulated. **B.** The vertex is OA. (Reproduced with permission from Yeomans ER: Operative vaginal delivery. In Yeomans ER, Hoffman BL, Gilstrap LC III, et al (eds): Cunningham and Gilstrap's Operative Obstetrics, 3rd ed. New York, NY: McGraw Hill; 2017.)

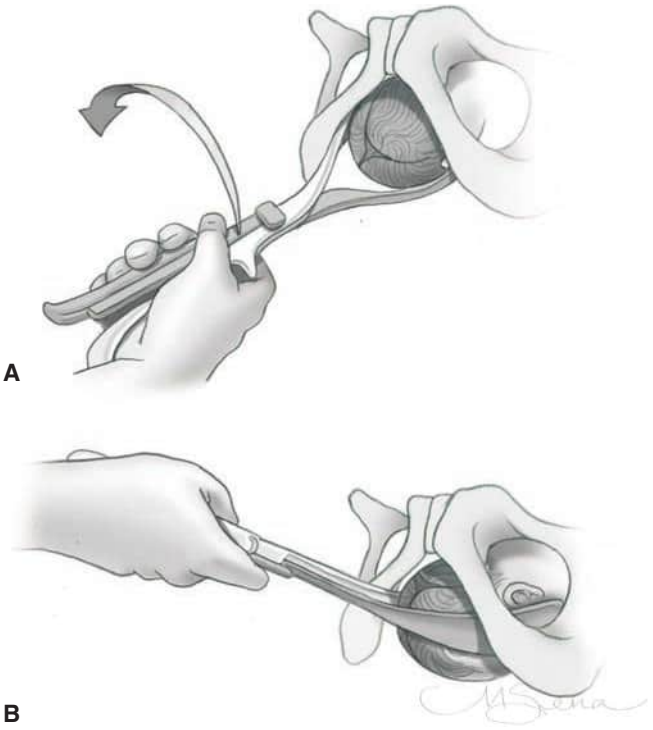

FIGURE 29-7 If LOA, the vertex is rotated from this position to OA (*arrow*). (Reproduced with permission from Yeomans ER: Operative vaginal delivery. In Yeomans ER, Hoffman BL, Gilstrap LC III, et al (eds): Cunningham and Gilstrap's Operative Obstetrics, 3rd ed. New York, NY: McGraw Hill; 2017.)

Once blades are placed satisfactorily, rotation to OA position is performed before traction is applied (Fig. 29-7). Next, gentle, intermittent, downward and outward traction is exerted concurrent with maternal efforts until the perineum begins to bulge. For most stations, the initial direction of traction is downward and brings the head beneath the symphysis.

With head descent, the vector of forces changes continuously and are gradually directed upward (Fig. 29-8). During the birth of the head, mechanisms of spontaneous delivery should be simulated as closely as possible. As a teaching tool for this, a *Bill axis traction device* can be attached over the finger guards of most forceps. The instrument has an arrow and indicator line. When the arrow points directly to the line, traction is along the path of least resistance.

It is impossible to ascertain the amount of force exerted by forceps for an individual patient. Thus, traction is ideally intermittent and relieved between contractions, as in spontaneous labor. Except when urgently indicated, delivery should be sufficiently slow, deliberate, and gentle to prevent undue head compression. It is preferable to apply traction only with each uterine contraction. Maternal pushing will augment these efforts.

With traction, as the occiput distends the vulva, an episiotomy may be performed if needed. The delivery may be completed in several ways. Some clinicians keep the forceps in place to control the head. However, this blade volume adds to vulvar distention and raises risks for laceration or episiotomy. To prevent this, the forceps may be removed, and delivery is then completed by maternal pushing (Fig. 29-9). Importantly, if blades are disarticulated and removed too early, the head

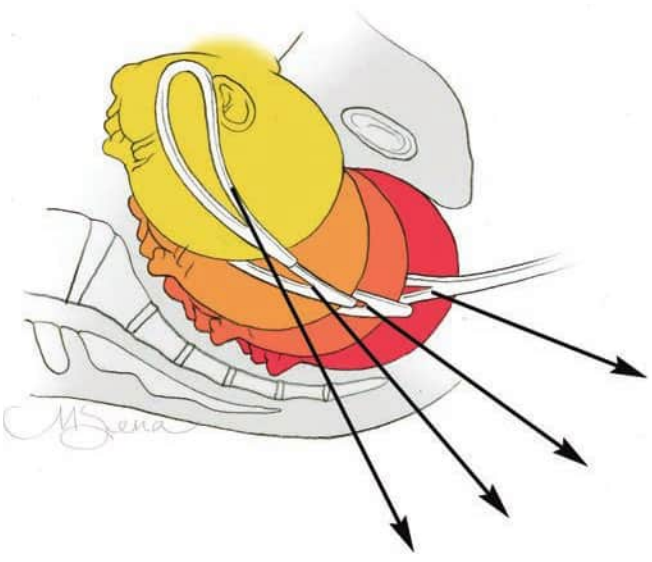

FIGURE 29-8 With low forceps, the direction of gentle traction for delivery of the head is indicated (*arrows*). (Reproduced with permission from Yeomans ER: Operative vaginal delivery. In Yeomans ER, Hoffman BL, Gilstrap LC III, et al (eds): Cunningham and Gilstrap's Operative Obstetrics, 3rd ed. New York, NY: McGraw Hill; 2017.)

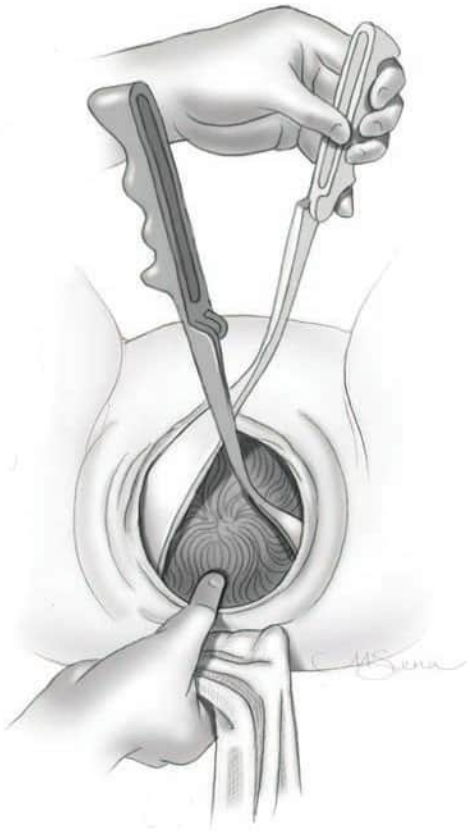

FIGURE 29-9 Branches are removed in the opposite order from that in which they were originally placed. The fingers of the right hand, covered by a sterile towel, bolster the perineum. The thumb is placed directly on the head to prevent sudden egress. (Reproduced with permission from Yeomans ER: Operative vaginal delivery. In Yeomans ER, Hoffman BL, Gilstrap LC III, et al (eds): Cunningham and Gilstrap's Operative Obstetrics, 3rd ed. New York, NY: McGraw Hill; 2017.)

may recede and prolong delivery. Pushing in some cases may be aided by the modified Ritgen maneuver. We emphasize bolstering of the perineum to control outward forces.

Manual Rotation

In many cases, OT and OP head positions are often imperfectly flexed and present a wider head diameter. This can slow fetal descent and lengthen second-stage labor. By manually rotating the fetal occiput into the anterior pelvis (OA positions), cephalopelvic proportions improve to help hasten spontaneous birth. This is usually reserved for second-stage labor. Compared with no attempt, manual rotation is associated with lower rates of cesarean delivery, OVD, severe perineal laceration, and chorioamnionitis (Blanc, 2021; Shaffer, 2011). If OVD is still required, the new OA position lowers rates of perineal trauma.

In the simplest cases, *digital rotation* can correct OT or OP positioning. With head molding, the sutures override one another to create a bony ridge. Two fingers hooked against this ridge and forces directed parallel to the skull can rotate the occiput toward the anterior pelvis. This is done between contractions, and advancements are then held in place during pushing. Progressive degrees of rotation are attained with each attempt, and several may be needed to ultimately rotate the occiput into the anterior pelvis.

Instead, with *manual rotation*, an open hand is inserted into the vagina. For ROP position, the right palm cups the fetal head and straddles the sagittal suture. The operator's fingers wrap to one side of the fetal face, and the thumb extends along the other side. Rotation is clockwise to bring the occiput to an ROA position (Fig. 29-10). With LOP position, rotation is counterclockwise with the left palm. Three actions are performed simultaneously between contractions. The fetal head is flexed to provide a smaller diameter for rotation and subsequent descent within the pelvis. Next, slight *destationing* of the fetal head moves the head to a level in the maternal pelvis with sufficient room to complete the rotation. Importantly, destationing should not be confused with *disengaging* the fetal head, which is proscribed. Third, we and others prefer also to place the other hand externally on the corresponding side of the maternal abdomen to pull the back of the fetus up and toward the midline in synchrony with internal head rotation. Barth (2015) provides an excellent summary of this technique.

Le Ray and associates (2007, 2013) reported a success rate >90 percent with manual rotation. Complication were uncommon. In their report of 796 rotations, no cords prolapsed. Two women sustained cervical lacerations, which required simple vaginal repair. Notably, this study allowed rotations at advanced cervical dilation prior to second-stage labor, which may have enhanced cervical injury risk. In 71 percent, fetal heart rate (FHR) was normal during rotation, but severe FHR abnormalities were noted in 10 percent. However, the need for cesarean delivery after successful manual rotation was not associated with FHR abnormalities. Failure to rotate the head does not mandate cesarean delivery, and options are described next.

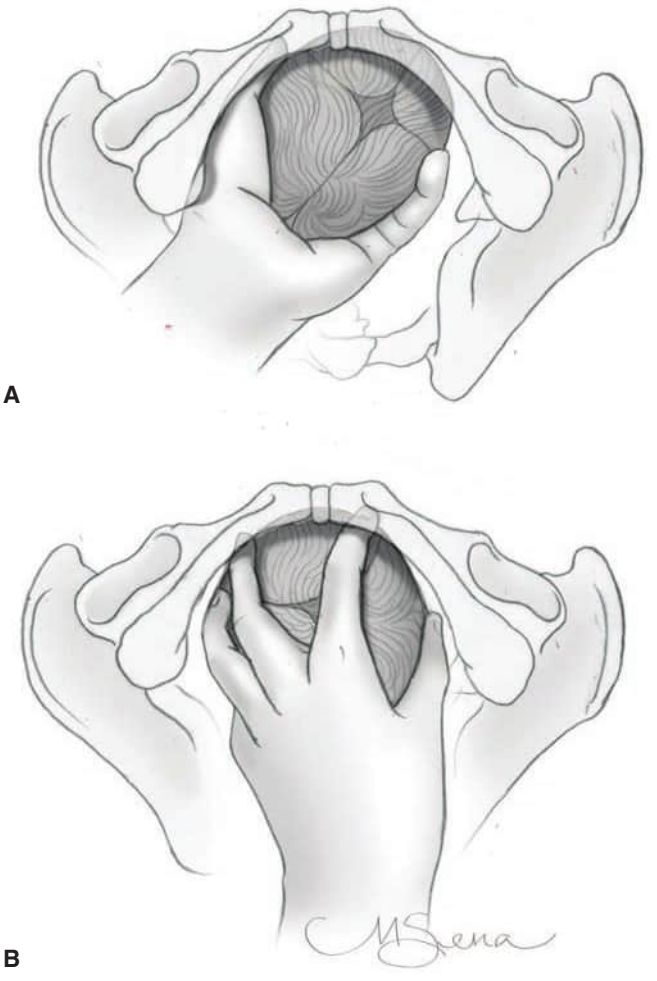

FIGURE 29-10 A. Manual rotation using the left hand, palm-up, to rotate from ROP. **B.** The head is flexed and destationed during clockwise rotation to reach an OA position. (Reproduced with permission from Yeomans ER: Operative vaginal delivery. In Yeomans ER, Hoffman BL, Gilstrap LC III, et al (eds): Cunningham and Gilstrap's Operative Obstetrics, 3rd ed. New York, NY: McGraw Hill; 2017.)

Persistent Occiput Posterior Positions

In cases with persistent OP positioning, the head may spontaneously deliver OP, may be manually or instrumentally rotated to an OA position, or may be delivered OP by forceps or vacuum (Bertholdt, 2019). In many cases, the cause of a persistent OP position and of the difficulty in accomplishing rotation is an anthropoid pelvis. This architecture opposes rotation and predisposes to posterior delivery (Fig. 2-16, p. 29).

With forceps delivery from an OP position, downward and outward traction is applied until the base of the nose passes under the symphysis (Fig. 29-11). The handles are then slowly elevated until the occiput gradually emerges over the perineum's fourchette. The forceps are directed downward again, and the nose, mouth, and chin successively emerge from the vulva.

OP delivery causes greater vulvar distention, and an episiotomy may be needed. OP deliveries have a higher incidence

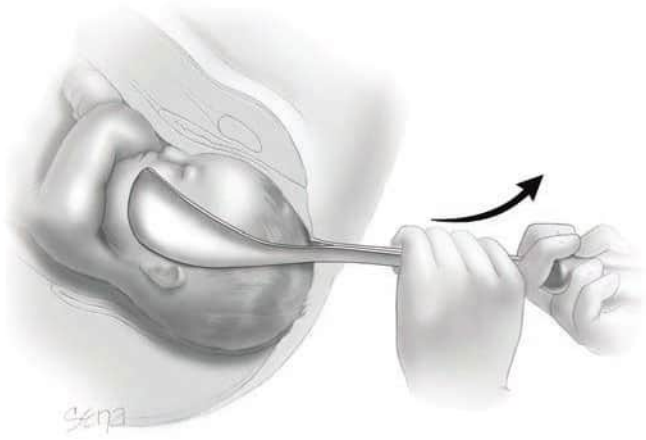

FIGURE 29-11 Outlet forceps delivery from an OP position. The head should be flexed after the bregma passes under the symphysis.

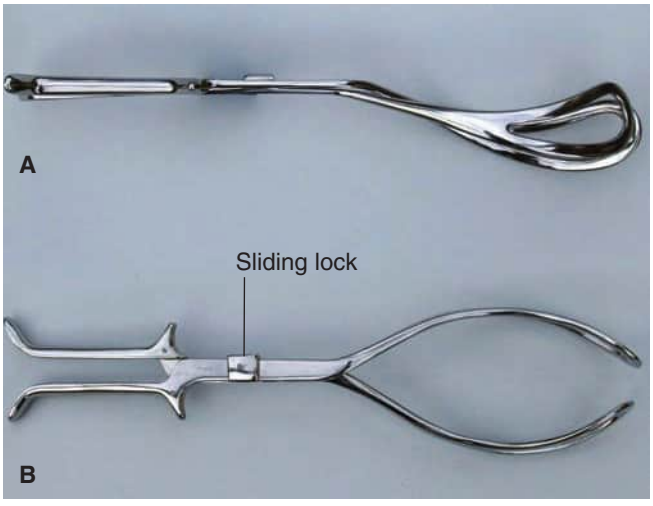

FIGURE 29-12 Kielland forceps. The characteristic features are minimal pelvic curvature **(A)**, sliding lock **(B)**, and light weight.

of severe perineal lacerations and of extensive episiotomy compared with OA positions (de Leeuw, 2008; Pearl, 1993). Also, newborns undergoing OVD from OP positions have a higher incidence of Erb and facial nerve palsies, 1 and 2 percent, respectively, than those delivered from OA positions. As expected, rotations to OA ultimately decrease perineal delivery trauma (Bradley, 2013).

For forceps rotations from an OP to OA position, Kielland forceps are preferred because they have a less pronounced pelvic curve (Fig. 29-12). *Cunningham and Gilstrap's Operative Obstetrics*, 3rd edition offers a more detailed description and illustration of this Kielland forceps procedure (Yeomans, 2017).

■ Occiput Transverse Positions

With occiput transverse (OT) fetal head positions, rotation is required for delivery. For this, the head may be manually or instrumentally rotated into an OA position. Manual rotation was described earlier in that section (p. 540).

Forceps rotation by experienced operators can offer high success rates with minimal maternal morbidity (Burke, 2012; Stock, 2013b). Either standard forceps or specialized forceps, such as Kielland forceps, are used. With the latter, each handle has a small knob, and branches are placed so that this knob faces the occiput.

Kielland described two methods of applying the anterior blade. In this example, placement with a left OT (LOT) position is described. With the wandering method, the anterior blade is first introduced into the posterior pelvis (Fig. 29-13). The blade is then arched around the face to an anterior position. To permit this sweep of the blade, the handle is held close to the left maternal buttock throughout the maneuver. The second blade is introduced posteriorly, and the branches are locked.

After checking the application, the provider pulls the handles of the Kielland forceps slightly to the patient's right to flex the fetal head and create a smaller diameter for rotation. The first and second fingers of the left hand are placed over the finger guards with the palm against the handles. This palm faces the maternal left. Concurrently, the first two fingers of the operator's right hand are placed against the anterior lambdoid suture. The fetal head is then elevated and slightly destationed. For rotation in a counterclockwise direction, the wrist of the left

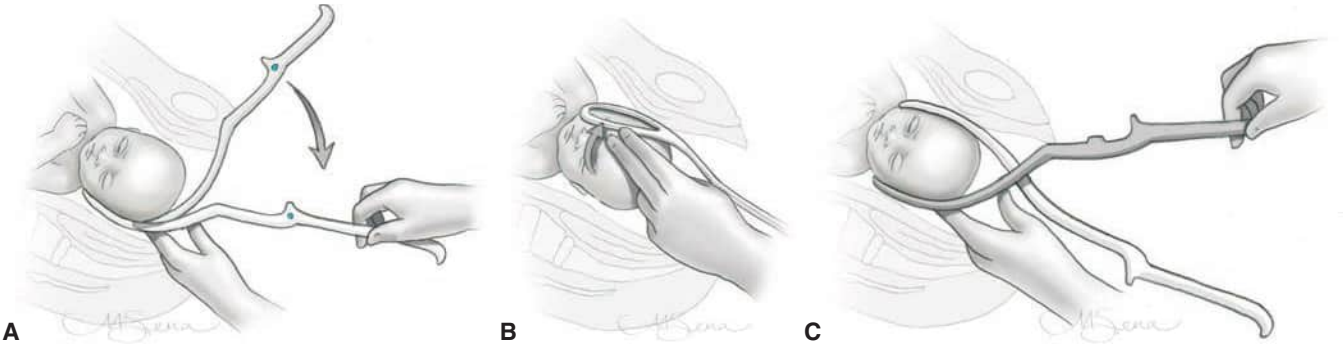

FIGURE 29-13 **A.** Application of the right branch of the Kielland forceps to a head in LOT position. The knob on this branch (*colored blue*) will ultimately face the occiput. **B.** The right branch is wandered to its final position behind the symphysis. **C.** Insertion of the left branch of the Kielland forceps directly posterior along the hollow of the sacrum. This branch is inserted to the maternal right of the anterior branch to aid in engaging the sliding lock. (Reproduced with permission from Yeomans ER: Operative vaginal delivery. In Yeomans ER, Hoffman BL, Gilstrap LC III, et al (eds): Cunningham and Gilstrap's Operative Obstetrics, 3rd ed. New York, NY: McGraw Hill; 2017.)

hand supinates, to direct this palm upward. Simultaneously, two fingers of the right hand press against the lambdoid suture ridge. This ensures that the fetal head turns with the blades and does not slip. As a newer adjunct, abdominal sonography can follow and document head rotation (Hinkson, 2021).

The second type of blade application introduces the anterior blade with its cephalic curve directed upward to curve under the symphysis. After it has been advanced far enough toward the upper vagina, it is turned on its long axis through 180 degrees to adapt the cephalic curvature to the head. The second blade is introduced posteriorly, and the branches are locked.

After rotation of the fetal occiput into the anterior pelvis, two acceptable methods for delivery are available. In one, the operator applies traction on the Kielland forceps using a bimanual grip described previously for conventional forceps (p. 539). When the posterior fontanel has passed under the subpubic arch, the handles can be elevated to the horizontal, but no further. Raising the handles above the horizontal may cause vaginal sulcus tears because of the reverse pelvic curve (Dennen, 1955). Alternatively, the Kielland forceps can be removed after rotation and replaced with conventional forceps. With this approach, moderate traction is first employed to seat the head before switching instruments.

Face Presentations

With a mentum anterior face presentation, OVD is an option. The blades are applied to the sides of the head along the occipitomental diameter, with the pelvic curve directed toward the neck (see Fig. 29-1). Downward traction is exerted until the chin appears under the symphysis. Then, by an upward movement, the face is slowly extracted, with the nose, eyes, brow, and occiput appearing in succession over the anterior margin of the perineum. *Forceps should not be applied to the mentum posterior presentation because vaginal delivery is impossible except in very small fetuses.*

VACUUM-ASSISTED DELIVERY

Vacuum Extractor Design

With vacuum-assisted OVD, suction is created within a cup placed on the fetal scalp such that traction on the cup aids fetal birth. In the United States, *vacuum extractor* is the preferred term, whereas in Europe it is commonly called a *ventouse* (Fig. 29-14). Theoretical benefits of this tool compared with forceps include simpler requirements for precise positioning on the fetal head and avoidance of space-occupying blades within the vagina to help mitigate maternal trauma.

Vacuum devices contain a cup, shaft, handle, and vacuum generator. Vacuum cups are metal or plastic and differ in their shape, size, and reusability. In the United States, plastic cups are generally preferred. Of these, the soft cup is a pliable bell-shaped dome, whereas the rigid type has a firm flattened mushroom-shaped cup and circular ridge around the cup rim (Table 29-2). When compared, rigid mushroom cups generate significantly more traction force (Hofmeyr, 1990; Muise, 1993). With OP positions or with asynclitism, the flatter cup also permits improved placement at the flexion point, which is typically less accessible with these head positions. The trade-off is that the flatter cups have higher scalp laceration rates. Thus, many manufacturers recommend soft bell cups for more straightforward OA deliveries.

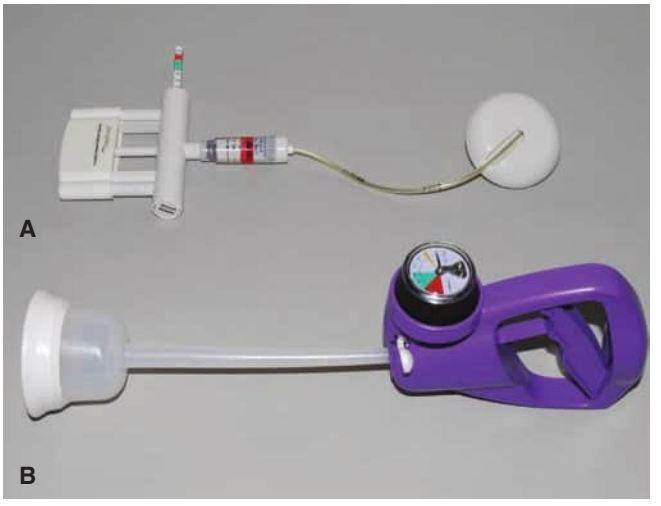

FIGURE 29-14 Vacuum delivery systems. **A.** The *Kiwi OmniCup* contains a handheld vacuum-generating pump, which is attached via flexible tubing to a rigid plastic mushroom cup. **B.** The *Mityvac Mystic II MitySoft Bell Cup* has a soft bell cup attached by a semirigid shaft to a handheld pump.

TABLE 29-2. Vacuum Cups for Operative Vaginal Delivery

Cup Style	Manufacturer
Soft Bell Cup	
GentleVac	OB Scientific
Kiwi ProCup	Clinical Innovations
MitySoft	CooperSurgical
Pearl Edge	CooperSurgical
Mityvac Reusable Silicone[a]	CooperSurgical
Secure Cup	Utah Medical Products
Soft Touch	Utah Medical Products
Tender Touch	Utah Medical Products
Tender Touch Ultra	Utah Medical Products
Velvet Touch[a]	Utah Medical Products
Silc Cup	Medela
CaesAid[a]	Medela
Rigid Mushroom Cup	
Flex Cup	Utah Medical Products
M-Style	CooperSurgical
Super M-Style	CooperSurgical
M-Select[b]	CooperSurgical
Kiwi OmniCup[b]	Clinical Innovations
Kiwi Omni-MT	Clinical Innovations
Kiwi Omni-C[c]	Clinical Innovations
Bird Cup[b]	Medela
Malmström Cup	Medela

[a]Reusable cups.
[b]Suitable for occiput posterior positions or asynclitism.
[c]For extractions through a hysterotomy incision during cesarean delivery.

Several investigators have compared outcomes with various rigid and soft cups. Metal cups yield higher success rates but greater rates of scalp injuries, including cephalohematomas (O'Mahony, 2010). In another study, Kuit and colleagues (1993) found that the only advantage of the soft cups was a lower incidence of scalp injury. In a review, Vacca (2002) concluded that fewer scalp lacerations occurred with the soft cup, but that the rate of cephalohematomas and subgaleal hemorrhage was similar between soft and rigid cups. Importantly, high-pressure vacuum generates large amounts of force regardless of the cup used (Duchon, 1998).

Aside from the cup, the shaft that connects the cup and handle may be flexible or semiflexible. Tubing-like flexible shafts may be preferred for OP positions or asynclitism to permit better seating of the cup. Last, the vacuum generator may be handheld and actuated by the operator, or it may be held and operated by an assistant.

Technique

An important step in vacuum-assisted OVD is proper cup placement over the *flexion point*. This pivot point maximizes traction, minimizes cup detachment, flexes the neck, and delivers the smallest head diameter through the pelvic outlet. This improves success rates, lowers scalp injury rates, and lessens perineal trauma because the smallest head diameter distends the vulva (Baskett, 2008).

The flexion point is found along the sagittal suture, approximately 3 cm from the posterior fontanel's center and approximately 6 cm from the anterior fontanel's center. Because most cup diameters measure 5 to 6 cm, when properly placed, the cup rim lies at the posterior fontanel's border and 3 cm from the anterior fontanel (Fig. 29-15). Placement of the cup more anteriorly on the fetal cranium—near the anterior fontanel—is ideally avoided as it leads to neck extension during traction unless the fetus is small. Such placement delivers a wider head diameter through the vaginal opening. Last, asymmetrical placement relative to the sagittal suture may worsen asynclitism. Cup placement in OA positions is seldom difficult. In contrast, if the indication for delivery is failure to descend caused by occipital malposition, cup positioning can be difficult.

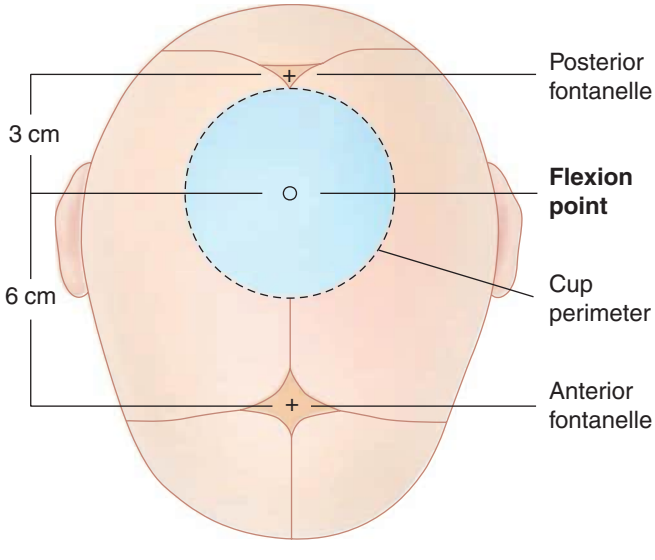

FIGURE 29-15 Drawing demonstrates correct cup placement at the flexion point. Along the sagittal suture, this spot lies 3 cm from the posterior fontanel and 6 cm from the anterior fontanel.

TABLE 29-3. Vacuum Pressure Conversions

mm Hg	cm Hg	Inches Hg	lb/in^2	kg/cm^2
100	10	3.9	1.9	0.13
200	20	7.9	3.9	0.27
300	30	11.8	5.8	0.41
400	40	15.7	7.7	0.54
500	50	19.7	9.7	0.68
600	60	23.6	11.6	0.82

During cup placement, maternal soft tissue entrapment predisposes the mother to lacerations and virtually ensures cup dislodgement, colloquially called a "pop off." Thus, the entire cup circumference should be palpated both before and after the vacuum has been created and again prior to traction to exclude such entrapment. Gradual vacuum creation is advocated by some and is generated by increasing the suction in increments of 0.2 kg/cm^2 every 2 minutes until a total negative pressure of 0.8 kg/cm^2 is reached (Table 29-3). That said, other studies have shown that negative pressure can be increased to 0.8 kg/cm^2 in <2 minutes without a significant difference in efficacy or in maternal and fetal outcomes (Suwannachat, 2011, 2012).

Once suction is created, the instrument handle is grasped, and traction is initiated. Similar to forceps delivery, traction angles mirror that in Figure 29-8 and should be steady without jerking or rocking. The number of needed pulls increases with higher station but typically ranges from one to four. Efforts are intermittent, and each pull is coordinated with maternal pushing. Manual torque to the cup is avoided as it can cause cup displacement or cephalohematomas and, with metal cups, "cookie-cutter"–type scalp lacerations. Thus, OA oblique positions are corrected not by rotation, but solely by downward outward traction. Similarly, for OP positions, rotational forces should not be applied. Instead, with correct flexion point placement and line of traction, the head will usually rotate by itself (van den Akker, 2019).

During pulls, the operator should place the nondominant hand within the vagina, with the thumb on the extractor cup and one or more fingers on the fetal scalp. So positioned, descent of the presenting part can be judged and the traction angle can be adjusted with head descent. In addition, the relationship of the cup edge to the scalp can be assessed to help detect cup separation.

Between contractions, some physicians will lower the suction levels to decrease scalp injury rates, whereas others will maintain suction in cases with a nonreassuring FHR to aid rapid delivery. No differences in maternal or fetal outcome were noted if the vacuum level was decreased between contractions or if an effort was made to prevent fetal loss of station (Bofill, 1997). Once the head is delivered, the vacuum pressure is relieved and the cup removed.

Vacuum extraction should be considered a trial. Without early and clear evidence of descent toward delivery, an

alternative delivery approach should be adopted. As a general guideline, progressive descent should accompany each traction attempt. Neither data nor consensus are available regarding the number of pulls required to effect delivery, the maximum number of cup pop-offs that can be tolerated, or optimal total duration of the procedure. Some manufacturers have recommendations regarding these (Clinical Innovations, 2018; CooperSurgical, 2018).

During a vacuum-assisted delivery trial, cup dislodgement due to technical failure or less than optimal placement should not be equated with dislodgement under ideal conditions of exact cup placement and optimal vacuum maintenance. Technical failures may merit either additional attempts at cup placement or, alternatively, a trial of forceps (Ezenagu, 1999; Williams, 1991). The least desirable cases are those in which traction without progress or multiple disengagements occur following correct cup application and appropriate traction. As with forceps, clinicians should embrace a willingness to abandon attempts at vacuum-assisted delivery if satisfactory progress is not made (American College of Obstetricians and Gynecologists, 2020a).

TRAINING

As the OVD rate has declined, so have opportunities for resident training (Fitzwater, 2015; Kyser, 2014). In accredited programs, the median number of these procedures completed by trainees has reached critically low levels, and for recent graduates it approximated only 20 (Accreditation Council for Graduate Medical Education, 2019; Dildy, 2016). For residents completing training in 2021, the Accreditation Council for Graduate Medical Education (2020) minimum requirement is 15 procedures.

To adapt, residency programs should have readily available skilled operators to teach these procedures by simulation as well as through actual cases (Spong, 2012). In one study, a 59-percent increase in forceps deliveries over 2 years was related to a single experienced and proactive instructor assigned to teach forceps to residents in labor and delivery (Solt, 2011).

In another, following implementation of a formal education program that included a manikin and pelvic model simulation, rates of neonatal morbidity and of severe maternal cervical, labial, and vaginal lacerations declined. However, OASIS rates were unchanged (Cheong, 2004). Gossett and associates (2016) found a 22-percent reduction in the OASIS rate following an OVD simulation curriculum.

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CHAPTER 30

Cesarean Delivery and Peripartum Hysterectomy

In the United States, the cesarean delivery rate rose most dramatically from 4.5 percent in 1970 to 32.9 percent in 2009. The rate has since plateaued and was 31.9 percent in 2018 (Martin, 2019). Some indications for performing cesarean delivery are shown in Table 30-1. More than 85 percent of these operations are performed for four reasons—prior cesarean delivery, labor dystocia or arrest, fetal jeopardy, or abnormal fetal presentation. The latter three compose the main indications for primary cesarean delivery (Barber, 2011; Boyle, 2013). Efforts to lower these rates are outlined in *Safe Prevention of the Primary Cesarean Delivery* by the American College of Obstetricians and Gynecologists (2019b).

Reasons for persistently elevated cesarean rates are not completely understood, but some explanations include the following:

1. Women are having fewer children, thus, a greater percentage of births are among nulliparas, who are at increased risk for cesarean delivery.
2. Average maternal age is rising, and older women, especially older nulliparas, have a higher cesarean delivery risk.
3. Electronic fetal monitoring use is widespread and associated with a higher cesarean delivery rate compared with intermittent fetal heart rate auscultation.
4. Most breech fetuses are now delivered by cesarean.
5. The frequency of operative vaginal delivery has declined.
6. Obesity, which is a cesarean delivery risk, has reached epidemic proportions.
7. Rates of cesarean delivery in women with preeclampsia have risen, whereas labor induction rates for these patients have declined.
8. The vaginal birth after cesarean (VBAC) rate has decreased from a high of 28 percent in 1996 to 13.3 percent in 2018 (Martin, 2019).
9. Assisted reproductive technology is more widely used and is linked with greater cesarean delivery rates (Luke, 2019).

DEFINITIONS

Cesarean delivery defines the birth of a fetus by laparotomy and then hysterotomy. This definition is not applied to removal of the fetus from the abdominal cavity in the case of uterine rupture or of abdominal pregnancy. Rarely, hysterotomy is performed in a woman who has just died or in whom death is expected soon—*postmortem* or *perimortem cesarean delivery* (Chap. 50, p. 897).

In some cases, abdominal hysterectomy is indicated after delivery. When performed at the time of cesarean delivery, the operation is *cesarean hysterectomy*. If done shortly after vaginal delivery, it is *postpartum hysterectomy*. *Peripartum hysterectomy* is a broader term that combines these two. In most cases, *total hysterectomy* is performed and removes the uterine body and cervix. *Supracervical hysterectomy* is selected less often and removes only the uterine body. With either, adnexa are not usually

TABLE 30-1. Some Indications for Cesarean Delivery

Maternal
Prior cesarean delivery
Abnormal placentation
Maternal request
Prior classical hysterotomy
Unknown uterine scar type
Prior uterine incision extension
Uterine incision dehiscence
Prior full-thickness myomectomy
Genital tract obstructive mass
Invasive cervical cancer
Prior trachelectomy
Permanent cerclage
Prior pelvic reconstructive surgery
Prior significant perineal trauma
Pelvic deformity
HSV or HIV infection
Cardiac or pulmonary disease
Cerebral aneurysm or arteriovenous malformation
Pathology requiring concurrent intraabdominal surgery
Perimortem cesarean delivery
Maternal-Fetal
Cephalopelvic disproportion
Failed operative vaginal delivery
Placenta previa or vasa previa
Placental abruption
Fetal
Nonreassuring fetal status
Malpresentation
Macrosomia
Congenital anomaly
Abnormal umbilical cord Doppler study
Thrombocytopenia
Prior neonatal birth trauma

HIV = human immunodeficiency virus; HSV = herpes simplex virus.

excised. In most instances, a *simple hysterectomy*, which is also a type I hysterectomy, is performed. However, for women with invasive cervical cancer, *radical hysterectomy* removes the uterus, parametrium, and proximal vagina to achieve tumor excision with negative margins. For cases of placenta percreta that extend toward the pelvic sidewall, similar radical excision of the parametrium may be needed.

CESAREAN DELIVERY RISKS

To provide accurate informed consent, knowledge of maternal and neonatal risks and benefits with surgery is essential. In broad terms, cesarean delivery generally has higher maternal surgical risks for the current and subsequent pregnancies compared with spontaneous vaginal birth. This is balanced against lower rates of perineal injury and short-term pelvic floor disorders. For the neonate, cesarean delivery generally offers lower rates of birth trauma and stillbirth but greater rates of initial respiratory difficulties.

Maternal Mortality and Morbidity

For the mother, death attributable solely to cesarean delivery is rare in the United States. A review of nearly 1.5 million pregnancies found maternal mortality rates of 2.2 per 100,000 cesarean deliveries compared with 0.2 per 100,000 vaginal births (Clark, 2008). In a metaanalysis of 203 studies, Guise and coworkers (2010) reported a maternal mortality rate of 13 per 100,000 with elective repeat cesarean compared with 4 per 100,000 with trial of labor.

Some element of this risk may stem from the underlying indication for the cesarean delivery. For example, long first-stage labor increases not only cesarean risk but also rates of maternal fever and postpartum hemorrhage (Blankenship, 2020). Additionally, in a study of more than 100,000 deliveries in China, where cesarean birth without a medical indication is common, the maternal mortality rate was not higher in those with nonindicated cesarean delivery than in women with spontaneous vaginal birth (Hou, 2017).

Similar to mortality rates, the overall frequencies of some maternal morbidities are increased with cesarean delivery. Villar and associates (2007) reported that maternal morbidity rates were twofold higher with cesarean delivery than with vaginal birth. Principal among these are infection, hemorrhage, and venous thromboembolism (VTE). In addition, anesthetic complications, which also rarely include death, have a greater incidence with cesarean delivery compared with vaginal birth (Cheesman, 2009; Hawkins, 2011). Adjacent organs infrequently may be injured, which is described in detail later (p. 563).

Women who undergo a cesarean delivery are much more likely to be delivered by a repeat operation in subsequent pregnancies. For women undergoing subsequent cesarean, the maternal risks just described are even greater (Cahill, 2006; Marshall, 2011; Silver, 2006). Specifically outlined in Chapter 31 (p. 580), abnormal placentation, wound and uterine infections, adjacent organ injury, cesarean hysterectomy, and blood transfusion are among the morbidity that accrues with multiple subsequent cesarean operations.

As an advantage, cesarean delivery is associated with lower rates of urinary incontinence and pelvic organ prolapse than is vaginal birth (Gyhagen, 2013a,b; Handa, 2011). Rates of anal incontinence appear uninfluenced by a vaginal or cesarean route (Blomquist, 2018; Nelson, 2019). In subgroup evaluation, operative vaginal delivery does carry an overall greater anal incontinence risk, which likely stems from higher sphincter injury rates with these procedures (Chap. 29, p. 535).

Pelvic floor advantages persist to some degree over time, but cesarean delivery is not totally protective. Moreover, longitudinal studies suggest that initial pelvic floor advantages gained from cesarean delivery are lost as women age (Dolan, 2010; MacArthur, 2011, 2013). During their State-of-the-Science Conference, the National Institutes of Health panel (2006) summarized that stress urinary incontinence rates after elective cesarean delivery are lower than those following vaginal delivery. However, the duration of this protection is unclear, particularly in older

and multiparous populations. Defining women who would be at highest long-term risk for pregnancy-related pelvic floor disorders might allow accurate delivery counseling (Jelovsek, 2018).

Neonatal Morbidity

Cesarean delivery is associated with a lower rate of fetal trauma (Linder, 2013; Moczygemba, 2010). Alexander and colleagues (2006) found that fetal injury complicated 1 percent of cesarean deliveries. Skin laceration was most common, but others included cephalohematoma, clavicular fracture, brachial plexopathy, skull fracture, and facial nerve palsy. Cesarean deliveries following a failed operative vaginal delivery attempt had the highest injury rate. The lowest rate—0.5 percent—occurred in the elective cesarean delivery group. That said, Worley and associates (2009) found that approximately a third of women who were delivered at Parkland Hospital entered spontaneous labor at term, and 96 percent of these delivered vaginally without adverse neonatal outcomes.

Cesarean Delivery on Maternal Request

Some women request elective cesarean delivery. Data regarding the true incidence of *cesarean delivery on maternal request (CDMR)* are poor. An older estimate in the United States was 5 percent (Declercq, 2005).

Reasons for the request include protection of pelvic floor support, convenience, fear of childbirth, and reduced risk of fetal injury. One retrospective study of more than 66,000 Chinese parturients compared outcomes of those who elected planned vaginal birth or requested primary cesarean delivery (Liu, 2015). Short-term serious maternal morbidity and neonatal mortality rates were similar. For the newborns, rates of birth trauma, infection, and hypoxic ischemic encephalopathy were low in both groups but statistically lower with cesarean delivery. Respiratory distress syndrome rates were greater in the CDMR cohort. A smaller study comparing these two routes of delivery support these findings (Larsson, 2011).

The debate surrounding CDMR includes two medical points: the concept of informed free choice by the woman, and the autonomy of the physician in offering CDMR. To address this, the National Institutes of Health (2006) held a State-of-the-Science Conference on Cesarean Delivery on Maternal Request. Notably, most of the maternal and neonatal outcomes examined had insufficient data to permit recommendations. Indeed, one of the main conclusions of the conference was that more high-quality research is needed to fully evaluate the issue. Guidelines from the American College of Obstetricians and Gynecologists (2020a) note that CDMR should not be performed before 39 weeks' gestation. It is ideally avoided in women desiring several children because of the earlier-described morbidity from accruing cesarean operations.

PATIENT PREPARATION

Delivery Availability

No nationally recognized standard of care currently dictates the acceptable time interval to begin cesarean delivery. Previously, a 30-minute decision-to-incision interval was recommended. However, Bloom and colleagues (2006) evaluated nearly 3000 cesarean deliveries performed for emergency indications. They reported that failure to achieve a cesarean delivery decision-to-incision time <30 minutes was not associated with a negative neonatal outcome. A subsequent systematic review echoed this finding (Tolcher, 2014). Despite this, when faced with an acute, catastrophic deterioration in fetal condition, cesarean delivery usually is indicated as rapidly as possible, and thus purposeful delays are inappropriate. The American Academy of Pediatrics and the American College of Obstetricians and Gynecologists (2017) recommend that facilities giving obstetrical care should have the ability to initiate cesarean delivery in a time frame that best incorporates maternal and fetal risks and benefits.

Informed Consent

Informed consent is a process and not merely a medical document. The consenting conversation should enhance a woman's awareness of her diagnosis and contain a discussion of medical and surgical care alternatives, procedure goals and limitations, and operative risks. For women with a prior cesarean delivery, the option of a trial of labor should be included for suitable candidates. For those desiring permanent sterilization or intrauterine device (IUD) insertion, consenting for these can be completed concurrently (Chaps. 38 and 39, pp. 665 and 684).

An informed patient may decline a particular recommended intervention, and a woman's decision-making autonomy must be respected. In the medical record, providers should document the reasons for refusal and should note that the intervention's value and the health consequences of not proceeding with it have been explained.

For Jehovah's Witnesses, informed consent discussions regarding blood products ideally begin early in pregnancy. Acceptable blood products vary widely among individual women, and a preoperative checklist of approved products allows superior preparation (Hubbard, 2015). In general, red cells, white cells, platelets, and plasma are considered primary blood components and are declined. However, certain clotting factors or cell fractions may be acceptable (Lawson, 2015). Before and after surgery, iron, folate, and, if necessary, erythropoietin are accepted agents to help maximize hemoglobin levels. Perioperatively, phlebotomy is limited, and pediatric collection tubes are preferable. Intraoperative options include prompt treatment of atony to limit blood loss and use of topical hemostatic agents, tranexamic acid, and desmopressin to promote clot formation. Red blood cell salvage can provide autologous donation. Normovolemic hemodilution and controlled hypotensive or hypothermic anesthesia can limit red cell losses. To minimize uncontrolled vessel bleeding, uterine artery embolization, occlusive vascular balloons, and other options are described in Chapter 44 (p. 779) (Scharman, 2017).

Timing of Scheduled Cesarean Delivery

With elective delivery before 39 completed weeks, adverse neonatal sequelae from neonatal immaturity are appreciable (Tita, 2009). To avoid these, assurance of fetal maturity before

scheduled elective surgery is essential. Supporting criteria include corroborative ultrasound measurements obtained prior to 20 weeks' gestation, fetal heart tones heard for the past 30 weeks, and passage of 36 weeks since an initial positive pregnancy test result (American Academy of Pediatrics, 2017).

Preoperative Care

Current perioperative care is guided by evidence-based enhanced recovery after surgery (ERAS) recommendations. Among these, solid food intake is stopped at least 6 hours before the procedure. Uncomplicated patients may consume moderate amounts of clear liquids up to 2 hours before surgery (American Society of Anesthesiologists, 2016). Bowel preparation is not recommended (Wilson, 2018).

The woman scheduled for cesarean delivery typically is admitted the day of surgery and evaluated by the obstetrical and anesthesia teams. Recently performed hematocrit and indirect Coombs test are reviewed. If the latter is positive, compatible blood availability must be ensured.

Regional analgesia is preferred for cesarean delivery. To minimize the lung injury risk from rare aspiration, gastric acid is ideally buffered. An oral antacid is consumed shortly before regional analgesia or induction of general anesthesia. One example is Bicitra, 30 mL orally in a single dose. This can be coupled with an intravenous (IV) dose of an H_2-receptor antagonist, which also raises gastric pH (Wilson, 2018).

Once the woman is supine, a wedge beneath the right hip and lower back creates a left lateral tilt to aid venous return and avoid hypotension. Data are insufficient to determine the value of fetal monitoring before scheduled cesarean delivery in women without risk factors. Our practice is to obtain a 5-minute tracing prior to elective cases. At minimum, fetal heart sounds should be documented in the operating room prior to surgery.

Of further preparations, hair removal at the surgical site does not lower surgical site infection (SSI) rates (Kowalski, 2016). However, if hair is obscuring, it is removed the day of surgery by clipping, which is associated with fewer SSIs than shaving (Tanner, 2011). Chemical depilation the night before surgery compared with clipping has similar SSI rates (Lefebvre, 2015). An electrosurgical grounding pad is placed near the surgical incision and typically on the lateral thigh. At Parkland Hospital, we typically insert an indwelling bladder catheter to collapse the bladder away from the hysterotomy incision, to avert urinary retention secondary to regional analgesia, and to allow accurate postoperative urine measurement. Small studies show that catheterization may be withheld in hemodynamically stable women. Catheter-related discomfort can be avoided, but urinary tract infection rates are not lower (Abdel-Aleem, 2014).

The risk of VTE is increased with pregnancy. In the United States in 2014, women with cesarean delivery had a VTE rate of 8 per 10,000, which almost doubled the rate for those with vaginal birth (Abe, 2019). Accordingly, for all women not already receiving thromboprophylaxis, the American College of Obstetricians and Gynecologists (2020c) recommends initiation of pneumatic compression stockings before cesarean delivery. These are usually discontinued once the woman ambulates. Consensus varies among organizations, and the American College of Chest Physicians suggests only early ambulation for women without risk factors who are undergoing cesarean delivery (Bates, 2012). For women already receiving prophylaxis or those with increased risk factors, they support escalation of prophylaxis. Last, the Royal College of Obstetricians and Gynaecologists (2015) is the most conservative and suggest pharmacological prophylaxis for the largest proportion of patients. These various methods and recommendations are discussed in Chapter 55 (p. 989).

Some women scheduled for cesarean delivery have a comorbidity that requires specific management in anticipation of surgery. Among others, these include insulin-requiring diabetes, coagulopathy or thrombophilia, chronic corticosteroid use, and significant reactive airway disease. Surgical preparations are discussed in the respective chapters covering these topics.

Infection Prevention

Antibiotic Prophylaxis

Cesarean delivery is considered a clean contaminated case, and postoperative febrile morbidity is common. Numerous trials show that a single dose of an antibiotic given at the time of cesarean delivery significantly decreases infectious morbidity (Smaill, 2014). Although more obvious for women in active labor who then require cesarean delivery, this practice also pertains to gravidas undergoing elective surgery. Depending on drug allergies, most recommend a single IV dose of a β-lactam antibiotic—either a cephalosporin or extended-spectrum penicillin. A 1-g dose of cefazolin (Ancef) is an efficacious and cost-effective choice. Additional doses are considered in cases with blood loss >1500 mL or with duration longer than 3 hours. Recommendations for a 2- or 3-g cefazolin dose in obese parturients are conflicting (Ahmadzia, 2015; Maggio, 2015; Swank, 2015; Young, 2015). The Centers for Disease Control and Prevention recommends a 2-g dose for weights ≥80 kg and 3 g for those ≥120 kg (Berríos-Torres, 2017). The American College of Obstetricians and Gynecologists (2020d) recognizes either dose as suitable for women ≥80 kg. One pharmacokinetic analysis in obese women showed sufficient tissue levels with a 2-g dose for cesarean deliveries lasting 1.5 hours. Authors recommended consideration for redosing in obese women if surgeries were longer (Grupper, 2017).

Evidence also supports extending the antibiotic spectrum (Markwei, 2021; Tita, 2008). One large randomized trial added azithromycin, 500 mg IV, to standard prophylaxis prior to cesarean delivery for women in labor or with ruptured membranes (Tita, 2016). Rates of SSIs and endometritis were significantly lower in the extended-spectrum group compared with those in the standard prophylaxis cohort.

In pregnant women with a history of infection with methicillin-resistant *Staphylococcus aureus* (MRSA), a single, 15-mg/kg dose of vancomycin can be added to the standard prophylaxis. Decolonization plays a limited role but may be considered prior to a planned cesarean delivery in women with known MRSA colonization (American College of Obstetricians and Gynecologists, 2020d).

Significant β-lactam allergy manifests as anaphylaxis, angioedema, respiratory distress, or urticaria. This merits prophylaxis with a single, 900-mg IV dose of clindamycin combined with a weight-based, 5-mg/kg dose of an aminoglycoside as an alternative. The 900-mg clindamycin dose is also used for obese patients. Some studies link higher SSI rates to regimens that lack a β-lactam (Wilhelm, 2020). Antepartum penicillin-allergy evaluation by a specialist may redefine the significance of the patient's prior reaction. Advantageously, this clarification may remove an allergy label and expanded options (Wolfson, 2021).

Antibiotic administration before surgical incision lowers postoperative infection rates without adverse neonatal effects compared with drug administration after umbilical cord clamping (Mackeen, 2014b; Sullivan, 2007). Prophylaxis is ideally administered within the 60 minutes prior to the start of planned cesarean delivery. For emergent delivery, antibiotics are given as soon as feasible.

Preoperative preparation of the abdominal wall skin immediately prior to surgery can help prevent SSIs. Chlorhexidine-alcohol or povidone-iodine solutions are suitable, but data favor chlorhexidine (Hadiati, 2020; Tolcher, 2019). However, adding a wiping of the skin with chlorhexidine the night before surgery was no better than placebo (Stone, 2020). Once abdominal preparation is completed and dry, surgical drapes cover the patient. One type has a cut-out window in the lower abdomen that is surrounded by an adhesive border. Others are *adhesive incisional drapes*, in which the skin and plastic drape must be incised together. The latter may slightly raise SSI rates (Eckler, 2019; Hadiati, 2020).

Although not our practice, preoperative vaginal cleansing with a 1-percent povidone-iodine scrub lowered endometritis and SSI rates in some studies (Haas, 2020; Roeckner, 2019). With povidone allergy, 4-percent chlorhexidine gluconate solution is an alternative. Last, some early evidence may support extending oral antibiotic prophylaxis for 48 hours postcesarean in obese women to lower SSIs (Valent, 2017).

Antibiotic prophylaxis against infective endocarditis is not recommended for most cardiac conditions. Exceptions are women with repaired or unrepaired cyanotic heart disease, prosthetic valves, or both. Prior infective endocarditis or cardiac transplantation with resulting valve regurgitation are others (American College of Obstetricians and Gynecologists, 2020d). Drug infusion is 30 to 60 minutes prior to expected delivery (Table 52-9, p. 935). Cesarean infection prophylaxis regimens also serve as appropriate endocarditis coverage.

Other Preventions

Glycemic control in diabetics lowers wound infection rates and is emphasized in Chapter 60 (p. 1068). Smoking is another modifiable risk (Avila, 2012). Intraoperative normothermia lowers wound infection rates in general surgery cases (Balki, 2020; Berríos-Torres, 2017). This tenet is logically extrapolated to cesarean delivery (Caughey, 2018).

In children delivered by cesarean, some evidence shows higher asthma and allergy rates (Kristensen, 2016). Gut microbiome differences between vaginal and cesarean birth groups are a suggested cause (Shao, 2019). With the hope to improve neonatal microbiota, swabbing the newborn mouth with a gauze that was incubated in the maternal vagina 1 hour before surgery has been described in preliminary studies. However, the American College of Obstetricians and Gynecologists (2019c) does not encourage this practice due to few data and the potential for transmission of harmful organisms.

Surgical Safety

The Joint Commission (2020) describes a protocol to prevent surgical errors. For cesarean delivery, all relevant documents are verified immediately before surgery, and a "time out" is completed. The "time out" requires attention of the entire team to confirm that the patient, site, and procedure are correct. Important discussions also include introduction of the patient-care team members, verification of prophylactic antibiotics, estimation of procedure length, and communication of anticipated complications. Additionally, requests for special instrumentation should be addressed preoperatively to prevent potential patient compromise and intraoperative delays.

Surgical fires are a specific safety focus. As prevention, surgeons ideally assess the fire risk at the procedure's start, allow adequate drying of alcohol-based skin antiseptics, and keep ignition sources off the patient or drapes when not in use (Food and Drug Administration, 2018; Wolf, 2013).

An instrument, sponge, and needle count before and after surgery is essential. Moreover, active communication during surgery should clearly convey items added to the operative field. At surgery completion, if counts are not reconciled, portable radiographic imaging for retained objects is done.

CESAREAN DELIVERY TECHNIQUE

Laparotomy

As with all surgery, a clear understanding of relevant anatomy is essential (Chap. 2, p. 12). For entry into the abdomen, a suprapubic transverse incision or a midline vertical one is chosen for cesarean delivery. Suitable transverse incisions are Pfannenstiel or Maylard incisions, and the Pfannenstiel type is selected most frequently.

Transverse incisions follow Langer lines of skin tension, and thus exert less stress on the closed wound. Compared with vertical ones, Pfannenstiel incisions offer superior cosmesis and lower incisional hernia rates. The Pfannenstiel incision, however, is often discouraged for cases in which a large operating space is essential or in which access to the upper abdomen may be needed. With transverse incisions, because of the layers created during incision of the internal and external oblique aponeuroses, purulent fluid can collect between these. Therefore, some favor a midline vertical incision for cases with high infection risks. Emergent entry is typically faster with vertical incision during primary and repeat cesarean delivery (Wylie, 2010). Last, neurovascular structures, which include the ilioinguinal and iliohypogastric nerves and superficial and inferior epigastric vessels, are often encountered with transverse incisions. Logically, bleeding, wound hematoma, and neurological disruption may more frequently complicate these incisions compared with vertical ones. The best incision for the morbidly

obese parturient is unclear (Smid, 2016). Our preference for women with morbid obesity is a periumbilical midline vertical incision (Chap. 51, p. 909).

The Maylard incision differs mainly from the Pfannenstiel in that the rectus abdominis muscle bellies and their investing rectus sheath are transected horizontally to widen the operating space. It is technically more difficult due to required muscle cutting and ligation of the inferior epigastric arteries, which lie laterally to these muscle bellies.

Once access is gained, metal handheld retractors provide exposure for hysterotomy. One metaanalysis with nearly 1700 women showed no lowering of postcesarean SSI rates with a disposable plastic barrier retractor (Alexis-O) (Waring, 2018).

Transverse Incisions

With the Pfannenstiel incision, the skin and subcutaneous tissue are incised using a low, transverse, slightly curvilinear incision. This is made at the pubic hairline, which is typically 3 cm above the superior border of the symphysis pubis. The incision is extended laterally to accommodate delivery—12 to 15 cm is typical.

Sharp dissection is continued through the subcutaneous layer to the fascia. The superficial epigastric vessels can usually be identified halfway between the skin and fascia, several centimeters from the midline, and these are coagulated.

The fascia is then incised sharply at the midline. The anterior abdominal fascia is typically composed of two visible layers, the aponeurosis from the external oblique muscle and a fused layer containing aponeuroses of the internal oblique and transverse abdominis muscles. Ideally, the two layers are individually incised during lateral extension of the fascial incision. The inferior epigastric vessels usually lie outside the lateral border of the rectus abdominis muscle and beneath the fused aponeuroses of the internal oblique and transverse abdominis muscles. Thus, although infrequently required, further lateral extension of the fascial incision may encounter these vessels. In this case, vessels ideally are identified and coagulated or ligated to prevent bleeding and vessel retraction.

Once the fascia is incised, the inferior fascial edge is grasped with Kocher clamps and elevated by an assistant as the operator separates the fascial sheath from the underlying rectus abdominis muscle either bluntly or sharply until the superior border of the symphysis pubis is reached. Next, the superior fascial edge is grasped and again, separation of fascia from the rectus muscle is completed. Blood vessels coursing between the sheath and muscles are clamped, cut, and ligated, or they are coagulated with an electrosurgery blade. Meticulous hemostasis is imperative to lower rates of incisional hematoma and infection. The fascial separation progresses cephalad and laterally to create a semicircular area above the transverse incision with a radius of approximately 8 cm. This will vary depending on fetal size. The rectus abdominis and pyramidalis muscles are separated in the midline to expose the transversalis fascia and peritoneum.

The transversalis fascia and preperitoneal fat are bluntly dissected away to reach the underlying peritoneum. The peritoneum near the upper end of the incision is opened carefully, either bluntly or by elevating it with two hemostats placed approximately 2 cm apart. This upper site lowers cystotomy risks. The tented fold of peritoneum between the clamps is examined and palpated to ensure that omentum, bowel, or bladder is not adjacent. The peritoneum is then incised. As the incision is extended cephalad above the arcuate line, the transverse fibers of the posterior rectus sheath are seen and are cut along with the peritoneum. The peritoneal incision is then extended downward to just above the peritoneal reflection over the bladder. Importantly, in women with prior intraabdominal surgery, including cesarean delivery, omentum or bowel may be adhered to the undersurface of the peritoneum. In women with obstructed labor, the bladder may be pushed remarkably cephalad.

Midline Vertical Incision

This incision begins 2 to 3 cm above the superior margin of the symphysis. It should be sufficiently long to allow fetal delivery, and 12 to 15 cm is typical. Sharp or electrosurgical blade dissection through the subcutaneous layers ultimately exposes the anterior rectus sheath. A small opening is made sharply with scalpel in the upper half of the linea alba. Placement here helps avoid potential cystotomy. Index and middle fingers are placed beneath the fascia, and the fascial incision is extended first superiorly and then inferiorly with scissors. Midline separation of the rectus muscles and pyramidalis muscles and peritoneal entry are similar to those just described for the Pfannenstiel incision.

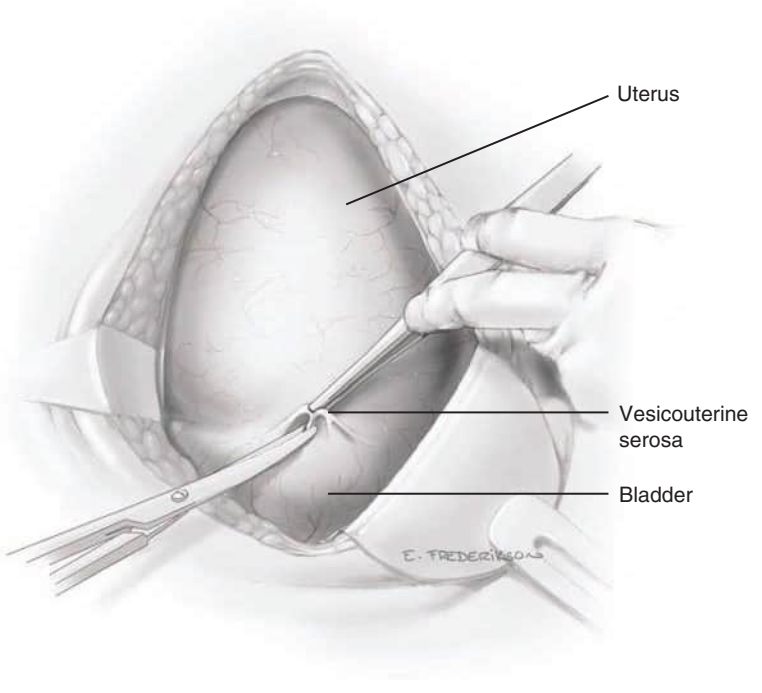

FIGURE 30-1 The loose peritoneum above the bladder reflection is grasped with forceps and incised with Metzenbaum scissors.

Hysterotomy

Most often, the lower uterine segment is incised transversely as described by Kerr in 1921. Occasionally, vertical incision confined solely to the lower uterine segment may be elected (Krönig, 1912). In contrast, a *classical incision* begins as a low vertical incision, which is then extended cephalad into the active portion of the uterine corpus. Last, a fundal or even posterior uterine incision may be selected for cases with placenta accreta syndrome.

Low Transverse Cesarean Incision

For most cesarean deliveries, this incision is preferred. Compared with a classical incision, it repairs easily, causes less incision-site bleeding, and promotes less bowel or omentum adherence to the myometrial incision. Located in the inactive segment, it is also less likely to rupture during a subsequent pregnancy.

Before hysterotomy, the surgeon palpates the fundus to identify degrees of uterine rotation. The uterus may be rotated so that one round ligament is more anterior and closer to the midline (Chap. 3, p. 46). In such cases, the uterus can be manually reoriented and held to permit centering of the incision. This avoids incision extension into and laceration of the adjacent uterine artery. A moist sponge may be used to pack protruding bowel away from the operative field.

The reflection of peritoneum at the upper margin of the bladder and overlying the lower uterine segment is grasped in the midline with forceps and incised transversely with scissors (Fig. 30-1). Following this initial incision, scissors are inserted between peritoneum and lower-uterine-segment myometrium. Open scissors are pushed laterally from the midline on each side. This transverse peritoneal incision extends almost the full length of the lower uterine segment. As the lateral margin on each side is approached, the scissors are directed slightly cephalad (Fig. 30-2). The lower edge of peritoneum is elevated, and the bladder is gently separated from the underlying lower uterine segment with blunt or sharp dissection within this vesicouterine space (Fig. 30-3). This bladder flap creation effectively moves the bladder away from the planned hysterotomy site. It also helps prevent bladder laceration if an unintended inferior hysterotomy extension occurs during fetal delivery. If dense adhesions complicate vesicouterine space dissection, sharp dissection is preferred. If unclear, the bladder and its upper border can be identified by distending or "back filling" it with fluid instilled through a Foley catheter (Saaqib, 2020).

In general, this caudad separation of bladder does not exceed 5 cm and usually is less. However, in instances in which cesarean hysterectomy is planned or anticipated, extended caudad bladder dissection is recommended to aid total hysterectomy and decrease the risk of cystotomy.

Some surgeons do not create a bladder flap. The main advantage is a shorter skin incision-to-delivery time. However, data supporting this practice are currently limited (O'Neill, 2014; Tuuli, 2012).

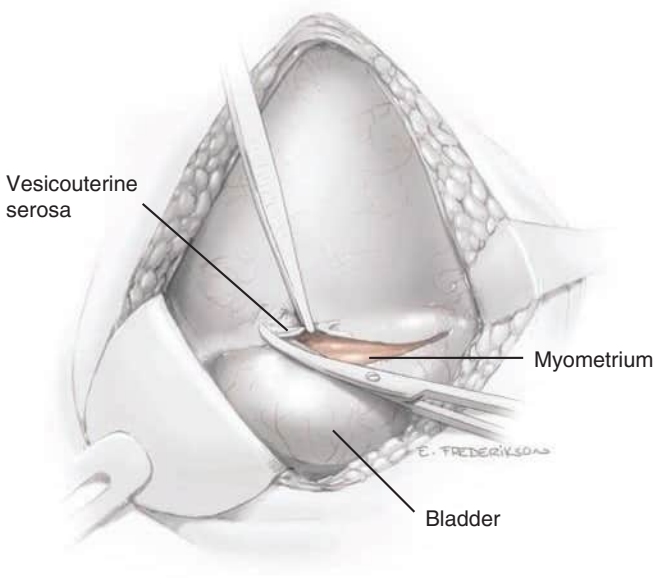

FIGURE 30-2 This peritoneal edge is elevated and incised laterally.

Uterine Incision. The uterus is entered through the lower uterine segment. Digital palpation to find the physiological border between firmer upper segment myometrium and the more flexible lower segment can guide placement. This is often at the level of the bladder flap incision.

For women with advanced or complete cervical dilation, the hysterotomy is placed relatively higher. Failure to adjust increases the risk of lateral extension of the incision into the

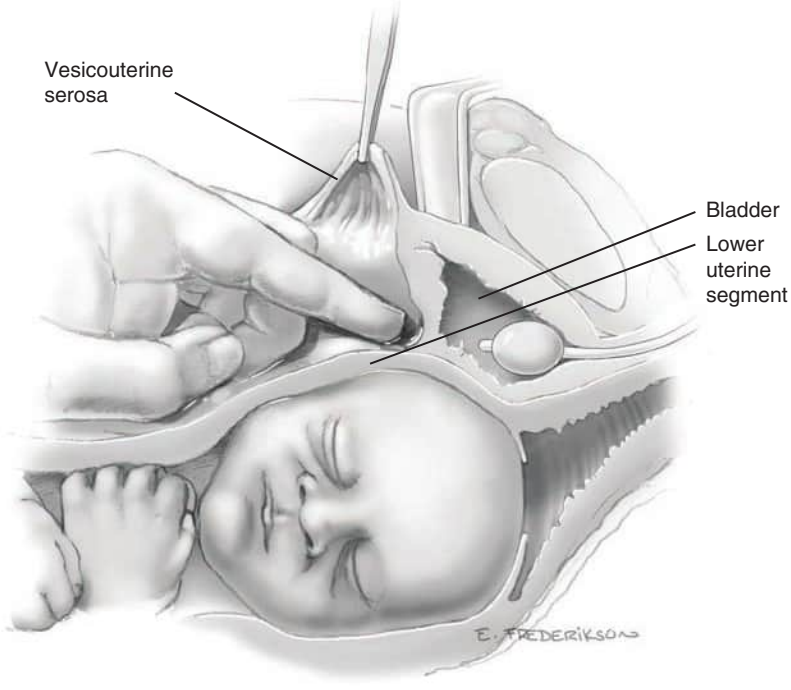

FIGURE 30-3 Cross section shows blunt dissection of the bladder off the uterus to expose the lower uterine segment.

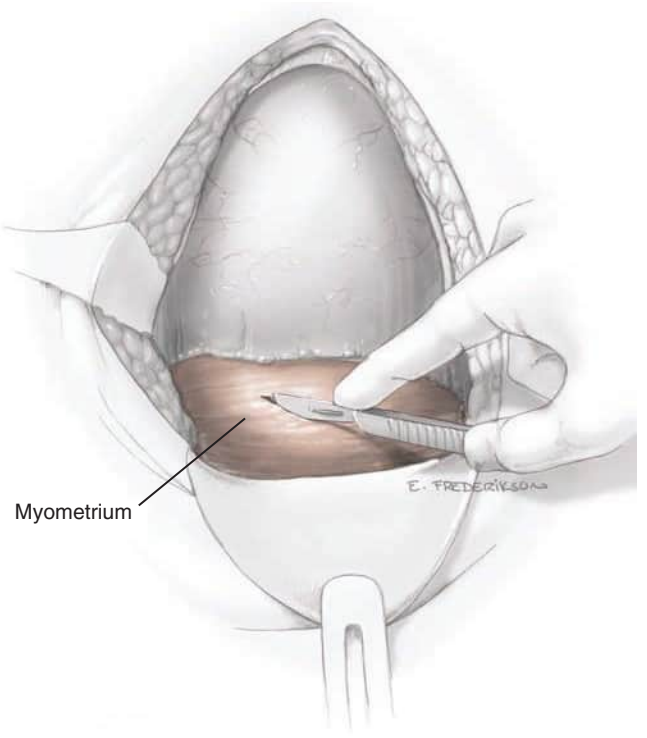

FIGURE 30-4 The myometrium is incised with shallow strokes to avoid cutting the fetal head.

uterine arteries. It may also lead to incision of the cervix or vagina rather than the lower uterine segment. Such incisions into the cervix distort postoperative cervical anatomy.

The uterus can be incised by various techniques. Each is initiated by using a scalpel to transversely incise the exposed lower uterine segment for 1 to 2 cm in the midline (Fig. 30-4). Repetitive shallow strokes help avoid fetal laceration. As the myometrium thins, a fingertip can then bluntly enter the uterine cavity. Once the uterus is entered, the hysterotomy is lengthened by simply spreading the incision, using lateral and slightly upward pressure applied with each index finger (Fig. 30-5). Instead, some evidence supports widening the lower-uterine-segment incision by pulling with fingers in a cephalocaudad direction to help lower hysterotomy extension rates (Morales, 2019; Xodo, 2016).

The goal is to create an incision sufficiently wide to deliver the presenting fetal part yet avoid overextending the incision. Extensions usually tear downward into the lower uterine segment or laterally into the uterine vessels. Extensive inferior tears may include the cervix or vagina. Risk factors for extensions include occiput posterior fetal head position, primary cesarean delivery, and advanced first-stage or second-stage labor (de la Torre, 2006; Karavani, 2020). Specific maneuvers to ameliorate this last high-risk setting are discussed in the next section.

Alternatively, if the lower uterine segment is thick and unyielding, cutting laterally and then slightly upward with bandage scissors will lengthen the incision. Importantly, when scissors are used, the index and middle fingers of the nondominant

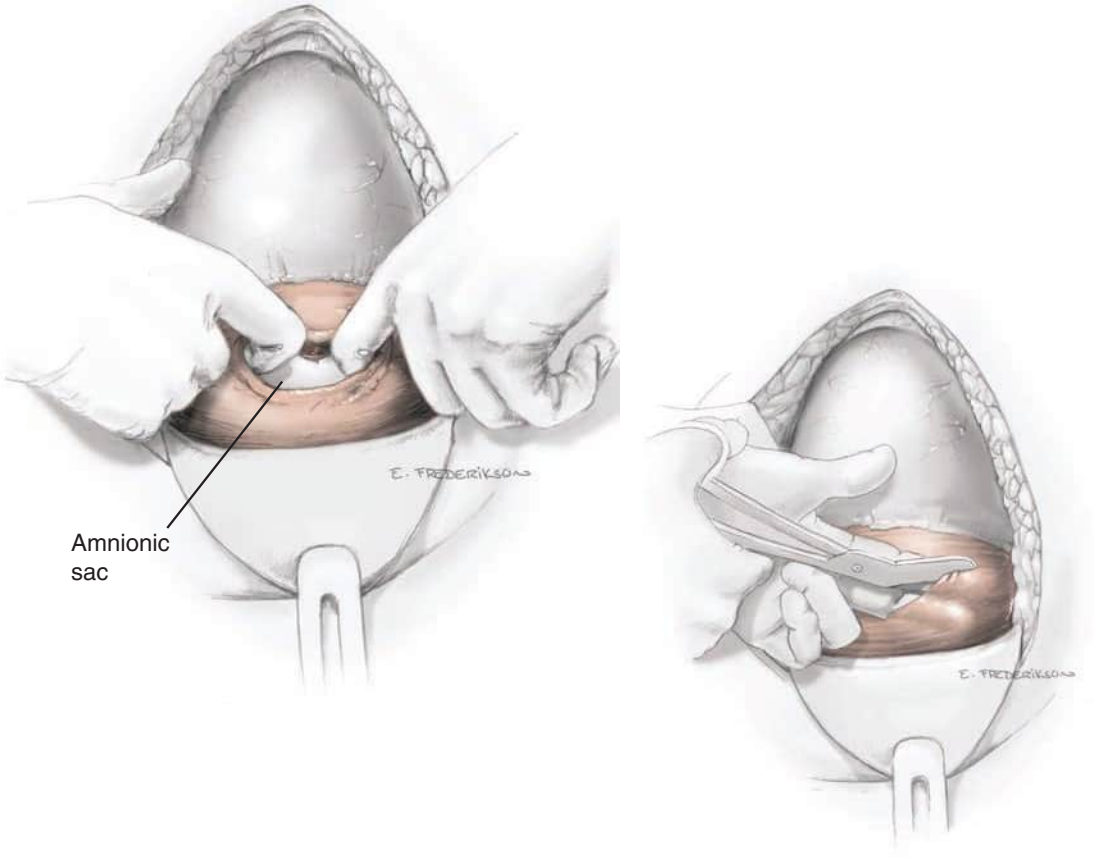

FIGURE 30-5 After entering the uterine cavity, the incision is extended laterally with fingers or with bandage scissors (*inset*).

hand are insinuated beneath the myometrium and above fetal parts to help avert fetal laceration. Comparing blunt and sharp expansion of the initial uterine incision, blunt stretch is associated with fewer unintended incision extensions, shorter operative time, and less blood loss. However, the rates of infection and need for transfusion do not differ (Asıcıoğlu, 2014; Saad, 2014).

During hysterotomy creation, if the placenta lies in the incision line, it must be either detached or incised. Placental function is thereby compromised, and thus delivery is expedited.

At times, a low transverse hysterotomy is selected but provides inadequate room for delivery. In such instances, one corner of the hysterotomy incision is extended cephalad into the contractile portion of the myometrium—a *J incision*. If this is completed bilaterally, a *U incision* is formed. Last, some prefer to extend in the midline—a *T incision*. As expected, these have been linked with higher intraoperative blood loss (Boyle, 1996; Patterson, 2002).

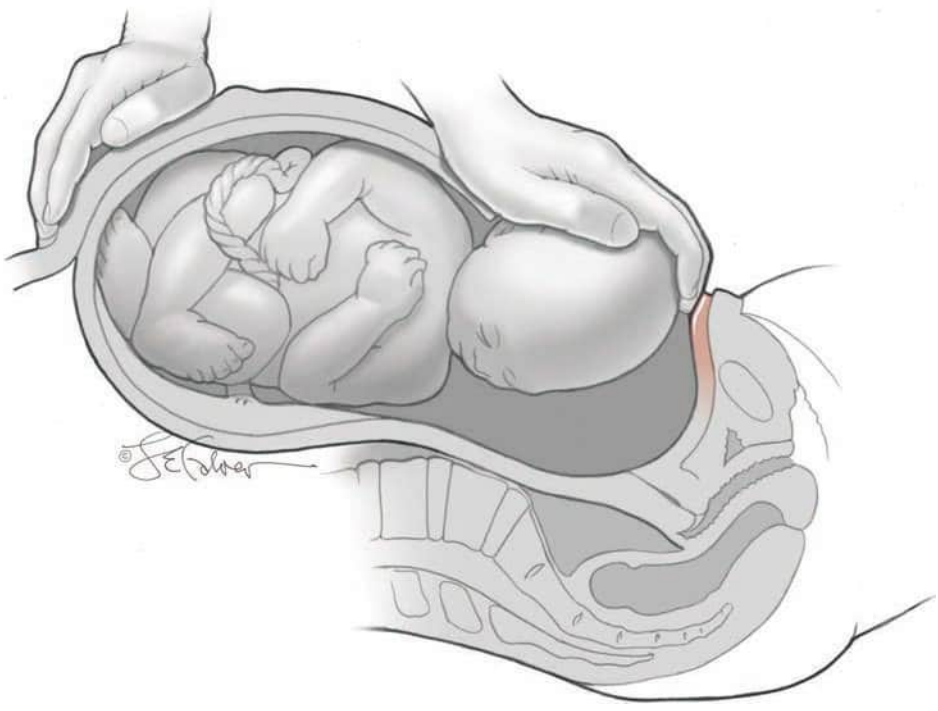

FIGURE 30-6 Delivery of the fetal head. (Figures 30-6 to 30-8: Reproduced with permission from Johnson DD: Cesarean delivery. In Yeomans ER, Hoffman BL, Gilstrap LC III, et al (eds): Cunningham and Gilstrap's Operative Obstetrics, 3rd ed. New York, NY: McGraw Hill; 2017.)

J-, U-, and T-incisions extend into the contractile portion, and a subsequent trial of labor after cesarean (TOLAC) is more likely to be complicated by uterine rupture. Similarly, from limited data, inferior hysterotomy extensions also are associated with higher rupture rates, and in our practice these preclude TOLAC (Goldfarb, 2011). The Royal College of Obstetricians and Gynaecologists (2015) notes insufficient evidence to support the general safety of TOLAC in women with a prior significant uterine extension and cautions for decisions to be individualized. Last, a prior classical incision, described later, or a fundal incision substantially raises the rupture risk during subsequent TOLAC. Thus, following a primary cesarean delivery complicated by these exceptional incision types, a conversation disclosing these events and their significance should ensue with the patient and are carefully described in the operative report.

Delivery of the Fetus.

With a cephalic presentation, a hand is slipped into the uterine cavity between the symphysis and fetal head. The head is elevated gently with the fingers and palm through the incision. Once the head enters the incision, delivery may be aided by modest fundal pressure (Fig. 30-6).

After a long labor with cephalopelvic disproportion, the fetal head may be tightly wedged in the birth canal. This situation raises the risk of hysterotomy extension, of associated blood loss, and of fetal skull fracture. First, a "push" method may be used. With this, upward pressure exerted by a hand in the vagina by an assistant will help to dislodge the head and push it cephalad. If this is anticipated, a patient in frog-leg position may allow easier vaginal access.

Second, as an alternative, a "pull" method grasps the fetal legs and brings them through the hysterotomy. The fetus is then delivered as one would complete a breech extraction. Support for this latter approach comes from small randomized trials and retrospective cohort studies (Berhan, 2014; Jeve, 2016). The main advantage appears to be lower uterine extension rates.

Another pull method attempts to free the head by placing a palm on each fetal shoulder and gently elevating them. Last, a least-common method uses a "fetal pillow." This is a distensible intravaginal balloon that is positioned below the head and then inflated to elevate the fetal head. Evidence for its superiority to the push method is limited and conflicting (Sacre, 2021; Seal, 2016).

Conversely, in women without labor, the fetal head may be unmolded and lack a leading cephalic point. The round head may be difficult to lift through the uterine incision in a relatively thick lower segment that is unattenuated by labor. In such instances, either forceps or a vacuum device may be used to deliver the fetal head. For this, the fetal head is manually grasped and turned to an occiput transverse position. In this example, the head is left OT (LOT) position. Two or more fingers of the right hand are introduced inside the hysterotomy and behind the fetal head (Fig. 30-7). Fingers of the left hand grasp the handle of the forceps. The blade's toe is gently introduced between the hand and fetal head. It is curved inward between the fetal head and the palmar surface of the fingers. For the upper blade, two or more fingers of the left hand are inserted into the right posterolateral aspect of the hysterotomy. The forceps handle is grasped by the right hand. The blade toe

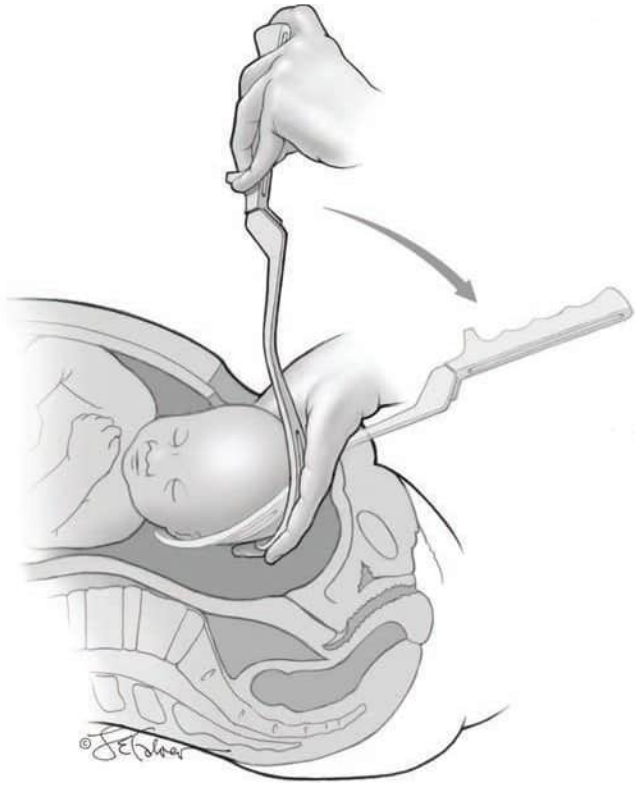

FIGURE 30-7 To place the first forceps blade, the operator's palm is slipped beneath the head. It is guided along the palm to ultimately lie across the fetal malar and lower parietal bone as in vaginal forceps application.

is then gently introduced along the posterior left lower uterine segment wall. It is curved inward between the fetal face and the palmar surface of the fingers (Fig. 30-8A). The fingers of the left hand are moved beneath the lower edge of this blade. Upward pressure against this edge will sweep or wander the blade into position. As the blade reaches its final position, the shank and handle come to rest in the midline, and the two handles are articulated (Fig. 30-8B). Traction is up and out to guide the occiput through the hysterotomy. Concurrent, gentle fundal pressure can be applied by an assistant.

After head delivery, a finger is passed across the fetal neck to determine whether it is encircled by one or more umbilical cord loops. If present, these are slipped over the head. The head is rotated to an occiput transverse position, which aligns the fetal bisacromial diameter vertically. The sides of the head are grasped with two hands, and gentle axial traction is applied until the anterior shoulder enters the hysterotomy incision. Next, by upward axial traction, the posterior shoulder is delivered. During delivery, abrupt or powerful lateral force is avoided to avert brachial plexus injury. With steady outward traction, the rest of the body then readily follows. Gentle fundal pressure may aid this.

With some exceptions, current American Heart Association recommends against routine neonatal suctioning immediately after birth, even with meconium present (Wyckoff, 2015). A fuller discussion of this and delayed umbilical cord clamping is found in Chapter 27 (p. 500). Specific to cesarean delivery, delayed clamping does not lower maternal hemoglobin levels on the first postoperative day (Jenusaitis, 2020; Purisch, 2019).

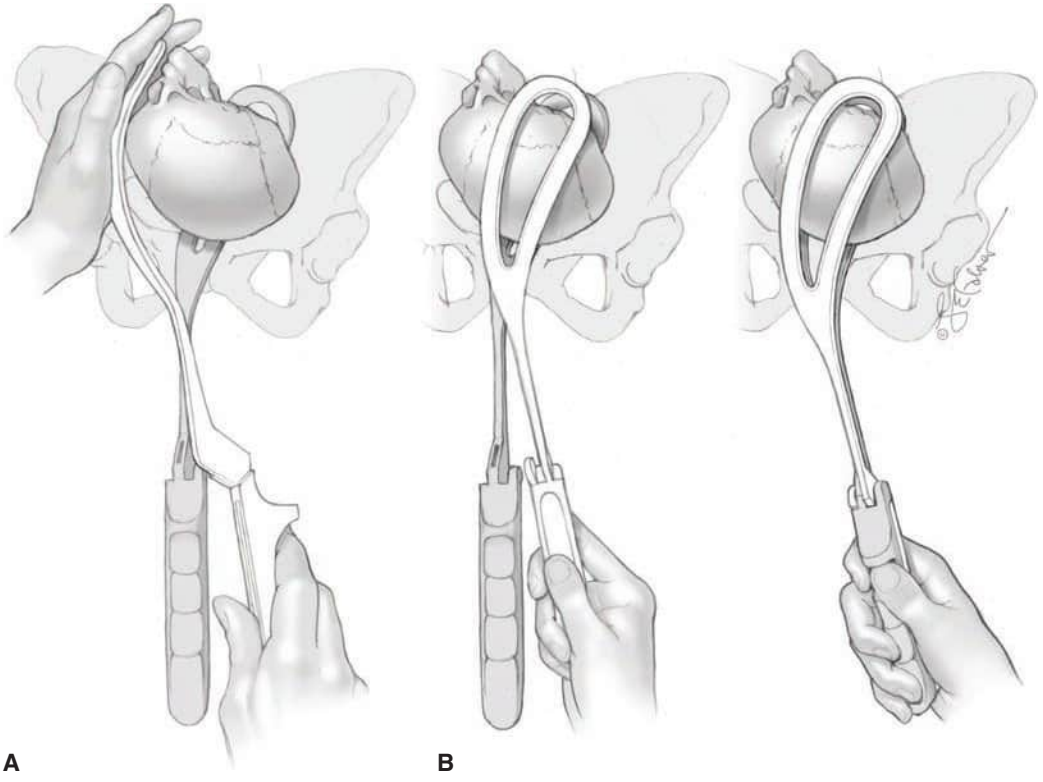

FIGURE 30-8 **A.** To apply the second blade, the operator's hand is inserted into the posterolateral aspect of the hysterotomy. The forceps blade is slipped inward across the palm. This hand then guides the blade to overlie the upper malar and parietal bones. **B.** Once positioned, the handles are interlocked. Slight upward and outward traction is used to lift the head through the incision.

After the umbilical cord is clamped, the newborn is given to the team member who will conduct care.

Comparing elective cesarean under neuraxial anesthesia and spontaneous vaginal deliveries, studies show that the need for neonatal resuscitation is not practically different between the two (Gordon, 2005). The American Academy of Pediatrics and the American College of Obstetricians and Gynecologists (2017) recommend that "a qualified person who is skilled in neonatal resuscitation should be in the delivery room." At Parkland Hospital, pediatric nurse practitioners attend uncomplicated, scheduled cesarean deliveries. Notably, as anticipated neonatal risks rise, so too should the resuscitative skills of the attendants (Wyckoff, 2015).

To promote breastfeeding, the American College of Obstetricians and Gynecologists (2020b) recommends skin-to-skin contact between newborn and mother in the delivery room. Although most randomized trials focus on vaginal birth, several small studies support such contact following cesarean delivery, and this is our practice (Frederick, 2020; Moore, 2016). Breastfeeding can be initiated the day of surgery.

Delivery of the Placenta. The uterine incision is observed for any vigorously bleeding sites. These should be quickly clamped with Pennington or ring forceps. Although some surgeons may prefer manual removal of the placenta, spontaneous delivery prompted by some gentle steady cord traction may reduce the risk of operative blood loss and infection (Anorlu, 2008; Baksu, 2005). Traction is coupled with fundal massage to hasten placental separation and delivery (Fig. 30-9).

Immediately after delivery and quick gross inspection of the placenta for missing portions, the uterine cavity is suctioned and wiped out with a gauze sponge to remove avulsed membranes, vernix, and clots. In the past, double-gloved fingers or ring forceps placed through the hysterotomy incision were used to dilate a closed cervix. This does not reduce infection or postpartum hemorrhage rates and is not our practice (Kirscht, 2017; Liabsuetrakul, 2018).

To help prevent uterine atony after birth, an IV infusion containing two ampules or 20 units of oxytocin per liter of crystalloid is infused at 10 mL/min. Some prefer higher infusion rates, however, nondilute boluses are avoided because of associated hypotension (Roach, 2013). Once the uterus contracts satisfactorily, the rate can be reduced. Although not available in the United States, an alternative is *carbetocin*, which is a longer-acting oxytocin derivative. It provides suitable, albeit more expensive, hemorrhage prophylaxis (Kalafat, 2021). Other choices for hemorrhage prophylaxis include misoprostol (Cytotec) and the ergots, namely methylergonovine (Methergine) and ergonovine (Ergotrate). A combination agent of oxytocin plus ergonovine (Syntometrine) is used outside the United States. Of agents, the World Health Organization (2018) recommends oxytocin for first-line use. Last, tranexamic acid (TXA) can be added to a standard oxytocin infusion to help prevent blood loss. Despite early encouraging evidence, methodology flaws have been cited (Franchini, 2018; Ker, 2016). With TXA in one large trial, rates of estimated blood loss >1000 mL or red-cell transfusion were lower than with placebo. But, TXA did not lower rates of common blood loss–related secondary clinical outcomes (Sentilhes, 2021). In contrast to prevention, treatment of atony is found in Chapter 42 (p. 734).

Uterine Repair. After placental delivery, the uterus is lifted through the incision and onto the draped abdominal wall. We favor exteriorizing and believe a relaxed, atonic uterus can be recognized quickly and massage applied. Incision and bleeding points are more easily visualized and repaired, especially if extensions were torn or the patient is obese. Adnexal exposure is superior, and thus, tubal sterilization is easier. In contrast, some clinicians prefer to close the hysterotomy with the uterus in situ. Comparing these two approaches, the Coronis Collaborative Group (2013) trial randomly assigned nearly 5000 parturients and found no differences in the endometritis or transfusion rate. In one large metaanalysis, nausea and vomiting and associated pain rates were comparable with either method (Zaphiratos, 2015).

Before hysterotomy closure, IUD insertion, if planned, is completed (Chap. 38, p. 668). Our practice is to perform a primary needle and sponge count prior to uterine incision closure completion. For closure, one end of the uterine incision is grasped to stabilize and maneuver the incision. The uterine incision is then closed with one or two layers of continuous 0- or no. 1 absorbable suture (Fig. 30-10). Chromic catgut suture is used by many, but some prefer synthetic delayed-absorbable polyglactin 910 (Vicryl). In subsequent pregnancy,

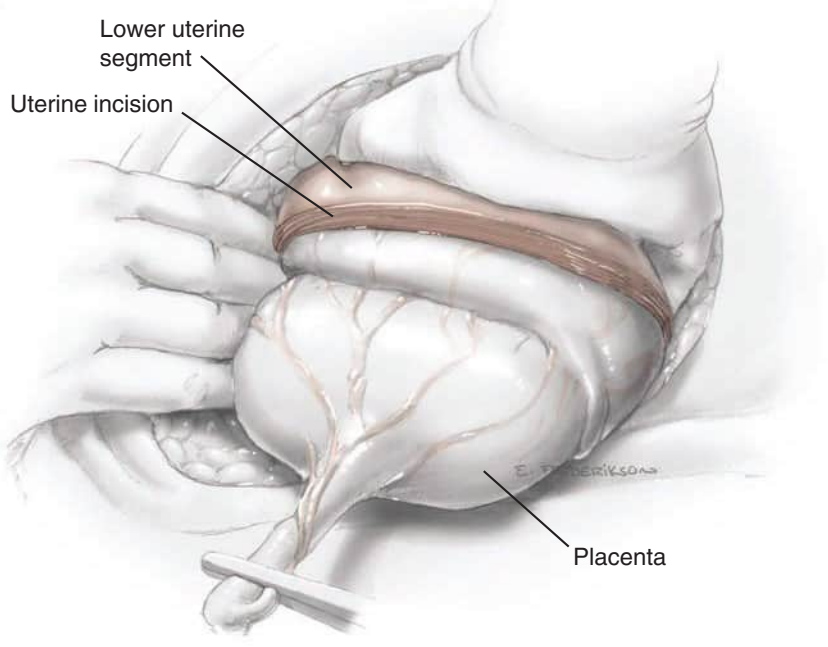

FIGURE 30-9 Placenta bulging through the uterine incision as the uterus contracts. A hand gently massages the fundus to help aid spontaneous placental separation.

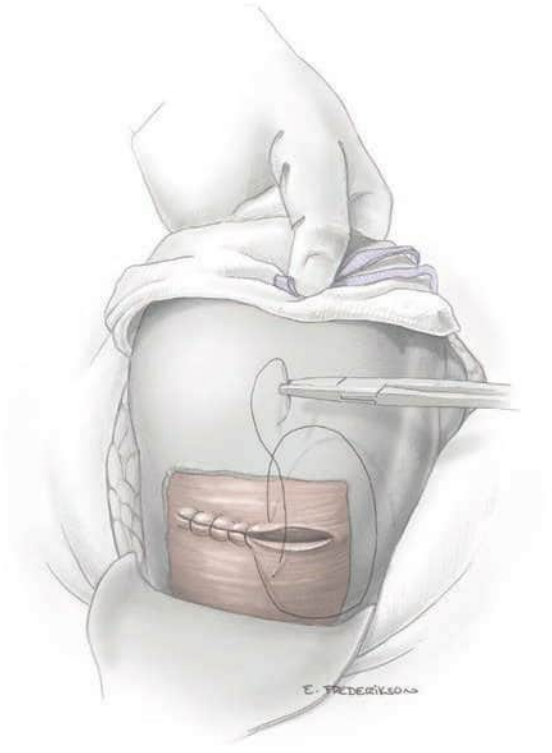

FIGURE 30-10 The cut edges of the uterine incision are approximated with a running, locking suture.

neither suture type is superior in mitigating against greater rates of adverse pregnancy outcomes such as uterine incision rupture (CORONIS Collaborative Group, 2016).

Single-layer closure is typically faster and is not associated with higher rates of infection or transfusion (CAESAR Study Collaborative Group, 2010; Dodd, 2014; Roberge, 2014). Moreover, most studies observed that the number of layers does not significantly affect complication rates in the next pregnancy (Chapman, 1997; CORONIS Collaborative Group, 2016; Durnwald, 2003). One randomized trial with nearly 1600 parturients found a slightly greater formation rate of cesarean scar niches at 3 months after double-layer closure (Stegwee, 2021).

At Parkland Hospital, we use a one-layer uterine closure with chromic catgut. The initial suture is placed just beyond one end of the uterine incision. A continuous, locking suture line for hemostasis is performed, and each suture penetrates the full myometrial thickness. The suture line then extends to a point just beyond the incision's opposite end. If bleeding sites or defects persist after a single layer, more sutures are required. Another layer of running suture or individually targeted figure-eight or mattress stitches are options.

Although not our routine practice, the peritoneum in the anterior cul-de-sac can be approximated with a continuous 2-0 chromic catgut suture line. Multiple randomized trials suggest that omission of this step causes no postoperative complications (Grundsell, 1998; Irion, 1996; Nagele, 1996). If tubal sterilization is planned, it is completed as described in Chapter 39 (p. 683).

Adhesions

Following cesarean delivery, adhesions commonly form within the vesicouterine space or between the anterior abdominal wall and uterus. With each successive pregnancy, the percentage of affected women and adhesion severity rise (Morales, 2007; Tulandi, 2009). Adhesions can significantly lengthen incision-to-delivery time and total operative time (Rossouw, 2013; Sikirica, 2012). Rates of cystotomy and bowel injury also are raised because of adhesive disease (Rahman, 2009; Silver, 2006).

Intuitively, scarring can be reduced by handling tissues delicately, achieving hemostasis, and minimizing tissue ischemia, infection, and foreign-body reaction. Most recent data on short- and long-term outcomes show no benefit to peritoneal closure (CAESAR Study Collaborative Group, 2010; CORONIS Collaborative Group, 2013, 2016; Kapustian, 2012). Similarly, most studies show no benefit from placement of an adhesion barrier at the hysterotomy site (Edwards, 2014; Kiefer, 2016).

Abdominal Closure

Any laparotomy sponges are removed, and the paracolic gutters and cul-de-sac are gently suctioned of blood and amniotic fluid. Some surgeons irrigate the gutters and cul-de-sac, especially in the presence of infection or meconium. Routine irrigation in low-risk women, however, leads to greater intraoperative nausea but not to lower postoperative infection rates (Eke, 2016; Viney, 2012).

Prior to abdominal closure, correct sponge and instrument counts are verified. The rectus abdominis muscle bellies are allowed to fall into place. The overlying rectus fascia is closed by a continuous, nonlocking technique with a delayed-absorbable suture. In patients with a higher risk for infection, monofilament suture may be preferable to braided material.

The subcutaneous tissue usually need not be closed if it is <2 cm thick. With thicker layers, however, closure is recommended to minimize seroma and hematoma formation, which can lead to wound infection, disruption, or both (Bohman, 1992; Chelmow, 2004). Adding a subcutaneous drain does not prevent significant wound complications (Hellums, 2007; Ramsey, 2005).

Skin is closed with a running subcuticular stitch of 4-0 delayed-absorbable suture, with adhesive glue, or with staples. In comparison, final cosmetic results and infection rates appear similar, skin suturing takes longer, but wound separation rates are higher with metal staples (Basha, 2010; Figueroa, 2013; Mackeen, 2014a, 2015). Poliglecaprone 25 (Monocryl) or polyglactin 910 (Vicryl) are both suitable (Tuuli, 2016). Outcomes with 2-octyl cyanoacrylate adhesive (Dermabond) were equivalent to sutures for Pfannenstiel incisions (Daykan, 2017; Siddiqui, 2013). A sterile thin abdominal wound dressing is sufficient. In obese women, most evidence favors against a negative-pressure wound vacuum atop the closed skin incision compared with a standard wound dressing to lower wound infection rates (Gillespie, 2021; Hussamy, 2019; Tuuli, 2020).

Joel-Cohen and Misgav Ladach Techniques

The Pfannenstiel-Kerr technique just described has been used for decades. Others include the more recent Joel-Cohen and Misgav Ladach techniques (Holmgren, 1999). These differ from traditional Pfannenstiel-Kerr entry mainly by their initial incision placement and greater use of blunt dissection.

The Joel-Cohen technique creates a straight 10-cm transverse skin incision 3 cm below the level of the anterior superior

iliac spines (Olofsson, 2015). The subcutaneous tissue layer is opened sharply 2 to 3 cm in the midline. This is carried down, without lateral extension, to the fascia. A small transverse incision is made in the fascia, and curved Mayo scissors are pushed laterally on each side and beneath intact subcutaneous fat to incise the fascia. With this incision completed, an index finger from each hand is inserted between the rectus abdominis muscle bellies and beneath the fascia. One finger is moved cranially and the other caudally, in opposition, to separate the bellies and further open the fascial incision. Then, a finger from each hand hooks under each belly to stretch the muscles laterally. The peritoneum is entered sharply, and this incision is sharply extended cephalocaudad. Entry with the Misgav Ladach technique differs in that the peritoneum is entered bluntly (Holmgren, 1999).

Modifications to the Joel-Cohen method abound. For emergency delivery, we begin along a line somewhat lower on the abdomen and similar to that for Pfannenstiel incision. For speed, we extend the initial fascial incision bluntly by hooking index fingers in the fascial incision's lateral corners and pulling laterally (Hofmeyr, 2009; Oloffson, 2015). Index fingers insinuated between the rectus bellies then move cephalocaudad in opposition to separate the muscle bellies. Blunt index-finger dissection enters the peritoneum, and again, cranial and caudad opposing stretch lengthens the peritoneal incision. Last, all the layers of the abdominal wall are grasped together and pulled laterally in opposition to further open the operating space.

These techniques have been associated with shorter operative times and with lower rates of intraoperative blood loss and postoperative pain (Mathai, 2013). They may, however, prove difficult for women with preexisting anterior rectus fibrosis and peritoneal adhesions (Bolze, 2013).

Classical Cesarean Incision

Indications. This incision is usually avoided because it encompasses the active upper uterine segment and thus is prone to rupture with subsequent pregnancies. Some indications stem from difficulty in exposing or safely entering the lower uterine segment. For example, a densely adhered bladder from previous surgery is encountered; a *leiomyoma* occupies the lower uterine segment; or the cervix is currently invaded by cancer. Women with prior radical trachelectomy for cervix cancer are usually delivered by classical incision. Massive maternal obesity can preclude safe access to the lower uterine segment. A classical incision is also preferred for placenta previa with anterior implantation, especially those complicated by placenta accreta syndrome. In extreme cases of this, the typical classical hysterotomy may be placed even higher in the uterine body or posteriorly to avoid the placenta. Fetuses with cephalic presentation are then delivered in a manner similar to total breech extraction.

In other instances, fetal indications dictate the need. *Transverse lie of a large fetus*, especially if the membranes are ruptured and the shoulder is impacted in the birth canal, usually requires a classical incision. Second, with a fetus presenting as a back-down transverse lie, the back precludes easy grasping of a leg through a transverse uterine incision for breech delivery. Here, a classical incision provides superior room. Third, in instances when the fetus is very small and breech, a classical incision may be preferable (Osmundson, 2013). In such cases, the poorly developed lower uterine segment provides inadequate space for the manipulations required for breech delivery. Or, less commonly, the small fetal head may become entrapped by a contracting uterine fundus following membrane rupture. With multiple fetuses, a classical incision again may provide needed room for extraction of fetuses that may be malpositioned or preterm (Osmundson, 2015). A large fetal malformation or conjoined twins may require the added space afforded by a classical incision.

Uterine Incision and Repair. A vertical uterine incision is initiated with a scalpel beginning as low as possible and preferably within the lower uterine segment (Fig. 30-11). If adhesions, insufficient exposure, a tumor, or placenta percreta preclude development of a bladder flap, then the incision is made above the level of the bladder. Described earlier (p. 553), back filling the bladder may aid this.

Once the uterus is entered with a scalpel, the incision is extended cephalad with bandage scissors until it is long enough to permit fetal delivery. With scissor use, the fetus can be better protected from laceration. Fingers of the surgeon's nondominant hand are insinuated between the myometrium and fetus to prevent scissor cuts. As the incision is opened, numerous large vessels that bleed profusely are commonly encountered within the myometrium. The remainder of fetal and placental delivery mirrors that with a low transverse hysterotomy.

For incision closure, one method employs a layer of 0- or no. 1 chromic catgut with a running stitch to approximate the

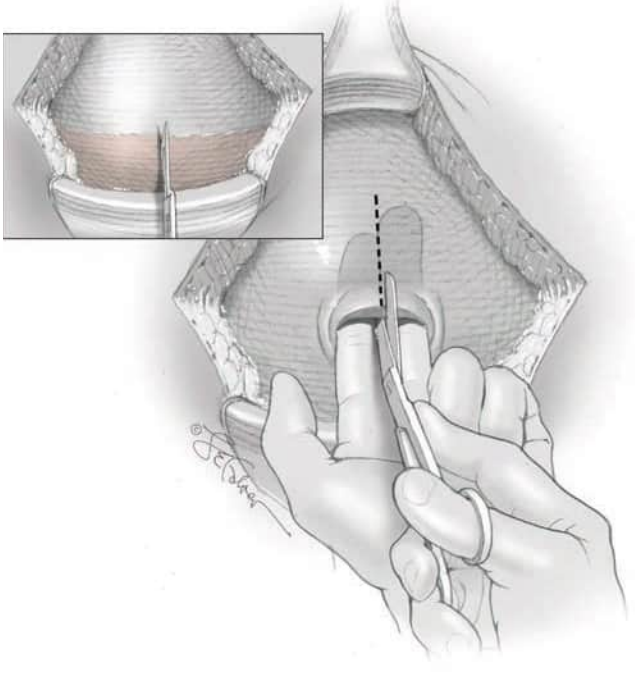

FIGURE 30-11 An initial small vertical hysterotomy incision is made in the lower uterine segment. Fingers are insinuated between the myometrium and fetus to avoid fetal laceration. Scissors extend the incision cephalad as needed for delivery. (Figures 30-11 and 30-12: Reproduced with permission from Johnson DD: Cesarean delivery. In Yeomans ER, Hoffman BL, Gilstrap LC III, et al (eds): Cunningham and Gilstrap's Operative Obstetrics, 3rd ed. New York, NY: McGraw Hill; 2017.)

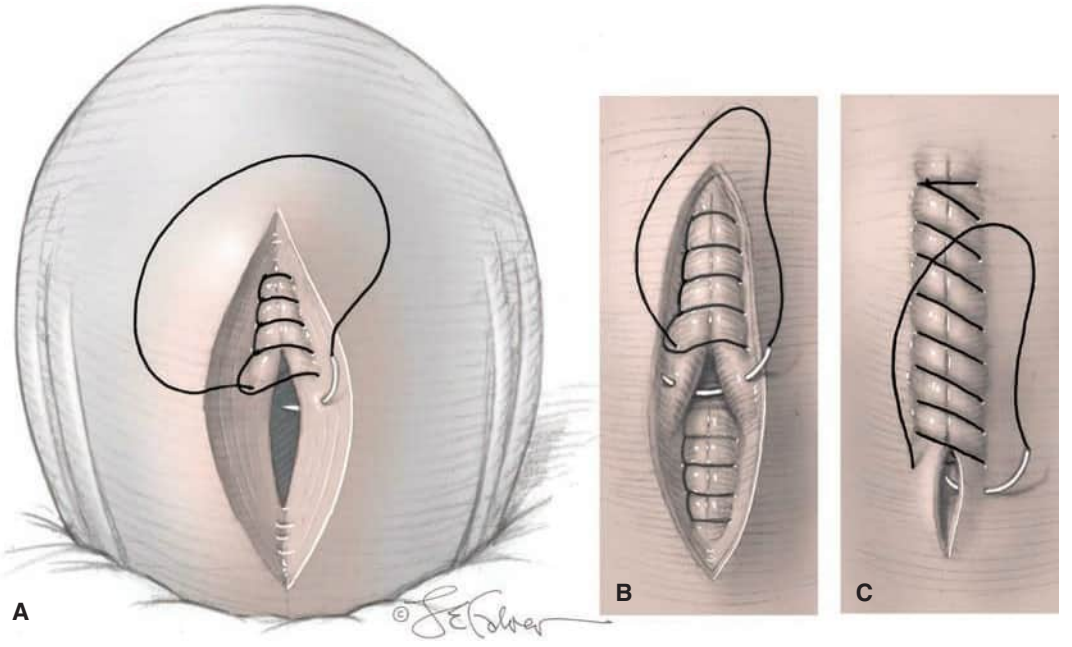

FIGURE 30-12 Classical incision closure. The deeper half (**A**) and superficial half (**B**) of the incision are closed in a running fashion. The serosa is then closed (**C**).

deeper length of the incision (Fig. 30-12). The outer layer of myometrium is then closed along its length with similar suture and with a running suture line. To achieve good approximation and to prevent the suture from tearing through the myometrium, it is helpful to have an assistant relieve tension by compressing the uterus on each side of the wound toward the midline as each stitch is placed.

PERIPARTUM HYSTERECTOMY

Indications

Hysterectomy is most commonly performed to arrest or prevent hemorrhage from intractable uterine atony, surgical trauma/tears, or abnormal placentation (Bateman, 2012; Kallianidis, 2020). It is more often completed during or after cesarean delivery but may be needed following vaginal birth. Among all deliveries, the peripartum hysterectomy rate in the United States approximates 1 per 1000 births and has risen significantly during the past few decades (Bateman, 2012; Govindappagari, 2016). During a 25-year period, the rate of peripartum hysterectomy at Parkland Hospital was 1.7 per 1000 births (Hernandez, 2012). Most of this rise is attributed to the increasing rates of cesarean delivery and its associated complications in subsequent pregnancy (Flood, 2009; Orbach, 2011). Of hysterectomies, approximately one half to two thirds are total, whereas the remaining cases are supracervical (Rossi, 2010; Shellhaas, 2009).

Major complications of peripartum hysterectomy include greater blood loss and risk of urinary tract damage. Blood loss is usually appreciable because hysterectomy is being performed for hemorrhage that frequently is torrential, and the procedure itself is associated with substantial bleeding. Although many cases with hemorrhage cannot be anticipated, those with abnormal implantation are often identified antepartum. Preparations for placenta accreta syndrome are discussed in Chapter 43 (p. 763) and are outlined by the American College of Obstetricians and Gynecologists (2018).

An important factor affecting the cesarean hysterectomy complication rate is whether the operation is performed electively or emergently. With anticipated or planned cesarean hysterectomy, rates of blood loss, blood transfusion, and urinary tract complications are lower those with emergent procedures (Briery, 2007; Glaze, 2008).

Hysterectomy Technique

Total or supracervical hysterectomy is performed using standard operative techniques. Adequate exposure is essential, but initially, placement of a self-retaining retractor such as a Balfour is not necessary. Rather, satisfactory exposure is obtained with cephalad traction on the uterus by an assistant, along with handheld Richardson or Deaver retractors. The bladder flap is deflected caudad to the level of the cervix if possible to permit total hysterectomy. In cases in which cesarean hysterectomy is planned or strongly suspected, extended bladder flap dissection is ideally completed before initial hysterotomy. Later attempts at bladder dissection may be obscured by bleeding, or excess blood may be lost during this dissection.

After cesarean delivery, the placenta is typically removed. In cases of placenta accreta syndrome for which hysterectomy is already planned, the placenta is usually left undisturbed in situ. If the hysterotomy incision is bleeding appreciably, it can be quickly reapproximated with full-thickness sutures, or Pennington or sponge forceps can be applied for hemostasis. If bleeding is minimal, neither maneuver is necessary.

The round ligament is divided close to the uterus between clamps, and each pedicle is ligated (Fig. 30-13). Either 0 or no.

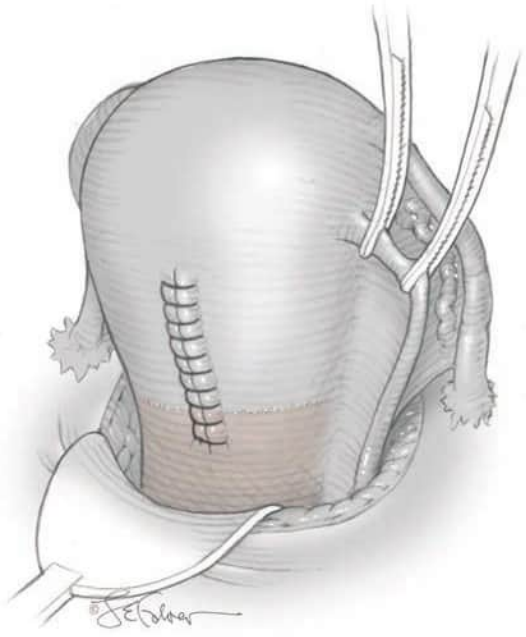

FIGURE 30-13 The round ligaments are clamped, ligated, and transected bilaterally. (Figures 30-13 to 30-21: Reproduced with permission from Cunningham FG, Gilstrap LC III: Peripartum hysterectomy. In Yeomans ER, Hoffman BL, Gilstrap LC III, et al (eds): Cunningham and Gilstrap's Operative Obstetrics, 3rd ed. New York, NY: McGraw Hill; 2017.)

1 suture can be used in either chromic gut or delayed-absorbable material. Division of the round provides access to the anterior leaf of the broad ligament, which is incised downward to meet the former bladder flap incision. The posterior leaf of the broad ligament adjacent to the uterus is bluntly or sharply perforated at a point beneath the fallopian tube, uteroovarian ligament, and ovarian vessels (Fig. 30-14). These structures together are then divided between sturdy clamps placed close to the uterus (Fig. 30-15). The lateral pedicle is doubly ligated. The medial clamp remains and is removed later with the entire uterine specimen. The posterior leaf of the broad ligament

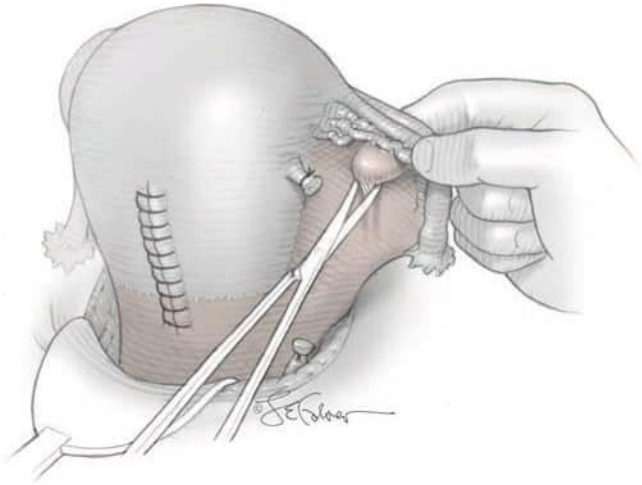

FIGURE 30-14 The posterior leaf of the broad ligament adjacent to the uterus is perforated just beneath the fallopian tube, uteroovarian ligaments, and ovarian vessels.

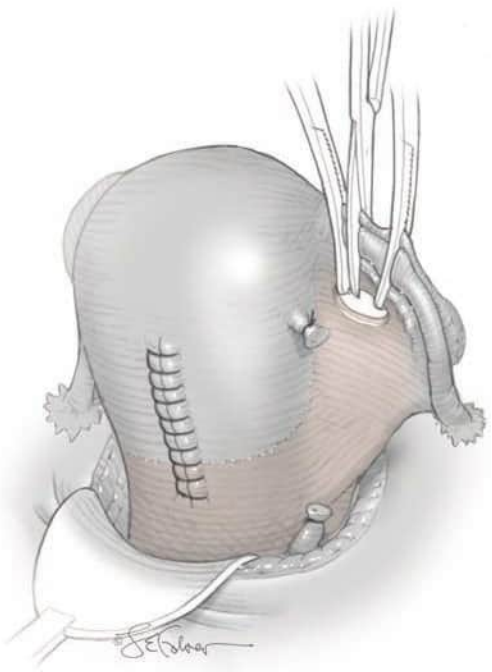

FIGURE 30-15 The uteroovarian ligament and fallopian tube are clamped and cut. The lateral pedicle is doubly ligated.

is then incised caudad toward the uterosacral ligaments (Fig. 30-16). The bladder and attached peritoneal flap are further deflected and dissected as needed. If the bladder flap is densely adhered, as it may be after previous hysterotomy incisions, careful sharp dissection is employed (Fig. 30-17).

Special care is required from this point on to avoid injury to the ureters, which pass beneath the uterine arteries. To help accomplish this, an assistant places constant traction to pull the

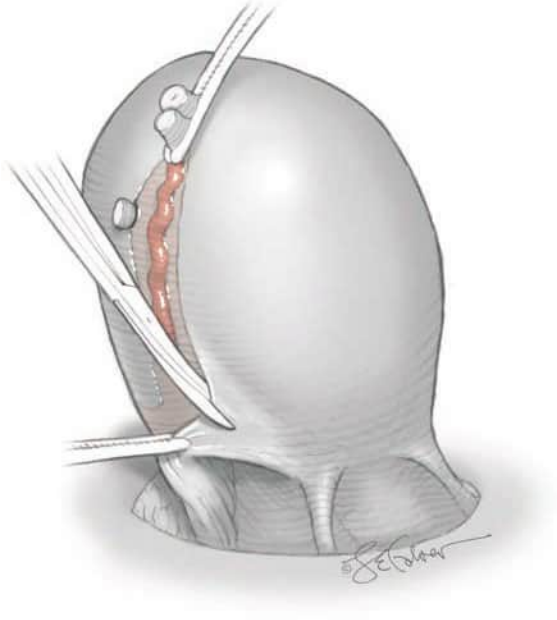

FIGURE 30-16 The posterior leaf of the broad ligament is divided inferiorly toward the uterosacral ligament.

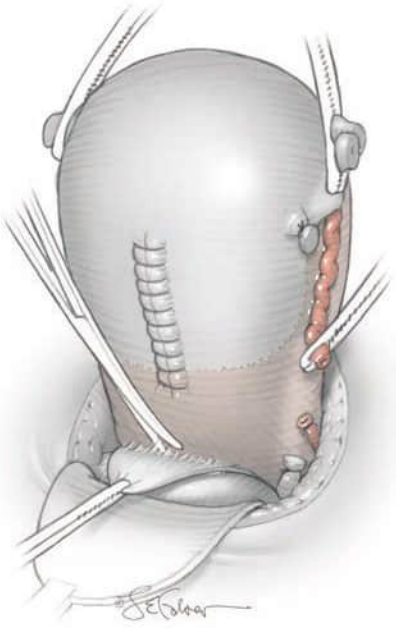

FIGURE 30-17 The bladder is dissected sharply from the lower uterine segment.

uterus in the direction away from the side on which the uterine vessels are being ligated. The ascending uterine artery and veins on either side are identified. These vessels are then clamped adjacent to the uterus (Fig. 30-18). For security, some may prefer two lateral clamps. The medial-most clamp helps prevent back bleeding from the uterus. The uterine vessels are divided, and the lateral tissue pedicle is doubly suture ligated. The medial clamp remains for later removal with the specimen. After securing the uterine vessels on one side, the round ligament, adnexal pedicle, and uterine vessels are then addressed on the contralateral side.

In cases with profuse hemorrhage, time and rapid hemostasis can be gained by quickly clamping and dividing all of the just-described pedicles. Once all are clamped, the surgical team can then return to ligate each pedicle individually.

Total Hysterectomy

Even if total hysterectomy is planned, we find it technically easier in many cases to finish the operation after amputating the uterine fundus and placing Ochsner or Kocher clamps on the cervical stump for traction and hemostasis. Self-retaining retractors also may be placed at this time. To remove the cervix, the bladder is mobilized further if needed. This carries the ureters caudad as the bladder is retracted beneath the symphysis. Bladder retraction can also help prevent laceration or suturing of the bladder during cervical excision and vaginal cuff closure.

The cardinal ligament, the uterosacral ligaments, and the many large vessels within these ligaments are clamped systematically with sturdy Heaney-type curved or straight clamps (Fig. 30-19). The clamps are placed as close to the cervix as possible, taking care not to include excessive tissue in each clamp. The tissue between the pair of clamps is incised, and the lateral pedicle is suture ligated. These steps are repeated caudally and bilaterally until the level of the lateral vaginal fornix is reached on each side. In this way, the descending branches of the uterine vessels are clamped, cut, and ligated as the cervix is separated from the cardinal ligaments.

If the cervix is effaced and dilated considerably, its softness may obscure palpable identification of the cervicovaginal junction. The junction location can be ascertained either through the open hysterotomy incision or through a vertical uterine incision made anteriorly in the midline at the level of the ligated uterine vessels. A finger is directed inferiorly through the incision to identify the free margin of the dilated, effaced cervix. The contaminated glove is replaced. Another useful method to

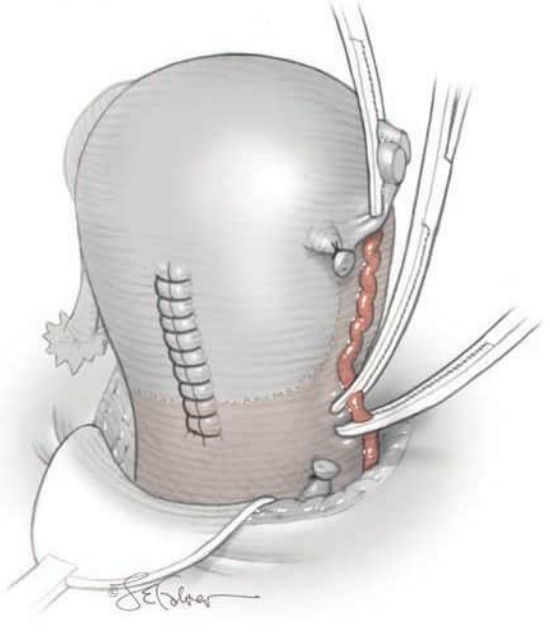

FIGURE 30-18 The uterine vessels are clamped. Once divided, the lateral vascular pedicle is doubly ligated to ensure hemostasis.

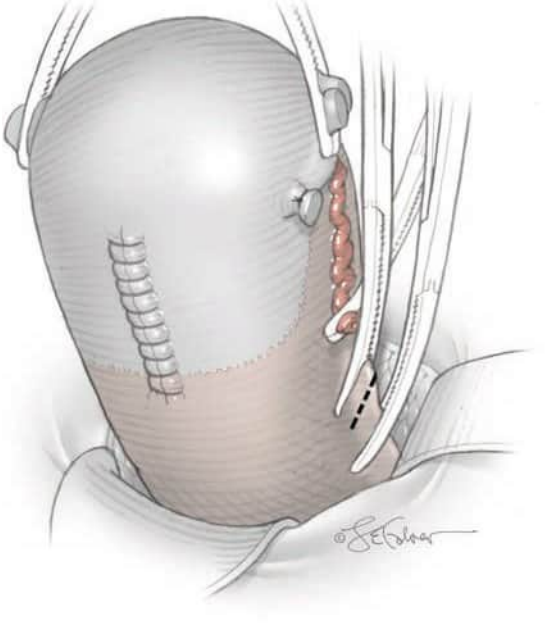

FIGURE 30-19 The cardinal ligaments are clamped, incised, and ligated.

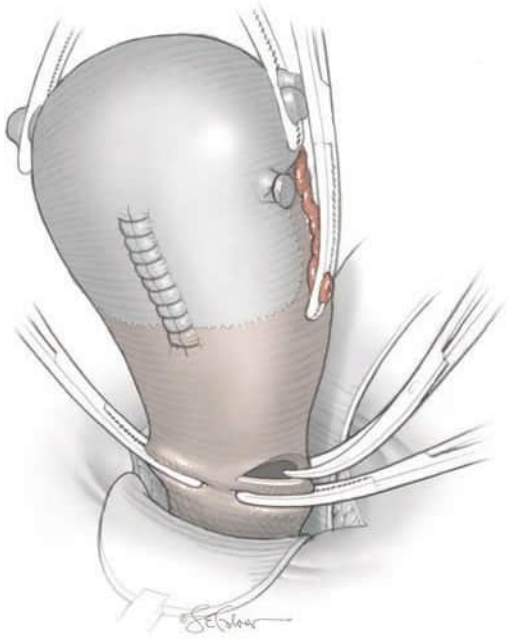

FIGURE 30-20 A curved clamp is placed across the lateral vaginal fornix below the level of the cervix, and the tissue incised medially to the point of the clamp.

identify the cervical margins in cases of planned hysterectomy is to transvaginally place four metal skin clips or brightly colored sutures at 12, 3, 6, and 9 o'clock positions on the cervical edges.

Immediately below the level of the cervix, a curved clamp is placed across the lateral vaginal fornix on each side, and the vagina is incised above the clamp (Fig. 30-20). The cervix is inspected to ensure that it has been completely removed. A transfixing suture is used for vaginal cuff closure as each clamp is removed. Interrupted stitches may be added to approximate the middle portion of the cuff (Fig. 30-21). Each lateral vaginal fornix is secured to the uterosacral ligaments to mitigate later vaginal prolapse. For cuff closure, some surgeons instead prefer to close the vagina by apposing the anterior and posterior vaginal walls with interrupted figure-eight sutures or running suture line.

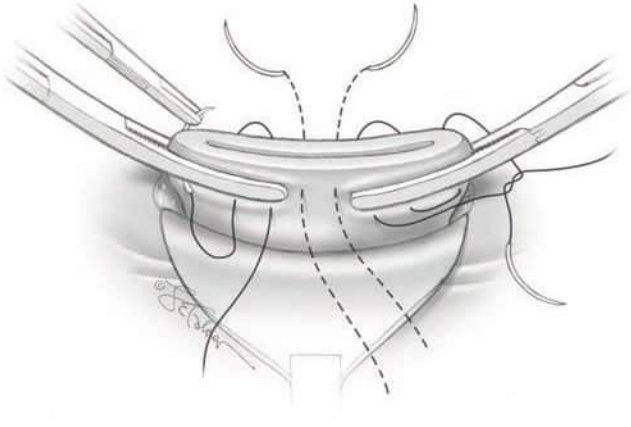

FIGURE 30-21 A transfixing stitch is placed on each side to close the lateral vaginal cuff. Interrupted stitches (dotted lines) may be needed to close any midline gap.

All sites are examined carefully for bleeding. One technique is to perform a systematic bilateral survey from the fallopian tube and ovarian ligament pedicles to the vaginal vault and bladder flap. Bleeding sites are ligated with care to avoid the ureters. The abdominal wall normally is closed in layers, as previously described for cesarean delivery (p. 558).

Supracervical Hysterectomy

To perform a subtotal hysterectomy, the uterine body is amputated immediately above the level of uterine artery ligation. The cervical stump may be closed with a continuous or interrupted suture line of chromic catgut or delayed-absorbable material. Subtotal hysterectomy is often all that is necessary to stop hemorrhage. It may be preferred for women who would benefit from a shorter surgery or for those with extensive adhesions that threaten significant urinary tract injury.

Salpingo-oophorectomy

Because of the large adnexal vessels and their close proximity to the uterus, it may be necessary to remove one or both adnexa to obtain hemostasis. Briery and colleagues (2007) reported unilateral or bilateral oophorectomy in a fourth of cases. Preoperative counseling for anticipated hysterectomy should include this possibility.

■ Urinary Tract or Bowel Injury

These injuries are rare during cesarean delivery. The bladder laceration rate approximates 2 injuries per 1000 cesarean deliveries, whereas that for ureteral trauma nears 0.3 events per 1000 cases (Güngördük, 2010; Oliphant, 2014). Bowel is damaged in about 1 in 1000 cesarean deliveries (Silver, 2006).

Cystotomy

Bladder laceration most commonly occurs during blunt or sharp dissection in the vesicouterine space to create the bladder flap, during peritoneal cavity entry, and during hysterotomy (Phipps, 2005; Rahman, 2009). Risks are prior cesarean delivery; comorbid adhesive disease; emergency cesarean delivery; cesarean hysterectomy, especially cases with morbidly adherent placenta; and surgery in second-stage labor compared with first-stage (Alexander, 2007; Salman, 2017; Silver, 2006).

Bladder injury is typically identified intraoperatively, and a clear-fluid gush or the Foley bulb are indicators. In suspected cases, cystotomy can be confirmed with retrograde instillation of fluid through a Foley catheter and into the bladder. Dilute sterile infant formula is a common, available option. Methylene blue–stained saline is another. Leakage of the indicator fluid aids laceration identification and delineation of its borders. The dome is lacerated most often, and trigone injuries make up the remainder (Phipps, 2005; Salman, 2017).

Prior to cystotomy repair, ureters are examined, and urine jets from each orifice are sought. Inspection can be done directly through the cystotomy, if at the dome. A separate diagnostic extraperitoneal cystotomy may be preferable if the laceration nears the trigone. To aid viewing, urine jets can be colored by IV dye, as described in the next section.

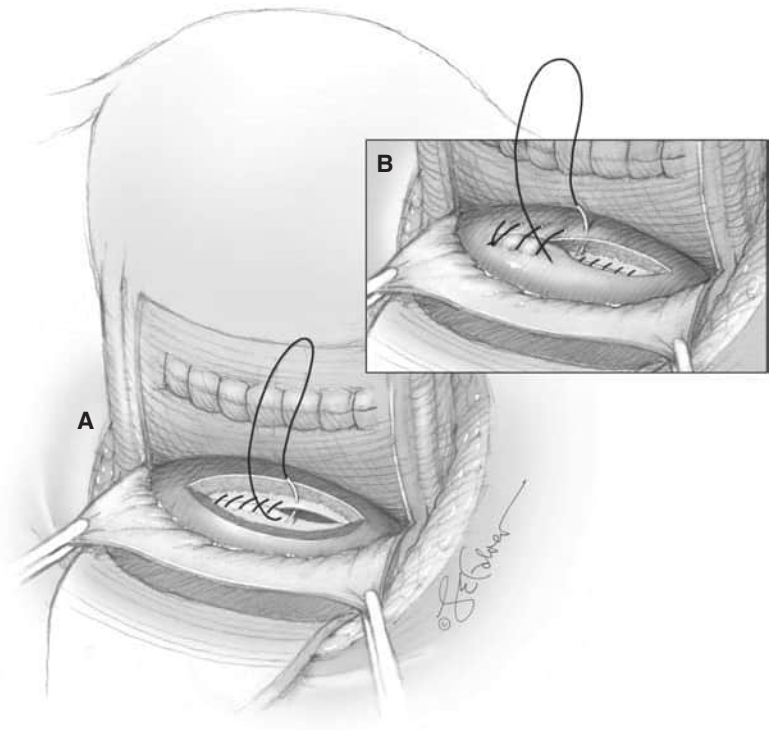

FIGURE 30-22 Cystotomy repair. **A.** The primary layer inverts the bladder mucosa with running or interrupted sutures of 3-0 delayed-absorbable or absorbable suture. **B.** Second and possibly a third layer approximate the bladder muscularis to reinforce the incision closure. (Reproduced with permission from Balgobin S: Urologic and gastrointestinal injuries. In Yeomans ER, Hoffman BL, Gilstrap LC III, et al (eds): Cunningham and Gilstrap's Operative Obstetrics, 3rd ed. New York, NY: McGraw Hill; 2017.)

Once ureteral patency is confirmed, the bladder can be closed with a two- or three-layer running closure using a 3-0 absorbable or delayed-absorbable suture (Fig. 30-22). The first layer inverts the mucosa into the bladder. Subsequent layers reapproximate the bladder muscularis. After the final layer, the bladder is filled with a marker fluid to demonstrate repair integrity. Leaking defects are closed with interrupted reinforcing stitches.

Postoperative care requires continuous bladder drainage for 7 to 14 days to permit healing and minimize the risk of fistula formation. Uropathogen prophylaxis during this drainage is not required. Prior to catheter removal, cystourethrography may not be needed for a simple, single laceration measuring under 1 cm (Glaser, 2019).

Larger lacerations in or near the trigone require careful attention. Specialists may be consulted, and in preparation, ureteral catheters, described in the next section, can be assembled. Ureteral orifices are directly inspected to document jets from both. If not seen, a ureteral catheter may be passed through the cystotomy and into each orifice to confirm patency. Once this is confirmed, repair should not disrupt the ureteral orifices, and stents may remain to ensure their patency.

Unrecognized cystotomy can manifest postoperatively as hematuria, oliguria, abdominal pain, ileus, ascites, peritonitis, fever, urinoma, or fistula. For diagnosis, retrograde cystography or abdominal computed tomography (CT) with cystography can be used (Tarney, 2013). Cystoscopy is also an option but may require a procedural room. Once cystotomy is identified, prompt repair is indicated (Balgobin, 2017).

Ureteral Injury

The ureter may be at risk during cesarean hysterectomy, especially those complicated by placenta accreta syndrome. (Woldu, 2014). Although not our practice, some advocate preoperative ureteral catheter placement to aid intraoperative ureter identification (Eller, 2009; Matsubara, 2013). Organization guidelines recommend individualization of this practice depending on anticipated placenta accreta syndrome complexity (American College of Obstetricians and Gynecologists, 2018; Collins, 2019). Further, initial dorsal lithotomy positioning of the patient for these cases can permit cystoscopy. Aside from hysterectomy, the ureter is also at risk during repair of hysterotomy extensions into the broad ligament or vagina (Safrai, 2020).

If ureteral injury is suspected, IV dye is administered, and the pelvis is directly inspected for extravasation. Of options, 50 mg of IV methylene blue may be given over 5 minutes. However, methylene blue carries the potential for inciting methemoglobinemia in patients with glucose-6-phosphate dehydrogenase deficiency. Another option is 25 or 50 mg of IV 10-percent sodium fluorescein, which stains bright yellow (Espaillat-Rijo, 2016; Grimes, 2017).

Next, brisk dye-stained urine jets are sought from each orifice to exclude ureteral kinking or ligation. Orifice viewing may be via cystoscopy, if available; through a comorbid traumatic cystotomy; or through an intentional diagnostic cystotomy. For the last, a midline extraperitoneal cystotomy in the bladder dome gives excellent exposure. Sluggish or absent jets may reflect patient hypovolemia, and ongoing volume resuscitation may yield expected orifice jets. If not, consultation with a specialist is typically requested to exclude ureteral injury.

While waiting, catheters and stents can be assembled. Semantically, *ureteral catheters* are diagnostic tools, and typically are inserted and removed in the same therapeutic intervention. Most stents are designed to remain indwelling for prolonged ureteral drainage. Both types are hollow to permit radiopaque medium injection and to allow urine egress through or around them (Corton, 2020).

To exclude ureteral obstruction, a 4F to 6F open-ended or whistle-tip catheter is threaded into one orifice. Once inserted, the catheter is advanced to the level of suspected obstruction. If the tool threads easily up toward the renal pelvis, obstruction is unlikely. In most, ureteral injury occurs at or below the pelvic brim, and the distance from the ureteral orifice to the brim approximates 13 cm (Jackson, 2019). Failure to easily advance the catheter may indicate ureteral kinking, ligation, or crush injury. The appearance of the catheter in the abdominal cavity indicates partial or complete transection (Balgobin, 2017).

Repair of ureteral injuries is dependent upon the type of injury and location.

First, kinked or ligated ureters can be relieved by release of ensnaring sutures. Crush injuries are inspected to ensure vital tissue. In these cases, stents are left to avert ureteral stricture. Ureteral stents range from 4F to 7F. Stents vary in length from 20 to 30 cm, and a 24-cm or 26-cm length is appropriate for most adults. Double-pigtail or double-J stents describe their tip shape, and the ends coil within the renal pelvis and bladder, respectively, to prevent stent migration (Corton, 2020). A Foley catheter remains for 7 to 10 days, and the ureteral stents are removed via cystoscopy after 14 days. Intravenous pyelography (IVP) is usually not necessary before removal of the stent if it was placed as a precautionary measure after relatively minor injury (Davis, 1999).

Crush injuries with devascularization, thermal injury, or transection require more extensive repair. If a healthy-appearing ureter can be reimplanted into the bladder without undue tension, then ureteroneocystostomy is preferable. For more proximal injuries, a ureteroureterostomy, a psoas hitch, or a Boari flap may be needed. An explanation of these more extensive procedures is found in *Cunningham and Gilstrap's Operative Obstetrics*, 3rd edition (Balgobin, 2017).

Unrecognized ureteral injury can mimic that of cystotomy with the addition of possible costovertebral angle tenderness. CT urography is a preferred initial diagnostic tool (Sharp, 2016). The duration of time from injury to identification directs repair. Those identified early are often suitable for immediate repair.

Bowel Injury

Serosal tears represent weak points in the small bowel. If obstruction develops postoperatively, these weak spots may perforate, leading to peritonitis. If serosal tears are few, they can be oversewn with either a fine absorbable or nonabsorbable suture (Davis, 1999). More significant lacerations are often repaired in consultation with a general surgeon or gynecologic oncologist.

POSTOPERATIVE CARE

Euvolemia Evaluation

During and after cesarean delivery, requirements for IV fluids can vary considerably. Current ERAS strategies aim for euvolemic replacement (Caughey, 2018). Administered fluids consist of either lactated Ringer solution or a similar crystalloid solution with 5-percent dextrose. Blood loss with uncomplicated cesarean delivery approximates 1000 mL. The average-sized woman with a hematocrit of 30 percent or more and with a normally expanded blood and extracellular fluid volume most often will tolerate blood loss up to 2000 mL without difficulty. Unappreciated bleeding through the vagina during the procedure, bleeding concealed in the uterus after its closure, or both commonly lead to underestimation.

Blood loss averages 1500 mL with elective cesarean hysterectomy, although this is variable (Pritchard, 1965). Most peripartum hysterectomies are unscheduled, and blood loss in these cases is correspondingly greater. Thus, in addition to close monitoring of vital signs and urine output, the hematocrit should be determined intra- or postoperatively as indicated.

Recovery Suite

The amount of vaginal bleeding is closely monitored for at least an hour in the immediate postoperative period. The uterine fundus is also identified frequently by palpation to ensure that the uterus remains firmly contracted. Criteria for transfer to the postpartum ward include minimal bleeding, stable vital signs, and adequate urine output.

Hospital Care until Discharge

Analgesia, Vital Signs, Intravenous Fluids

Several schemes are suitable for postoperative pain control. First, adding intrathecal opioid or epidural opioid such as morphine to neuraxial analgesia can provide 12 to 24 hours of postoperative relief (American College of Obstetricians and Gynecologists, 2019a; Caughey, 2018). Sedation and respiratory depression rise with increasing intrathecal opioid doses. Postoperative monitoring protocols reflect this and are outlined in Chapter 25 (p. 472) (Bauchat, 2019). Other potential side effects include pruritus, nausea, or vomiting (Sultan, 2016). Despite these, long-acting neuraxial analgesia is recommended instead of intermittent parental opioid dosing (American Society of Anesthesiologists, 2016). For additional relief, nonsteroidal antiinflammatory drugs (NSAIDs) can alternate with acetaminophen (Ong, 2010). Breakthrough pain can be relieved by oxycodone 2.5 to 5 mg every 4 hours (Bollag, 2021). Neonatal sedation is a concern, and total oxycodone doses higher 30 mg/d are not recommended (American College of Obstetricians and Gynecologists, 2019a). Instead, for severe breakthrough pain, intramuscular (IM) meperidine, 50 to 75 mg every 3 to 4 hours, or IM morphine, 10 to 15 mg every 3 to 4 hours, is an option.

For those without neuraxial anesthesia, a transversus abdominis place (TAP) block can be considered (Fig. 2-2, p. 14). Patient-controlled analgesia (PCA) also is reasonable. One PCA regimen uses IV morphine given as needed as a 1-mg dose with a 6-minute lockout interval and maximum dose of 30 mg in 4 hours. An additional 2-mg booster dose is permitted for a maximum of two doses.

After transfer to her room, the woman is assessed at least hourly for 4 hours, and thereafter at intervals of 4 hours. Deep breathing and coughing are encouraged to prevent atelectasis. Vital signs, uterine tone, urine output, and vaginal and incisional bleeding are evaluated. The hematocrit is routinely measured the morning after surgery. It is checked sooner if blood loss was significant or if postoperative hypotension, tachycardia, oliguria, or other evidence suggests hypovolemia. If the hematocrit is significantly lower than the preoperative level, the measurement is repeated and a search for the cause is instituted. Clinical and objective thresholds for transfusion are described fully in Chapter 44 (p. 771). If ongoing blood loss is not expected, iron therapy is preferred to transfusion.

Postpartum, the patient begins to mobilize and excrete her physiologically expanded extravascular volume. Thus, maintenance IV fluid proves adequate after surgery until consistent oral intake is reestablished. If urine output falls below 30 mL/hr, however, a woman should be reevaluated promptly. The cause of the oliguria may range from unrecognized blood loss to an antidiuretic effect from infused oxytocin.

Women undergoing unscheduled cesarean delivery may have pathological retention or constriction of the extracellular fluid compartment caused by severe preeclampsia, sepsis syndrome, vomiting, prolonged labor without adequate fluid intake, or increased blood loss. Women with these complications are generally observed in the recovery room until improved.

Bladder and Bowel Function

A Foley catheter is often required to accurately assess urinary output. For women not needing such monitoring, organizations differ in their recommendations. The Society for Obstetric Anesthesia and Perinatology suggests removal after 6 to 12 hours and cites the urinary retention risks associated with long-acting neuraxial anesthesia (Bollag, 2021). The ERAS Society recommends immediate postoperative removal (Macones, 2019). The prevalence of urinary retention following cesarean delivery approximates 5 percent (Chap. 36, p. 643). Failure to progress in labor and postoperative narcotic analgesia are identified risks (Chai, 2008; Liang, 2007).

In uncomplicated cases, liquids or solid food may be offered within hours of surgery and advanced as tolerated (Guo, 2015; Macones, 2019). Some degree of adynamic ileus follows virtually every laparotomy but is negligible after most cesarean deliveries. Postoperative ileus symptoms include abdominal distention, colic, and an inability to pass flatus or stool. With persistent nausea and vomiting or with prolonged bowel function delay, radiological imaging may help exclude bowel obstruction. A plain abdominal radiograph is a frequent first choice. However, in the general population, this study is diagnostic in only 50 to 60 percent of small-bowel obstruction (SBO) cases (Maglinte, 1997). Thus, a radiograph may best serve as a triage tool in cases in which ileus is the suspected diagnosis. Notably, an enlarged postpartum uterus can compress the rectosigmoid and prevent it from filling with gas. Thus, findings suggesting a distal colonic obstruction may confuse true cases of transient ileus (Kammen, 2000). CT with IV and oral contrast provides greater accuracy for SBO diagnosis. Last, although uncommon, an unrecognized bowel injury may underlie otherwise unexplained fever and bowel dysfunction. Again, CT would be the more diagnostic examination.

For treatment of ileus, IV fluids compensate for poor oral intake and losses from emesis. Electrolyte imbalances are corrected to improve bowel motility and avoid bowel edema. Nasogastric decompression is necessary only with persistent vomiting or severe distention.

For prevention, surgical goals strive to minimize bowel manipulation, avoid excess IV fluids or profound hypovolemia, and limit surgery length (Bragg, 2015). After surgery, gum chewing enhances early bowel function recovery (Ciardulli, 2018). Among studies, chewing was initiated immediately or up to 12 hours later, lasted 15 to 60 minutes, and was repeated in at least three sessions daily (Pereira Gomes Morais, 2016).

Ambulation and Wound Care

As discussed earlier, women undergoing cesarean delivery have an increased VTE risk compared with those delivering vaginally (Chap. 55, p. 989). Early ambulation lowers this risk. Walking to the bathroom begins, initially with assistance. Brief walks are encouraged. For women with marked abdominal laxity, an abdominal binder can aid comfortable deep coughing and ambulation. Evidence supporting routine application for all parturients is limited and conflicting (Chankhunaphas, 2020; Gillier, 2016).

Although not evidence based, we remove the surgical dressing after 24 hours and inspect the incision daily. One small randomized trial showed no wound healing effects if removed at 6 hours (Peleg, 2016). By the third postpartum day, showering does not harm the incision. Prior to this, a plastic covering can maintain dryness during showers. If used, staples are often removed on the fourth postoperative day. In their place, tape strips can remain for 1 week to reinforce skin edge integrity. If potential superficial wound separation, without infection, is a concern, staples can remain for 7 to 10 days.

Hospital Discharge

For uncomplicated cesarean delivery, the average hospitalization length is 3 to 4 days (Buie, 2010). Data from studies suggest that earlier discharge is feasible for properly selected women and newborns (Bayoumi, 2016; Tan, 2012). Protocols ideally include earlier reevaluation for neonatal jaundice. However, discharge before 96 hours leads to a greater neonatal readmission rate (Jones, 2020).

Activities during the first week are limited to self-care and newborn care with assistance. Driving can be resumed when pain does not limit the ability to brake quickly and when narcotic medications are not in use. In women with cesarean delivery, intercourse was resumed in 44 percent by 6 weeks postpartum, 81 percent by 3 months, and 97 percent at 1 year (McDonald, 2013). After the puerperium, the quality of sexual functioning does not differ between those undergoing spontaneous vaginal birth or cesarean delivery (Chang, 2015; Fehniger, 2013; Rogers, 2014). Return to work is variable. Six weeks is commonly cited, although many women use the Family and Medical Leave Act to allow up to 12 weeks for recovery and newborn bonding.

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CHAPTER 31

Prior Cesarean Delivery

By the beginning of the 20th century, cesarean delivery had become a relatively safe procedure. However, rupture of the uterine scar with subsequent labor was appreciated early. This danger resulted in the oft-quoted remark by Cragin (1916) that "Once a cesarean, always a cesarean." During the intervening 50 years, enthusiasm developed to allow many of these women to be delivered vaginally. But, as chronicled next, this support has waned during the past three decades. So, as we reach the 100-year mark of Cragin's pronouncement, the issue remains largely unsettled.

100 YEARS OF CONTROVERSY

Despite Cragin's early philosophy, some practitioners did allow labor in a subsequent pregnancy after a cesarean delivery. Eastman (1950) described a 30-percent postcesarean vaginal delivery rate at Johns Hopkins Hospital. He also reported a 2-percent uterine rupture rate and associated 10-percent maternal mortality rate. As modern techniques made cesarean delivery safer, observational studies during the 1960s suggested that postcesarean vaginal delivery was a reasonable option (Pauerstein, 1966, 1969). Germane to this is that through the 1960s, the overall cesarean delivery rate approximated only 5 percent. Since then, as the primary cesarean rate has escalated, the repeat cesarean delivery rate followed (Rosenstein, 2013).

During the 1980s, a National Institutes of Health (NIH) Consensus Development Conference on Vaginal Birth After Cesarean (1981) was convened, and the participants questioned the necessity of routine repeat cesarean delivery. With support and encouragement from the American College of Obstetricians and Gynecologists (1988, 1994), enthusiastic attempts were begun to increase the practice rate of *vaginal birth after cesarean—VBAC*. These attempts were highly successful, and VBAC rates rose from 3.4 percent in 1980 to a peak of 28.3 percent in 1996. This rate and a concomitant decline in total cesarean delivery rate for the United States, are shown in Figure 31-1. Also, a new lexicon was developed to describe these practices and outcomes (Table 31-1).

However, with the higher postcesarean vaginal delivery rate, reports of uterine rupture-related maternal and perinatal morbidity and mortality began to appear (McMahon, 1996; Sachs, 1999). These complications dampened prevailing enthusiasm for a *trial of labor after cesarean section (TOLAC)*. They also prompted the American College of Obstetricians and Gynecologists (1998) to caution that such trials should be attempted only in appropriately equipped institutions with physicians *readily available* to provide emergency care. Less than a year later, the College (1999) recommended that physicians should be *immediately available* when pursuing a TOLAC. Many believe that this one-word change—from *readily* to *immediately* available—was an impetus for the resulting decade-long decline in national VBAC rates illustrated in Figure 31-1 (Cheng, 2014; Leeman, 2013).

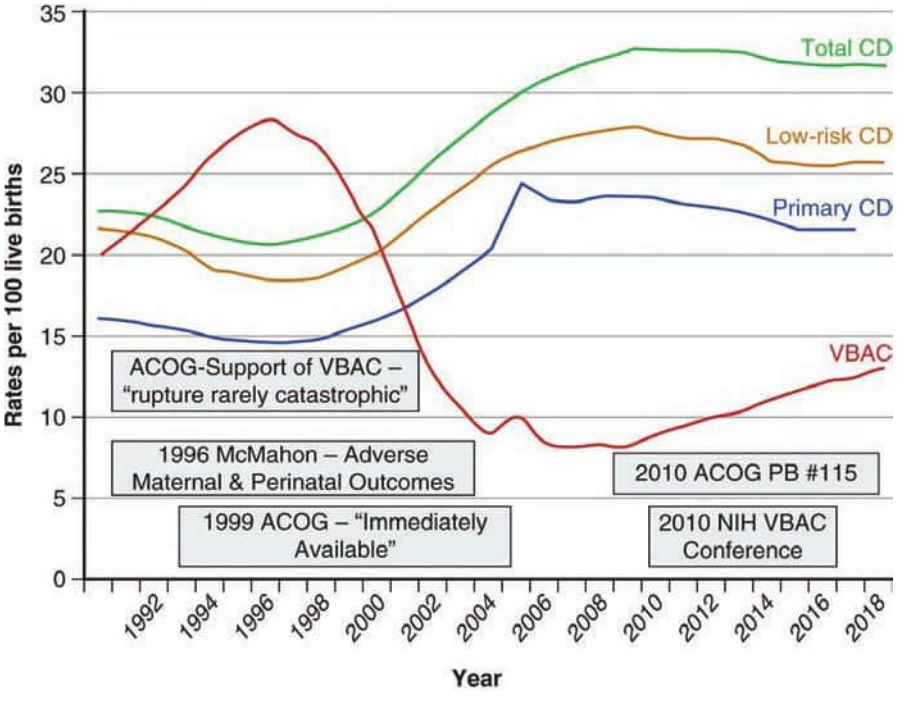


FIGURE 31-1 Total, primary, and low-risk cesarean delivery (CD) rates and vaginal birth after previous cesarean (VBAC) rates in the United States, 1989–2018. Epochs denoted within rectangles represent contemporaneous ongoing events related to these rates. ACOG = American College of Obstetricians and Gynecologists; NIH = National Institutes of Health; PB = practice bulletin. (Data from Hamilton, 2015, 2016; Martin, 2019; National Institutes of Health: NIH Consensus Development Conference, 2010.)

Using birth certificate data for 2013, Curtin and associates (2015) reported that only 1 in 5 women with one prior cesarean delivery attempted a TOLAC. In women with two or more prior cesarean deliveries, less than 1 in 10 women attempt a TOLAC, and half resulted in successful vaginal deliveries. At Parkland Hospital, although only 15 percent of women choose a TOLAC, the VBAC rate is 86 percent.

Thus, multiple interrelated factors—both medical and nonmedical—undoubtedly contributed to declining VBAC rates. Because of this, in 2010 the NIH convened a Consensus Development Conference Panel to study the issue. The panel report included a contemporaneous summary concerning the risks and benefits of repeat cesarean versus vaginal delivery. These findings were subsequently described and coupled with current recommendations by various professional organizations. As shown in Figure 31-1, it would seem that this report was followed by a slight rise in the VBAC rate.

In a cross-sectional analysis between 1990 and 2009, the proportion of women with a prior cesarean delivery who underwent a TOLAC peaked in 1995, and slightly more than half of these women chose this option (Fig. 31-2). After this, the proportion of women *attempting* TOLAC declined to a nadir of 16 percent in 2006 and subsequently rose to 21 percent through 2009. Additionally, the percentage of VBACs reached its peak of 70 percent in 2000 but subsequently declined to a nadir of 38 percent in 2006 (Uddin, 2013).

TABLE 31-1. Acronyms Used to Describe Management of Women with a Prior Cesarean Delivery

CD: cesarean delivery
TOL: trial of labor
VBAC: vaginal birth after CD
TOLAC: trial of labor after CD
Failed TOLAC: resulting in CD
Successful TOLAC: resulting in VBAC
ERCD: elective repeat cesarean delivery
Scheduled ERCD: CD planned before labor
Unscheduled ERCD: planned scheduled CD but indications for early delivery, e.g., spontaneous labor, abruption, etc.
Uterine rupture:
Complete: all uterine wall layers separated
Incomplete: uterine dehiscence with uterine muscle separated but peritoneum intact

INFLUENCING FACTORS

For the woman with a prior cesarean delivery, planning for future pregnancies and delivery route should begin with preconceptional counseling and be addressed again early in prenatal care. Importantly, decisions made throughout pregnancy regarding delivery mode are subject to continuing revisions as dictated by exigencies that arise during pregnancy. Assuming no mitigating circumstances, there are two basic choices. First,

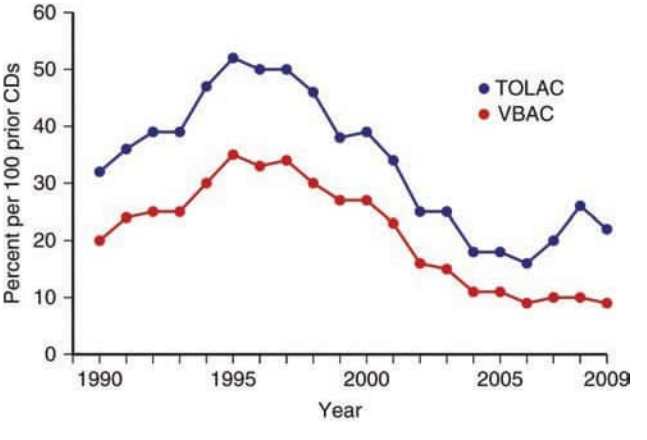


FIGURE 31-2 Percentage of women with a prior cesarean delivery who attempted a trial of labor (TOLAC) compared with the successful vaginal delivery (VBAC) rate for the United States 1990–2009. (Data from Centers for Disease Control and Prevention; National Center for Health Statistics; Curtin, 2015; Simon, 2013; Uddin, 2013).

TABLE 31-2. Some Factors That Influence a Successful Trial of Labor in a Woman with Prior Cesarean Delivery (CD)

Low-Risk	Favors Success	Increased Failure Rate	High-Risk[a]
Transverse incision	Teaching hospital	Single mother	Classical or T incision
Prior vaginal delivery	White race	Advanced maternal age	Prior uterine rupture
Appropriate counseling	Spontaneous labor	Macrosomic fetus	Patient refusal
Sufficient personnel and equipment	Prior indication of fetal malpresentation	Obesity	Transfundal surgery
	1 or 2 prior low transverse incisions	Current breech	Obstetrical contraindication, e.g., previa
	Nonrecurrent indication	Multifetal pregnancy	Prior open maternal–fetal surgery
	Current preterm pregnancy	Preeclampsia	Inadequate obstetrical or anesthesia staff coverage
		EGA >40 weeks	
		Low vertical incision	
		Unknown incision	
		Labor induction	
		Medical disease	
		Multiple prior CDs	
		Education <12 years	
		Short interdelivery interval	
		Liability concerns	

[a]Most consider these absolute contraindications.
EGA = estimated gestational age.

a *TOLAC* offers the goal of achieving a *VBAC*. If cesarean delivery becomes necessary during the trial, it is a *failed TOLAC*. A second choice is *elective repeat cesarean delivery (ERCD)*. This includes scheduled cesarean delivery as well as unscheduled but planned cesarean delivery for spontaneous labor or another delivery indication.

The decision regarding delivery mode should weigh clinical factors known to influence TOLAC success as well as benefits and risks (Table 31-2). As expected, TOLAC rates vary between institutions and providers. Last, economics, staffing, and medicolegal factors also may shape the decision to offer TOLAC.

DELIVERY ROUTE RISKS

As evidence mounted that the uterine rupture risk might be greater than expected, the American College of Obstetricians and Gynecologists (1988, 1994, 1998, 1999, 2015, 2019a,d) issued updated bulletins supporting TOLAC but also urging a more cautious approach. *It is problematic that both options have risks and benefits to mother and fetus but that these are not always congruent.*

Maternal Risks

Rates of uterine rupture and associated complications clearly are increased with TOLAC. As shown in Table 31-1, uterine rupture typically is classified as either: (1) *complete*, when all uterine wall layers are separated, or (2) *incomplete*, when the uterine muscle is separated but the visceral peritoneum is intact. Incomplete rupture is also commonly referred to as *uterine dehiscence* (Chap. 42, p. 742). It is these risks that underpin most of the angst in attempting TOLAC. Despite this, some argue that these factors should weigh only minimally in the decision because their absolute risk is low. For example, a systematic review by Guise and coworkers (2010) concludes that the uterine rupture risk was significantly elevated in women undergoing TOLAC—absolute risk of 0.47 percent and relative risk of 20.7—compared with women choosing ERCD.

The Maternal-Fetal Medicine Units (MFMU) Network conducted a prospective study at 19 medical centers (Landon, 2004). Shown in Table 31-3 are outcomes of nearly 18,000 women attempting TOLAC that were compared with those of more than 15,000 gravidas undergoing ERCD. The absolute risk of uterine rupture was 0.7 percent compared with no reported uterine ruptures in the ERCD cohort. Various reports suggest either no or an increased mortality risk for ERCD compared with attempted TOLAC (Guise, 2010; Wen, 2004).

Maternal morbidity estimates also are conflicting. The review by Guise and coworkers (2010) observed no significant differences in hysterectomy or transfusion risk. But, another metaanalysis reported that women undergoing TOLAC were approximately half as likely to require transfusion or hysterectomy compared with those undergoing ERCD (Mozurkewich, 2000). Conversely, in the MFMU Network study, the risks for transfusion and infection were significantly greater for women attempting TOLAC (Landon, 2004). A recent large retrospective Canadian cohort study compared maternal and neonatal outcomes (Young, 2018). The absolute rates of severe maternal morbidity and mortality were low. However, women attempting TOLAC had significantly higher adjusted risk ratios of uterine rupture (6.41), severe postpartum hemorrhage with transfusion (2.80), and composite maternal morbidity (1.96) compared with women who underwent ERCD. This disparity is also found among other studies. Importantly, compared with a successful TOLAC, the risk of these major complications was fivefold greater with a failed TOLAC (Rossi, 2008).

TABLE 31-3. Complications in Women with a Prior Cesarean Delivery Enrolled in the Study by the NICHD MFMU, 1999–2002

Complication	TOLAC n = 17,898 No. (%)	ERCD n = 15,801 No. (%)	Odds Ratio (95% CI)	*p* value
Maternal				
Uterine rupture	124 (0.7)	0	NA	<.001
Uterine dehiscence	119 (0.7)	76 (0.5)	1.38 (1.04–1.85)	.03
Hysterectomy	41 (0.2)	47 (0.3)	0.77 (0.51–1.17)	.22
Thromboembolic disease	7 (0.04)	10 (0.1)	0.62 (0.24–1.62)	.32
Transfusion	304 (1.7)	158 (1.0)	1.71 (1.41–2.08)	<.001
Uterine infection	517 (2.9)	285 (1.8)	1.62 (1.40–1.87)	<.001
Death	3 (0.02)	7 (0.04)	0.38 (0.10–1.46)	.21
Perinatal				
Antepartum stillbirth[a]				
37–38 weeks	18 (0.4)	8 (0.1)	2.93 (1.27–6.75)	.008
≥39 weeks	16 (0.2)	5 (0.1)	2.70 (0.99–7.38)	.07
Intrapartum stillbirth[a]	2	0	NA	NS
Term HIE[a]	12 (0.08)	0	NA	<.001
Term neonatal death[a]	13 (0.08)	7 (0.05)	1.82 (0.73–4.57)	.19

[a]Denominator is 15,338 for the TOLAC group and 15,014 for the ERCD group.
CD = cesarean delivery; CI = confidence interval; ERCD = elective repeat cesarean delivery; HIE = hypoxic ischemic encephalopathy; NA = not applicable; MFMU = Maternal–Fetal Medicine Units Network; NICHD = National Institute of Child Health and Human Development; NS = not significant; TOLAC = trial of labor after cesarean delivery.

Perinatal Risks

In the Canadian study cited previously, rates of composite severe neonatal morbidity and mortality were higher among women delivering after an attempted VBAC compared with those delivering by ERCD—adjusted odds ratio (aOR) 1.49 (Young, 2018). In this study failed VBAC was also associated with a significantly increased rate of neonatal death—aOR 3.22. Both the prospective MFMU Network study shown in Table 31-3 and review by Guise (2010) found significantly higher *perinatal mortality* rates with TOLAC compared with ERCD. In the latter review, the perinatal mortality rate with TOLAC was 0.13 percent compared with 0.05 percent for ERCD. In the Canadian study cited previously, adjusted risk ratios for neonatal death (3.22) and for composite severe neonatal morbidity and mortality (1.49) were significantly higher among women delivering after an attempted TOLAC compared with those delivering by ERCD (Young, 2018). In another study of nearly 25,000 women with a prior cesarean delivery, the TOLAC-related perinatal death rate was 1.3 per 1000 among 15,515 women (Smith, 2002). Although this absolute risk is small, it is 11 times greater than the perinatal risk found in 9014 women with ERCD.

TOLAC also appears to be associated with a higher risk of *hypoxic ischemic encephalopathy (HIE)* compared with that for ERCD. The MFMU Network study reported the incidence of encephalopathy at term to be 46 per 100,000 TOLACs compared with zero cases in women undergoing ERCD (Landon, 2004). In the review by Guise (2010), the absolute risk of *transient tachypnea of the newborn* was slightly higher with ERCD compared with TOLAC—4.2 versus 3.6 percent. But, neonatal bag and mask ventilation was used more often in newborns delivered following TOLAC than in those delivered by ERCD—5.4 versus 2.5 percent. The 5-minute Apgar scores or neonatal intensive care unit admission rates for newborns delivered by TOLAC did not differ from those delivered by ERCD.

TRIAL OF LABOR SELECTION CONSIDERATIONS

Both patients and providers ideally would like individualized risks when counseling regarding the chance of successful TOLAC. However, few high-quality data guide selection of suitable TOLAC candidates. Several TOLAC/VBAC calculators can be used at entry to prenatal care and again at the time of labor to assist in successful TOLAC prediction. However, these have not been validated as predictors of adverse maternal outcomes, such as uterine rupture. Similarly, algorithms and nomograms to aid prediction fail to demonstrated reasonable prognostic value (Grobman, 2007b, 2008, 2021; Metz, 2013; Wyckoff, 2020). Lipschuetz and colleagues (2020) applied newer statistical analysis techniques to help improve prognostic accuracy.

Despite the limitations of these predictive tools, several points are pertinent to candidate evaluation and are described subsequently. Current recommendations of the American College of Obstetricians and Gynecologists (2019d) are that most

TABLE 31-4. Types of Prior Uterine Incisions and Estimated Risks for Uterine Rupture

Prior Incision	Estimated Rupture Rate (%)
One low transverse	0.2–0.9
Multiple low transverse	0.9–1.8
Low-vertical[a]	1–7
Classical	2–9
T-shaped	4–9
Prior preterm CD	"Increased"
Prior uterine rupture	
Lower segment	2–6
Upper uterus	9–32

[a]See text for definition.
CD = cesarean delivery.
Data from the American College of Obstetricians and Gynecologists, 2017; Cahill, 2010b; Chauhan, 2002; Landon, 2006; Macones, 2005a,b; Martin, 1997; Miller, 1994; Sciscione, 2008; Society for Maternal-Fetal Medicine, 2012; Tahseen, 2010.

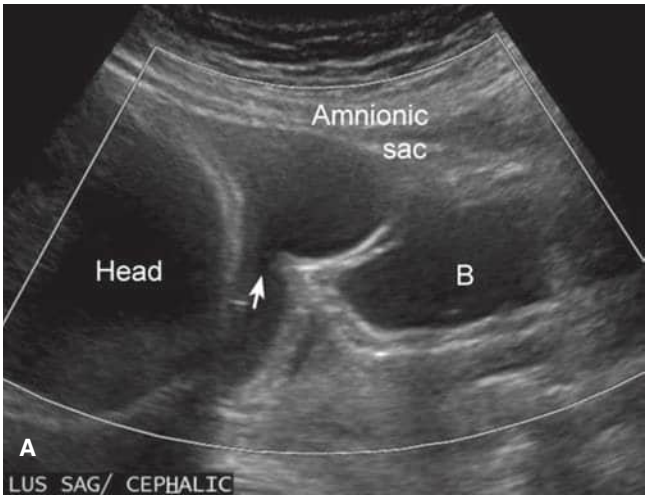
women with one prior low transverse hysterotomy are candidates, and if appropriate, they should be counseled regarding both TOLAC and ERCD options. It is further recommended that home birth is a contraindication for TOLAC.

■ Prior Uterine Incision

Prior Incision Type

The type and number of prior cesarean deliveries are overriding factors in recommending TOLAC (see Table 31-2). And these caveats aim to avoid intrapartum uterine rupture. As shown in Table 31-4, women with one prior low transverse hysterotomy have the lowest risk of symptomatic scar separation. However, asymptomatic dehiscence or complete rupture is still a concern in these women (Fig. 31-3). The uterine rupture risk in women with a prior vertical incision that did not extend into the fundus is unclear. Martin (1997) and Shipp (1999) and their associates reported that these low vertical uterine incisions do not have a higher risk for rupture compared with low transverse incisions. The American College of Obstetricians and Gynecologists (2015) concluded that although evidence is limited, women with a prior vertical incision in the lower uterine segment without fundal extension may be candidates for TOLAC. This is in contrast to prior classical or T-shaped uterine incisions, which are considered by most as contraindications to labor.

The highest risks are with prior vertical incisions extending into the fundus. Importantly, women with a classical uterine scar may rupture before labor onset, and this may even occur before term. Chauhun and colleagues (2002) reviewed 157 women with a prior classical cesarean incision. They used a policy of fetal lung maturity assessment at 36 weeks and then delivery if mature. With a mean gestational age of 35.6 weeks at delivery, they reported one uterine rupture at 29 weeks that resulted in fetal death; 9-percent uterine dehiscence rate; and 25-percent risk of maternal morbidity. For a woman with a



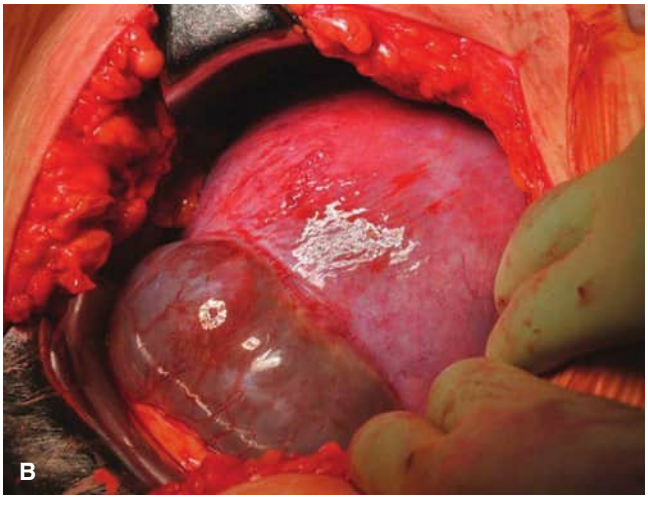


FIGURE 31-3 Extensive "uterine window" in a woman at term with one prior low transverse cesarean delivery. **A.** Transabdominal sonogram shows the uterine defect (*arrow*), bulging amnionic sac, and adjacent anatomy. B = Bladder. **B.** At the time of cesarean delivery, the amnionic sac is seen protruding through the defect and is visible beneath the thin vesicocervical peritoneum. (Reproduced with permission from Dr. Angela Seasley.)

prior classical cesarean delivery, the authors concluded that uterine rupture and dehiscence are neither predictable nor preventable despite early delivery. The risk for earlier rupture is even greater in women who have undergone open maternal-fetal surgery (Chmait, 2019; Goodnight, 2019). The American College of Obstetricians and Gynecologists (2021) recommends delivery between $36^{0/7}$ and $37^{0/7}$ weeks for a prior classical incision.

Although few indications dictate a primary classical incision, 53 percent of women undergoing cesarean delivery between $24^{0/7}$ weeks and $25^{6/7}$ weeks have such an incision (Osmundson, 2013). By 28 weeks' gestation, the risk drops to 35 percent and declines to <10 percent by 32 weeks. The likelihood of classical uterine incision is also increased by noncephalic presentations. In those instances—for example, preterm breech fetus with an undeveloped lower segment—the "low vertical" incision almost invariably extends into the active segment. From their review, Moramarco and colleagues (2020) reported that prior preterm

classical cesarean delivery was associated with a 1-percent risk for rupture. Lannon and coworkers (2015) compared 456 women with a prior periviable cesarean delivery with more than 10,000 women whose prior cesarean delivery was done at term. The uterine rupture rate was 1.8 percent in the prior periviable group and 0.4 percent in the prior term group. Of the uterine ruptures in the periviable group, half were in women whose prior uterine incision was described as low transverse. Harper and associates (2009) did not confirm these findings.

The type of uterine incision cannot be confirmed in all women. Unless clinical circumstances raise concern for a prior classical uterine incision, the American College of Obstetricians and Gynecologists (2019d) consider these women as potential TOLAC candidates.

Special consideration is given to women with uterine malformations who have undergone cesarean delivery. Earlier reports suggested that the uterine rupture risk in a subsequent pregnancy was greater than the risk in those with a normal uterus and a prior low transverse hysterotomy (Ravasia, 1999). However, in a study of 103 women with müllerian duct anomalies, there were no cases of uterine rupture (Erez, 2007).

Prior Incision Closure

As discussed in Chapter 30 (p. 558), the low transverse uterine incision can be sutured in either one or two layers. One metaanalysis compared single- versus double-layer closure and locking versus nonlocking suture for uterine closure (Roberge, 2014). The uterine dehiscence or rupture rates for these closures did not differ significantly. Both single-layer closure and closure that locked the first layer, however, were associated with a reduced myometrial thickness during subsequent sonographic measurement. In contrast, Bennich and coworkers (2016) reported that a double-layer closure did not increase the residual myometrial thickness when saline contrast sonography was done several months postpartum. Our practice at Parkland Hospital is to routinely suture the lower-segment incision with one running, locking suture line.

Number of Prior Cesarean Incisions

At least three studies report a doubling or tripling of the uterine rupture rate in women with two compared with one prior transverse hysterotomy (Macones, 2005a; Miller, 1994; Tahseen, 2010). In contrast, an analysis of the MFMU Network database did not confirm this (Landon, 2006). Namely, in 975 women with multiple prior cesarean deliveries, the rupture rate was 0.9 percent and not significantly different from the 0.7-percent rate in 16,915 women with a single prior operation.

Imaging of Prior Incision

Sonographic measurement of a prior hysterotomy incision has been used to predict rupture risk. Large defects in a nonpregnant uterus forecast a greater risk (Osser, 2011). Naji and coworkers (2013a,b) found that the *residual myometrial thickness* decreased as pregnancy progressed and that rupture risk correlated positively with a thinner scar.

Jastrow and colleagues (2010a) did a systematic review of women with a prior low transverse hysterotomy incision who underwent third-trimester sonographic evaluation. They concluded that a uterine scar defect was strongly predicted by a thin lower uterine segment. They defined this segment as the smallest measurement between urine in the maternal bladder and amniotic fluid. That said, they could not find an ideal threshold value to recommend safe TOLAC. This same group subsequently recruited 1856 women contemplating vaginal birth after a single low transverse incision, and they sonographically measured lower uterine segment thickness between $34^{0/7}$ and $38^{6/7}$ weeks (Jastrow, 2016). Women were grouped into three risk categories for uterine rupture during TOLAC based on measurements: high risk <2.0 mm; intermediate risk 2.0 to 2.4 mm; and low risk ≥2.5 mm. The TOLAC rates were 9, 42, and 61 percent in the three categories, respectively. Of the 984 TOLACs, there were no symptomatic uterine ruptures. At Parkland Hospital, we do not assess the lower uterine segment in women with a prior cesarean delivery.

Prior Uterine Rupture

Women who have previously sustained a uterine rupture are at greater risk for recurrence. As shown in Table 31-4, those with a prior lower-segment rupture have up to a 6-percent recurrence risk, whereas prior upper-segment rupture confers a 9- to 32-percent risk (Reyes-Ceja, 1969; Ritchie, 1971). Sheth (1968) described outcomes of 21 subsequent pregnancies in 13 women who underwent uterine rupture repair. Rupture recurred in four pregnancies—approximately 20 percent. Usta and colleagues (2007) reported similar results. Fox and associates (2014) reported 14 women with prior uterine rupture and 30 women with prior uterine dehiscence. In 60 subsequent pregnancies, they noted no uterine ruptures or severe complications if women underwent ERCD prior to labor onset or immediately at the onset of preterm labor. Delivery is recommended between $36^{0/7}$ and $37^{0/7}$ weeks' gestation (American College of Obstetricians and Gynecologists, 2021).

Interdelivery Interval

Magnetic resonance imaging studies of myometrial healing suggest that complete uterine involution and restoration of anatomy may require at least 6 months (Dicle, 1997). As a potential risk for uterine rupture, the relationship between interdelivery interval and uterine rupture in 2409 women with one prior cesarean delivery was examined (Shipp, 2001). There were 29 women with a uterine rupture—1.4 percent. Interdelivery intervals ≤18 months were associated with a threefold greater risk of symptomatic rupture during a subsequent TOLAC compared with intervals >18 months. Similarly, Stamilio and associates (2007) noted a threefold augmented risk of uterine rupture in women with an interpregnancy interval <6 months compared with one ≥6 months.

Prior Vaginal Delivery

Prior vaginal delivery, either before or after a cesarean birth, significantly improves the prognosis for a successful TOLAC (Grinstead, 2004; Hendler, 2004; Mercer, 2008). Prior vaginal delivery also lowers the TOLAC-related risk of subsequent uterine rupture and other morbidities (Cahill, 2006; Hochler, 2014; Zelop, 1999).

Prior Cesarean Delivery Indication

Women with a nonrecurring indication—for example, breech presentation—have the highest successful TOLAC rate—nearly 90 percent (Wing, 1999). Those with a prior cesarean delivery for fetal compromise have an approximately 80-percent VBAC rate, and for those done for labor arrest, VBAC rates approximate only 60 percent (Bujold, 2001; Peaceman, 2006).

Prior second-stage cesarean delivery can be associated with second-stage uterine rupture in a subsequent pregnancy (Jastrow, 2013). A secondary analysis of the MFMU Cesarean Registry revealed that a prolonged second stage of labor—exceeding 3 hours—during TOLAC will often lead to VBAC. However, adverse maternal outcomes including uterine rupture or dehiscence were observed to be more common as the second stage lengthens (Hehir, 2018).

Fetal Size and Lie

Most studies show that increasing fetal size is inversely related to VBAC rates. The risk for uterine rupture is less robustly linked. Zelop and colleagues (2001) studied outcomes of almost 2750 women undergoing TOLAC, and the uterine rupture rate increased—albeit not significantly—with rising fetal weight. The rate was 1.0 percent for fetal weight <4000 g, 1.6 percent for >4000 g, and 2.4 percent for >4250 g. Similarly, others have found associated increased risks for uterine rupture with fetuses >4000 g (Jastrow, 2010b). With preterm fetuses, compared with term ones, women who attempt a TOLAC have similar or higher VBAC rates and lower uterine rupture rates (Durnwald, 2006; Quiñones, 2005).

Few studies address the choice of TOLAC for a singleton term breech fetus. Very limited data suggest a possible link with adverse perinatal outcome (Azria, 2012; Macharey, 2017). Data supporting external cephalic version for breech presentation with a prior cesarean scar also are limited and are derived from small studies (Impey, 2018; Weill, 2017). From these, version success and adverse event rates appear comparable with women without a prior cesarean delivery. The American College of Obstetricians and Gynecologists (2020) does not consider a prior uterine incision to be a contraindication for attempted version. At Parkland Hospital, we do not attempt version or vaginal breech delivery in these women.

Multifetal Gestation

Twin pregnancy does not appear to increase the risk of uterine rupture. In one study of 1850 women with twins, the VBAC rate was 45 percent, and the rupture rate was 0.9 percent (Ford, 2006). Similar studies by Cahill (2005) and Varner (2007) and their coworkers reported rupture rates of 0.7 to 1.1 percent and VBAC rates of 75 to 85 percent. According to the American College of Obstetricians and Gynecologists (2019d), women with twins and a prior low transverse hysterotomy can safely undergo TOLAC.

Maternal Obesity

Multiple studies have reported an inverse relationship between prepregnancy body mass index (BMI) and successful TOLAC rates (Juhasz, 2005; Wu, 2019). Hibbard and associates (2006) reported the following rates: 85 percent with a normal BMI, 78 percent with a BMI between 25 and 30, 70 percent with a BMI between 30 and 40, and 61 percent with a BMI ≥40.

Fetal Death

Most women with a prior cesarean delivery and fetal death in the current pregnancy would prefer a vaginal delivery. Although fetal concerns are obviated, available data suggest that maternal risks are increased. Nearly 46,000 women with a prior cesarean delivery in the MFMU Network database had a total of 209 fetal deaths at an average gestational age of 32.8 weeks (Ramirez, 2010). Of the 158 women who elected TOLAC, the VBAC rate was 87 percent. In the entire TOLAC group, the uterine rupture rate was 2.4 percent, and in 116 women who underwent an induction of labor, the rupture rate was 3.4 percent. Labor induction for second-trimester fetal demise has a low complication rate (Bahar, 2021).

LABOR AND DELIVERY CONSIDERATIONS

Timing

The American College of Obstetricians and Gynecologists (2019a) recommends delaying nonmedically indicated deliveries until 39 completed weeks of gestation or beyond. Data from Tita and colleagues in Figure 31-4 show significant and appreciable adverse neonatal morbidity has been reported with ERCD before 39 completed weeks (Chiossi, 2013; Clark, 2009). Thus, if ERCD is planned, it is essential that the fetus be mature. Conversely, delaying delivery beyond 40 weeks is associated with higher neonatal morbidity rates.

Accurate pregnancy dating is paramount prior to ERCD. The American College of Obstetricians and Gynecologists (2019c) offers guidelines to assist in accurate pregnancy dating using a combination of last menstrual period and sonography. The most accurate method to confirm or establish gestational age is by sonographic measurement of an early embryo-fetus.

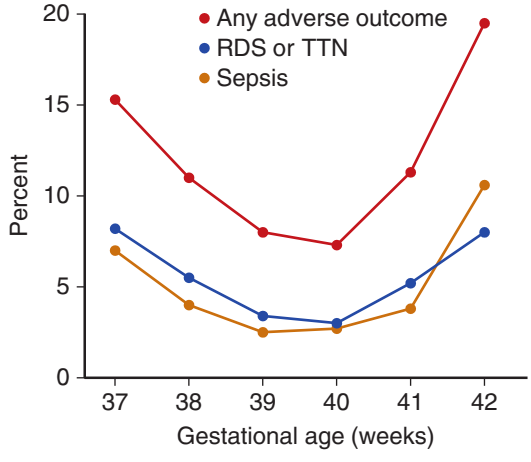


FIGURE 31-4 Neonatal morbidity rates seen with 13,258 elective repeat cesarean deliveries. Any adverse outcome includes death. Sepsis includes suspected and proven. RDS = respiratory distress syndrome; TTN = transient tachypnea of the newborn.

Intrapartum Care

Because uterine rupture during TOLAC may be unpredictable, the American College of Obstetricians and Gynecologists (2019d) recommends that labor in women attempting TOLAC should be undertaken in facilities that can provide emergency cesarean delivery for situations associated with immediate threats to the life of the women or her fetus. If those resources are not available, the College recommends discussion of the hospital's resources and availability of providers with the patient considering TOLAC. Ultimately, the best alternative may be referral to an institution with resources appropriate for TOLAC.

Some argue that these provisions deny women full access to choices. For example, in an earlier survey of Ohio hospitals, 15 percent of Level I, 63 percent of Level II, and 100 percent of Level III institutions met these requirements (Lavin, 2002). Moreover, an obstetrical anesthesia workforce survey reported that due to staffing limitations, TOLAC was allowed in only 88 percent of hospitals with ≥1500 annual deliveries, in 59 percent of those with 500 to 1499 deliveries, and in 43 percent of those with <500 deliveries (Traynor, 2016).

Cervical Ripening and Labor Stimulation

Labor induction is associated with a higher TOLAC failure rate compared with spontaneous labor. The risks for uterine rupture, however, are less clear with induction or augmentation, with the exception of prostaglandin E_1 (PGE_1)—misoprostol—which is contraindicated (American College of Obstetricians and Gynecologists, 2019d). Of other considerations, induction or augmentation is ideally avoided in women with an unknown prior incision type, an unfavorable cervix, or pregnancy >40 weeks. At Parkland Hospital we do not induce or augment labor pharmacologically in women electing TOLAC. Instead, we attempt induction only by amniotomy.

Oxytocin

Use of oxytocin for labor induction or augmentation has been *implicated* in increased uterine rupture rates in women undergoing TOLAC (Zelop, 1999). In the MFMU Network study reported by Landon (2004), uterine rupture was more frequent in women induced with oxytocin alone—1.1 percent—compared with those presenting in spontaneous labor—0.4 percent. Labor augmentation was associated with uterine rupture in 0.9 percent. Among women in this cohort without a prior vaginal delivery, the uterine rupture risk associated with oxytocin induction was 1.8 percent—a fourfold greater risk compared with spontaneous labor (Grobman, 2007a). In contrast, in one case-control study, induction was not associated with a higher rupture risk (Harper, 2012a). Cahill (2008) and Goetzl (2001) and their coworkers reported a dose-related risk of rupture with oxytocin.

Prostaglandins

Various prostaglandin preparations commonly employed for cervical ripening or labor induction are discussed in Chapter 26 (p. 489). Wing and colleagues (1998) compared misoprostol versus oxytocin for labor induction in women with a prior cesarean delivery. They terminated their trial after two of the first 17 women assigned to misoprostol developed a uterine rupture. Other studies confirmed this. The American College of Obstetricians and Gynecologists (2019d) recommends that misoprostol should not be used for cervical ripening or labor induction in women at term with a prior cesarean delivery or major uterine surgery.

Studies using other prostaglandin agents for labor induction are contradictory. Ravasia and coworkers (2000) compared uterine rupture rates in 172 women given PGE_2 gel with 1544 women in spontaneous labor. The rupture rate of 2.9 percent was significantly greater in women treated with PGE_2 gel compared with 0.9 percent in those with spontaneous labor. Lydon-Rochelle and associates (2001) found similar results. In the MFMU Network study cited previously, however, the uterine rupture rate was 1.4 percent when any prostaglandin was used in combination with oxytocin (Landon, 2004). But, in the subgroup of 227 women in whom labor was induced with a prostaglandin alone, there were no ruptures. Similar findings were reported with intravaginal prostaglandins, which were not associated with a greater uterine rupture risk (Macones, 2005b). These latter investigators, along with Kayani and colleagues (2005), found that sequential use of a prostaglandin followed by oxytocin was associated with a threefold greater rupture risk compared with spontaneous labor.

Mechanical Methods

In a retrospective study of 2479 women with a prior cesarean delivery, the uterine rupture risk using a transcervical Foley catheter for labor induction (1.6 percent) was not significantly greater than that with spontaneous labor (1.1 percent)—or with amniotomy with or without oxytocin (1.2 percent) (Bujold, 2004). In 101 women induced with a balloon catheter, a 50-percent successful TOLAC rate and no uterine ruptures was reported (Sarreau 2020). In contrast, Hoffman and coworkers (2004) described 138 women who underwent preinduction cervical ripening with a Foley catheter compared with 536 women who entered labor spontaneously. The inordinately high intrapartum uterine rupture rate of 6.5 percent following Foley catheter cervical ripening was greater than the 1.9-percent rate with spontaneous labor.

Epidural Analgesia

Concerns that epidural analgesia for labor might mask the pain of uterine rupture have not been verified. Fewer than 10 percent of women with scar separation experience pain and bleeding, and fetal heart rate decelerations are the most likely sign of rupture (Kieser, 2002). That said, Cahill and associates (2010a) documented that more frequent episodes of epidural catheter dosing were associated with increasing uterine rupture rates. VBAC rates are similar, and in some cases higher, among women with labor epidural analgesia compared with those using other analgesia forms (Landon, 2005). Perhaps related, almost a fourth of VBAC deliveries were completed with either forceps or vacuum (Inbar, 2017). The American Academy of Pediatrics and the American College of Obstetricians and Gynecologists (2017) have concluded that epidural analgesia may safely be used during TOLAC.

Uterine Scar Exploration

Following VBAC, some clinicians routinely document the integrity of a prior scar by placing a hand through the dilated cervix and along the inner surface of the lower uterine segment. But, routine uterine exploration is considered by others to be unnecessary. In a longitudinal study of 3469 women who had a VBAC, seven uterine dehiscences and one uterine rupture yielded an overall event rate of 0.23 percent (Silberstein, 1998). These investigators concluded that transcervical evaluation need only be performed for those with severe third-stage bleeding.

Currently, the benefits of routine scar evaluation in the asymptomatic woman are unclear, however, surgical correction of a dehiscence is necessary for associated significant bleeding. At Parkland Hospital, we routinely examine the lower uterine segment following a VBAC and document its integrity. A large tear, a breach into the peritoneal cavity, and presence of active bleeding favor a decision for laparotomy and repair.

UTERINE SCAR RUPTURE

Diagnosis

Progress of labor in women attempting TOLAC is similar to normal labor, and no specific pattern presages uterine rupture (Graseck, 2012; Harper, 2012b). Before hypovolemic shock develops, symptoms and physical findings in women with uterine rupture may appear bizarre unless the possibility is kept in mind. For example, hemoperitoneum from a ruptured uterus may result in diaphragmatic irritation with pain referred to the chest. This may suggest a diagnosis of pulmonary or amnionic fluid embolism instead of uterine rupture. As the example shown in Figure 31-5, the most common sign of uterine rupture is a nonreassuring fetal heart rate pattern with variable decelerations that may evolve into late decelerations and bradycardia. In one report of 36 cases during TOLAC, fetal signs of uterine rupture were evident in 24, maternal signs in eight, and a combination of maternal and fetal in three (Holmgren, 2012). Few women experience cessation of contractions following uterine rupture, and the use of intrauterine pressure catheters does not assist reliably in the diagnosis (Rodriguez, 1989).

The clinical appearance of uterine rupture associated with a TOLAC may mirror that of placental abruption but with little appreciable pain or tenderness. Also, because most women in labor are treated for discomfort with either narcotics or epidural analgesia, pain and tenderness may not be readily apparent. Ultimately, the diagnosis of uterine rupture becomes evident because of fetal distress and occasionally because of maternal hypovolemia from concealed hemorrhage.

If the fetal presenting part has already entered the pelvis with labor, loss of station may be detected by pelvic examination. If the fetus is partly or totally extruded from the uterine rupture site, abdominal palpation or vaginal examination may be helpful to identify the presenting part, which will have moved away from the pelvic inlet. A firm contracted uterus may at times be felt alongside the fetus. Emergent sonography in the labor unit may be helpful.

Management

With rupture and expulsion of the fetus into the peritoneal cavity, the chances for intact fetal survival are poor. *Fetal condition depends on the degree to which the placental implantation remains intact, although this can change within minutes.* The only chance of intact fetal survival is afforded by immediate delivery—most often by laparotomy—otherwise, hypoxia is inevitable. If rupture is followed by total placental separation, very few neurologically intact fetuses will be salvaged.

Thus, even in the best of circumstances, some fetal outcomes will be impaired. The Utah experiences are instructive here (Holmgren, 2012). Of the 35 laboring patients with uterine rupture, the decision-to-delivery time was <18 minutes in 17, and none of these infants had an adverse neurological outcome. Of the 18 born >18 minutes from decision time, the three infants with long-term neurological impairments were delivered at 31, 40, and 42 minutes. There were no deaths, but severe neonatal neurological morbidity developed in 8 percent of this group of 35 women with uterine rupture. Importantly, delivery within 30 minutes did not prevent every case of low cord pH or low 5-minute Apgar score. When uterine rupture was identified and delivery was accomplished is less than 30 minutes, there was no long-term neonatal morbidity. In the MFMU Network study cited earlier, seven of the 114 uterine ruptures associated with TOLAC—6 percent—were complicated by development of neonatal encephalopathy (Spong, 2007).

Neonatal mortality rate is likewise increased several fold. In a study using the Swedish Birth Registry, the risk of neonatal death following uterine rupture was 5 percent (Kaczmarczyk, 2007).

Maternal deaths from uterine rupture are uncommon. Of 2.5 million women who gave birth in Canada between 1991 and 2001, there were 1898 cases of uterine rupture, and four of these—0.2 percent—resulted in maternal death (Wen, 2005). In other regions of the world, however, maternal mortality rates are

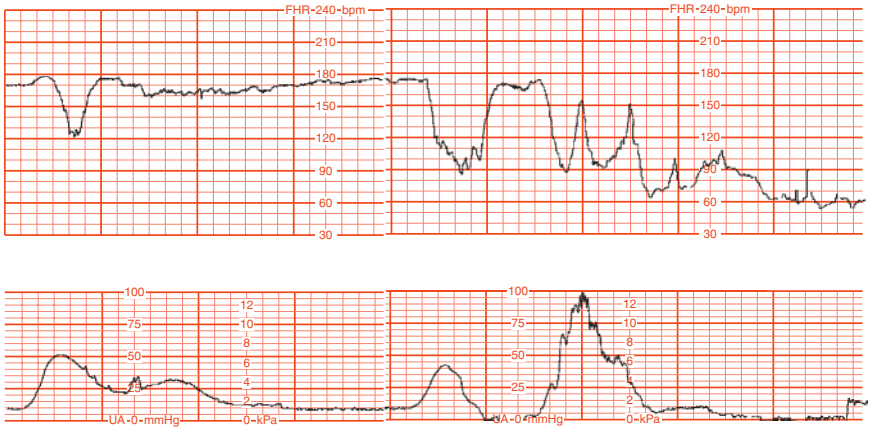


FIGURE 31-5 Fetal heart rate tracing in a woman whose uterus ruptured during labor while pushing. The rupture apparently stimulated a reflex push, after which uterine tone diminished and fetal bradycardia worsened.

much higher. From rural India, the maternal mortality rate associated with uterine rupture was 30 percent (Chatterjee, 2007).

Following complete rupture during TOLAC, hysterectomy may be required. In selected cases, however, suture repair with uterine preservation may be performed. Subsequent pregnancy following such repair was described earlier (p. 576). Bladder injury may be comorbid, and interrogation of its integrity is prudent (Chap. 30, p. 563) (Phipps, 2005; Webb, 2000).

MULTIPLE REPEAT CESAREAN DELIVERIES

The incidences of some common complications for women with a prior transverse cesarean delivery who undergo an ERCD were shown in Table 31-3 (Landon, 2004). Rates of these complications and of other serious maternal morbidity rise with the number of prior cesarean deliveries (Marshall, 2011).

First, the incidence of *placenta accreta spectrum (PAS)*, which includes placenta accreta, increta, or percreta increases markedly with the number of previous hysterotomies. In an MFMU Network cohort of 30,132 women who had from one to six repeat cesarean deliveries, a significant association between an accruing number of cesarean deliveries and PAS in women with placenta previa was noted (Fig. 31-6) (Silver, 2006). The PAS rate grew from 11 percent for women with a placenta previa undergoing their second cesarean delivery to 67 percent for women undergoing their fifth (Fig. 43-12, p. 761). Indeed, almost half of cesarean

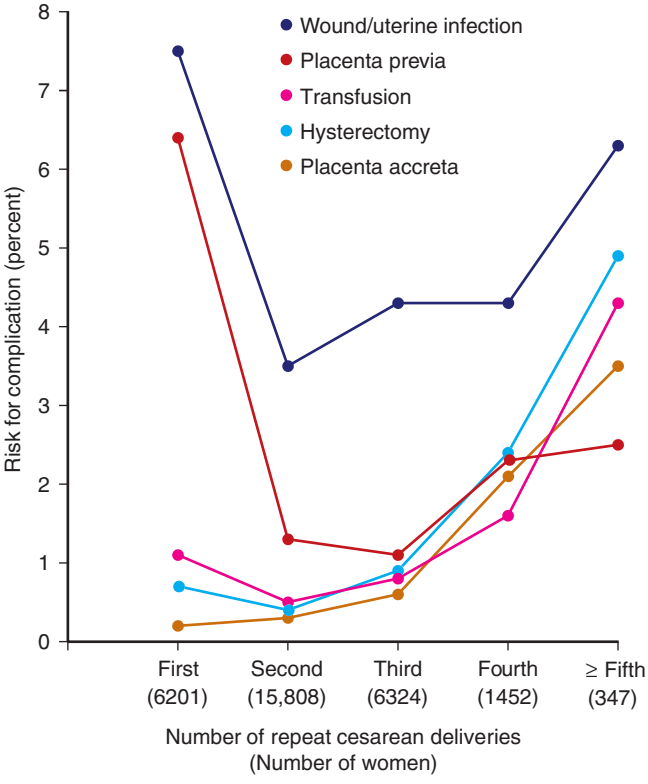


FIGURE 31-6 Maternal-Fetal Medicine Units Network: rates of some complications with increasing number of repeat cesarean deliveries.

TABLE 31-5. Some Recommendations of Professional Societies Concerning TOLAC

	Counseling	Facilities	Other
ACOG (2019d)	Offer to most women with 1 prior LTCD; consider for 2 prior LTCDs	Safest with ability for immediate CD; patients should be allowed to accept increased risk when not available	Not precluded: twins, macrosomia, prior low vertical or unknown incision type
SOGC	Offer to women with 1 prior LTCS; with >1 prior CD then VBAC likely successful but increased risks	Should deliver in hospital in which timely CD is available; the woman and provider must be aware of hospital resources and availability of obstetrical, anesthetic, pediatric, and operating room staff	Oxytocin or Foley catheter induction safe, but PGs not recommended; macrosomia, diabetes, postterm pregnancy, twins are not contraindications
RCOG (2015)	Offer to most women with singleton, cephalic fetus at ≥37 weeks with 1 prior LTCD; with >1 prior CD then VBAC likely successful but increased risks, offer after counseling by senior obstetrician, VBAC checklists should be considered	Suitable delivery suite with continuous intrapartum care and monitoring; immediate cesarean delivery and advanced neonatal resuscitation	Uncertainty about safety and efficacy with postterm, twin gestation, macrosomia, and advanced maternal age; induction and augmentation associated with two- to threefold increased risk of uterine rupture

ACOG = American College of Obstetricians and Gynecologists; CD = cesarean delivery; LTCS = low transverse cesarean delivery; PG = prostaglandins; RCOG = Royal College of Obstetricians and Gynaecologists; SOGC = Society of Obstetricians and Gynaecologists of Canada; TOLAC = trial of labor after cesarean delivery; VBAC = vaginal birth after cesarean.

TABLE 31-6. Conservative Approach to TOLAC

Review and follow ACOG guidelines
Education and counseling
Preconceptionally
Provide ACOG patient pamphlet
Prenatal care: early counseling and delivery planning
Develop preliminary delivery plan
Revisit delivery plan at least each trimester
Be willing to alter decision
Confirm facility capabilities
Risk assessment
Review and document operative note(s)
Review relative/absolute contraindications
Reconsider risks as pregnancy progresses
Careful consideration and counseling if:
>1 prior transverse CD, unknown incision, twins, macrosomia
Labor and delivery
Review previous medical records/operative notes
Cautions for induction: unfavorable cervix, high station
Consider AROM
Avoid prostaglandins
Respect oxytocin and know when to quit
Continuous EFM
Beware of abnormal labor progress
Respect EFM pattern abnormalities
Be ready to abandon TOLAC
Recommend against home birth

ACOG = American College of Obstetricians and Gynecologists; AROM = artificial rupture of membranes; CD = cesarean delivery; EFM = electronic fetal monitoring; TOLAC = trial of labor following cesarean delivery.

hysterectomies done at Parkland Hospital are in women with one or more prior cesarean deliveries (Hernandez, 2013).

Other maternal morbidity data come from the same MFMU Network cohort and are shown in Figure 31-6 (Silver, 2006). In addition, rates of bowel or bladder injury, admission to an intensive care unit or need for ventilator therapy, maternal mortality, and length of surgery and hospitalization showed significantly rising trends. Similar results have been reported by others (Nisenblat, 2006; Usta, 2005). More difficult to quantify are risks for bowel obstruction and pelvic pain from peritoneal adhesive disease, both of which increase after each successive cesarean delivery (Andolf, 2010; Mankuta, 2013).

From the United Kingdom Obstetric Surveillance System (UKOSS), adverse sequelae in women with five or more cesarean deliveries were described (Cook, 2013). These women had significantly higher rates of morbidity compared with those with one prior operation. Specifically, the major hemorrhage rate increased 18-fold; visceral damage, 17-fold; critical care admissions, 15-fold; and delivery <37 weeks, sixfold. Much of this morbidity was in the 18 percent who had a placenta previa or PAS. This same study showed higher neonatal complication rates stemming mainly from indicated premature delivery.

VAGINAL BIRTH AFTER CESAREAN—2021

Unfortunately for women and their providers, no large randomized trials compare maternal or neonatal outcomes in those pursuing either TOLAC or ERCD. Most studies have compared *actual* routes of delivery rather than the *intended* route of delivery. Thus, we agree with Scott (2011) regarding a common-sense approach. The woman—and if she wishes, her partner—are encouraged to actively participate with the provider in an informed-consent discussion. Patient decision aids often assist shared decision making (Poprzenczny, 2020). Although the absolute rates of adverse maternal and neonatal outcomes are low, TOLAC is associated with a higher rate of both maternal and neonatal morbidity and mortality compared with ERCD.

Counseling should include documentation of the prior uterine incision and discussion of risks, benefits, and probable outcomes associated with TOLAC or ERCD. This includes consideration of risks involving future pregnancies. Ideally, counseling begins preconceptionally and continues throughout pregnancy, with flexible options extending up to delivery. For women who desire TOLAC despite a factor that increases their specific risk, additions to the consent form are recommended by the American College of Obstetricians and Gynecologists (2019d). Bonanno and colleagues (2011) have provided such an example. Tsakiridis and coworkers (2018) have compared national guidelines of societies in the United States, Canada, and the United Kingdom. A composite of these recommendations of professional society guidelines is shown in Table 31-5 (Dy, 2019). Guidelines that tend to be more conservative are shown in Table 31-6.

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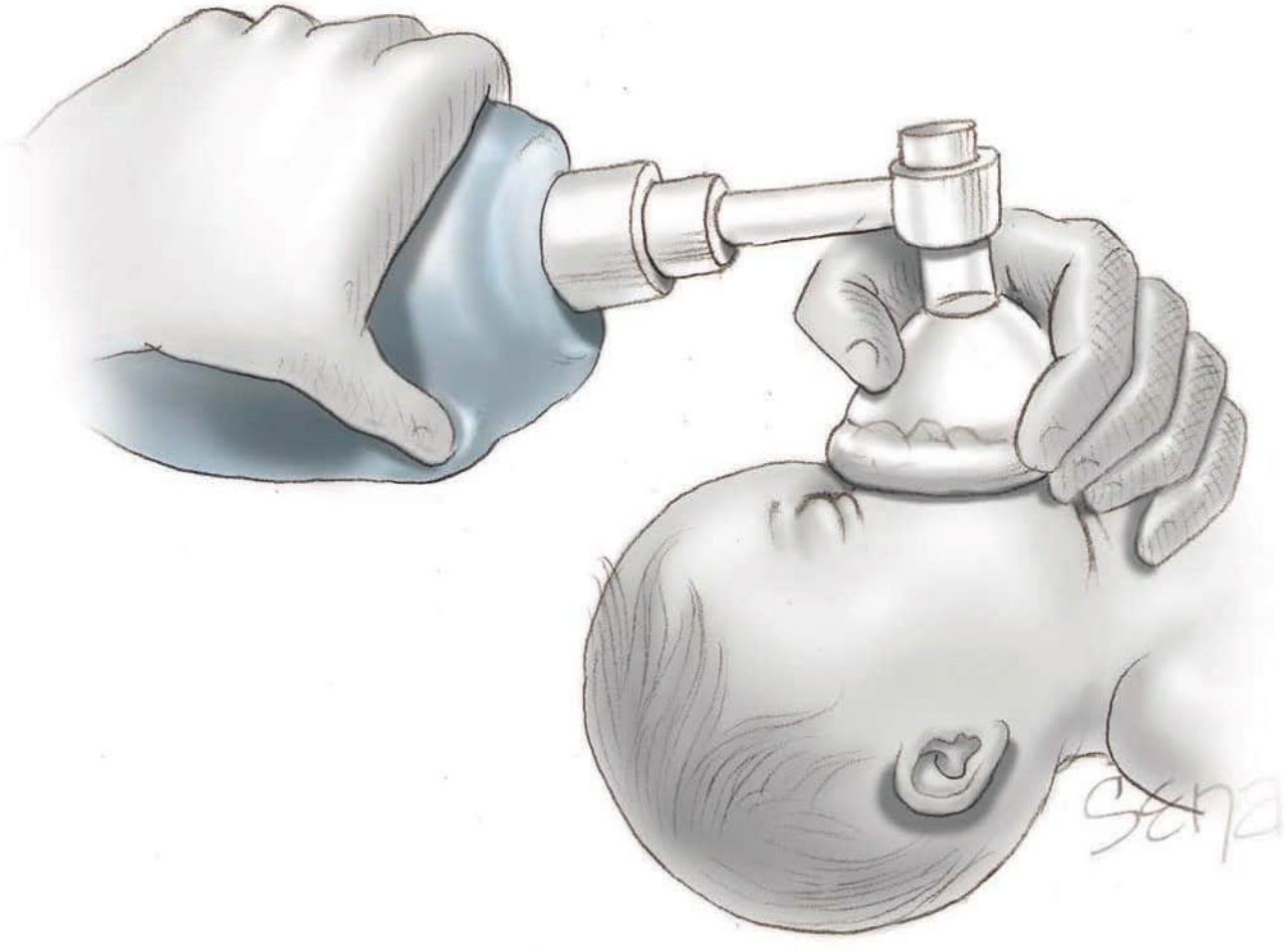
SECTION 9

THE NEWBORN



CHAPTER 32

The Newborn

In most instances at delivery, the newborn is healthy and vigorous, but at times, special care may be needed. For this reason, the American Academy of Pediatrics and the American College of Obstetricians and Gynecologists (2017a) recommend that every birth should be attended by at least one qualified individual. This person should be skilled in the initial steps of newborn care and positive-pressure ventilation, and their only responsibility is management of the newborn. This usually is a pediatrician, nurse practitioner, anesthesiologist, nurse anesthetist, or specially trained nurse. However, in their absence, the responsibility for neonatal resuscitation falls to the obstetrical attendant. Thus, obstetricians should be well versed in measures for immediate care of the newborn.

The number and qualifications of personnel who attend the delivery will vary depending on the anticipated risk, the number of babies, and the hospital setting. A qualified team with full resuscitation skills should be present for high-risk deliveries and immediately available for every resuscitation. This team should not be on call at home or in a remote area of the hospital. Moreover, team training through frequent simulation practice is recommended for all who may be called to attend deliveries (Aziz, 2020).

TRANSITION TO AIR BREATHING

Immediately following birth, the newborn must promptly convert from placental to pulmonary gas exchange. Pulmonary vascular resistance must fall, pulmonary perfusion must rapidly rise, and unique fetal vascular shunts must begin to close to separate the systemic and pulmonary circulations. These shunts include the patent ductus arteriosus and patent foramen ovale, described in Chapter 7 (p. 128). Lung aeration is not only critical for pulmonary gas exchange. Specifically, recent studies suggest that it is responsible for initiating cardiovascular changes at birth (Hooper, 2019).

In utero, the fetal lungs are filled with amnionic fluid, which must be cleared quickly for air breathing. Various means contribute, and these mechanisms may depend on gestational age and mode of delivery. First, in term fetuses, a large release of fetal adrenaline late in labor stimulates pulmonary epithelial cells to stop secreting and instead to start reabsorbing lung liquid due to sodium-channel activation (te Pas, 2008). This mechanism is likely a minor one, as blockade of the receptors for sodium-channel activation reduces or delays but does not prevent liquid clearance from the lungs at birth (Buchiboyina, 2017).

As a second method, mechanical forces aid lung fluid clearance. Early reports described expulsion of lung liquid by compression of the fetal thorax and abdomen as they passed through the birth canal (Karlberg, 1962; Saunders, 1978). By this mechanism, up to a third of lung liquid is expelled in a jet of fluid from the nose and mouth once the respiratory tract is exposed to the lower outside pressure. However, it appears that uterine contractions force a change in fetal posture, which compresses the thorax and raises intrathoracic pressures. This expels lung liquid early in labor more so than the "vaginal squeeze" theory (Hooper, 2019; te Pas, 2008; Vyas, 1981).

In a third mechanism, a significant amount of lung liquid is cleared after birth (Hooper, 2019). In animal studies, most lung aeration occurs during inspiration—within three to five

breaths after birth (Hooper, 2007). The transpulmonary pressure gradient during inspiration promotes movement of fluid into the interstitial tissue. No liquid clears between breaths. From the interstitium, fluid is gradually cleared, probably by the pulmonary circulation and lymphatic vessels. It is possible for lung interstitial tissue pressure to rise to a point that fluid can actually move back into the airspaces during expiration unless positive end-expiratory pressure opposes liquid reentry (Siew, 2009). This may contribute to development of *transient tachypnea of the newborn*.

As fluid is replaced by air, compression of the pulmonary vasculature is reduced considerably, and in turn, resistance to blood flow is lowered. With the fall in pulmonary arterial blood pressure, the ductus arteriosus normally closes.

High, negative intrathoracic pressures are required to permit the initial entry of air into the fluid-filled alveoli. Normally, from the first breath after birth, progressively more residual air accumulates in the lung. With each successive breath, lower pulmonary opening pressure is required. In the normal mature newborn, by approximately the fifth breath, pressure-volume changes achieved with each respiration are very similar to those of the adult. Thus, the breathing pattern shifts from shallow episodic inspirations characteristic of the fetus to regular, deeper inhalations.

As a last mechanism, surfactant is synthesized by type II pneumocytes. It lowers alveolar surface tension and helps maintain lung inflation by preventing alveolar collapse. Insufficient surfactant, which is common in preterm neonates, leads promptly to respiratory distress syndrome (Chap. 34, p. 615).

In utero, umbilical venous return is the main source of preload for the left ventricle. Namely, the fetal pulmonary blood flow is very low due to high pulmonary vascular resistance and is unable to provide sufficient venous return to maintain left ventricular output (Hooper, 2019).

Clamping the umbilical cord reduces preload for the left ventricle and thus reduces cardiac output. Until the lungs aerate and pulmonary blood flow increases, the reduced cardiac output will manifest as bradycardia. If cord clamping is delayed until after the lungs have aerated, the transition is smoother and cardiac output does not fall (Bhatt, 2013). This understanding has led to interest in delayed (physiological) cord clamping, especially if it can be done after successful inflation of the lung. Specialized resuscitation trolleys have been developed to aid this practice, and several international randomized trials are underway.

CARE IN THE DELIVERY ROOM

The International Liaison Committee on Resuscitation (ILCOR) updated its scientific review for neonatal delivery room care and resuscitation (Wyckoff, 2020). This review is used by the American Academy of Pediatrics and the American Heart Association to develop the neonatal resuscitation guidelines for North America (Aziz, 2020).

Immediate Care

Before and during delivery, several determinants of neonatal well-being are carefully considered. Risk factors can include: (1) poor maternal health status; (2) prenatal complications, including any suspected fetal malformations; (3) preterm gestational age; (4) labor complications; (5) long duration of labor and ruptured membranes; (6) anesthesia that may affect placental perfusion; (7) difficult delivery; and (8) various medications given during labor and their dosages, administration routes, and timing.

When risk factors are present, neonatal resuscitation providers should be present for the delivery. This team readies equipment, ensures that adequate personnel are present, delegates roles and responsibilities, and considers contingency plans to stabilize the newborn. In preparation, a neonatal provider will ask the delivery provider regarding expected gestational age, amnionic fluid color, additional maternal and fetal risk factors, and the management plan for umbilical cord clamping (Weiner, 2021). Several neonatal conditions are associated with a nonvigorous presentation. These may include immaturity, hypoxemia or acidosis from any cause, sepsis, recent drugs administered to the mother, meconium-stained amnionic fluid, and central nervous system developmental abnormalities. Those related to the respiratory tract are lung abnormalities, upper airway obstruction, pneumothorax, and meconium aspiration.

Umbilical Cord Management

Obstetrical and pediatric care teams should ideally discuss plans regarding umbilical cord management prior to delivery. Deferred cord clamping provides transfusion of placental blood to the newborn. In term neonates, delaying cord clamping by 30 to 60 seconds raises hemoglobin levels at birth and improves iron stores during infancy. The only reported negative outcome is hyperbilirubinemia and a higher subsequent rate of phototherapy (Gomersall, 2021). In preterm neonates, deferred cord clamping may reduce rates of blood transfusion, intraventricular hemorrhage, and necrotizing enterocolitis and improves survival rates (Seidler, 2021).

Delayed cord clamping should be performed in preterm and term newborns who do not require resuscitation at birth. There should be no delay if a newborn requires resuscitation or if placental abruption, cord avulsion, or bleeding placenta previa or vasa previa complicates delivery. Cord milking is a reasonable alternative to immediate cord clamping for late preterm and term newborns. It should be avoided in neonates <28 weeks' gestation (American College of Obstetricians and Gynecologists, 2020a; Gomersall, 2021; Seidler, 2021).

Newborn Resuscitation

Approximately 10 percent of newborns require some degree of active resuscitation to stimulate breathing, and 1 percent need extensive care. Perhaps not coincidentally, the neonatal death rate with home birth in the United States is small but still fourfold greater than attended hospital births (Grünebaum, 2020).

When deprived of adequate gas exchange, either before or after birth, neonates demonstrate a well-defined sequence of events leading to apnea (Fig. 32-1). With oxygen deprivation and carbon dioxide (CO_2) elevation, there is a transient period of rapid breathing, and if it persists, breathing stops, which

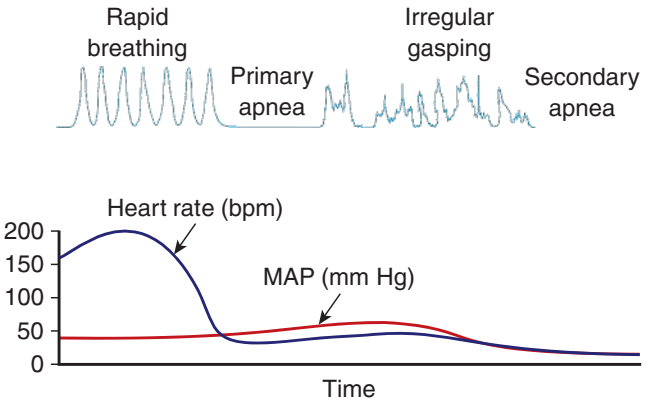


FIGURE 32-1 Physiological changes associated with primary and secondary apnea in the newborn. bpm = beats per minute; HR = heart rate; MAP = mean arterial pressure. (Reproduced with permission from Kattwinkel J: Textbook of Neonatal Resuscitation, 6th ed. Elk Grove Village, American Academy of Pediatrics and American Heart Association, 2010.)

is termed *primary apnea*. This stage is accompanied by a fall in heart rate and loss of neuromuscular tone. Simple stimulation will usually reverse primary apnea. If oxygen deprivation and asphyxia persist, however, the newborn will develop deep gasping respirations, followed by *secondary apnea*. This latter stage is associated with a further decline in heart rate, fall in blood pressure, and loss of neuromuscular tone. Neonates in secondary apnea will not respond to stimulation and will not spontaneously resume respiratory efforts. Unless ventilation is assisted, death follows.

Clinically, primary and secondary apneas are initially indistinguishable. When a response to stimulation is not immediate, resuscitation with effective ventilation of the apneic newborn must begin quickly. Effective positive-pressure ventilation is the most critical intervention in neonatal resuscitation.

Resuscitation Protocol

Initial Assessment

Immediately after birth and usually during the delay for umbilical cord clamping, newborn tone, respiratory effort, and heart rate are evaluated (Fig. 32-2). Most term neonates are vigorous by 10 to 30 seconds after birth (Ersdal, 2012). For these, initial steps of warming the newborn can be done on the mother's chest or abdomen. Direct skin-to-skin contact with the mother and drying and covering the newborn with a warm blanket will help maintain euthermia (36.5 to 37.5°C). A vigorously crying newborn does not require routine oral suctioning (Aziz 2020; Foster, 2017). Instead, bulb suctioning to remove secretions is best reserved for those who cannot clear secretions on their own due to apnea or copious secretions. Additional routine care steps include drying, gentle stimulation by rubbing the newborn's back, and continued observation during the transition period.

If not vigorous or if preterm, the neonate is carried to a prewarmed radiant warmer for initial newborn care steps. The initial wet birth blanket is removed to allow newborn drying. Cold stress is associated with multiple neonatal morbidities and

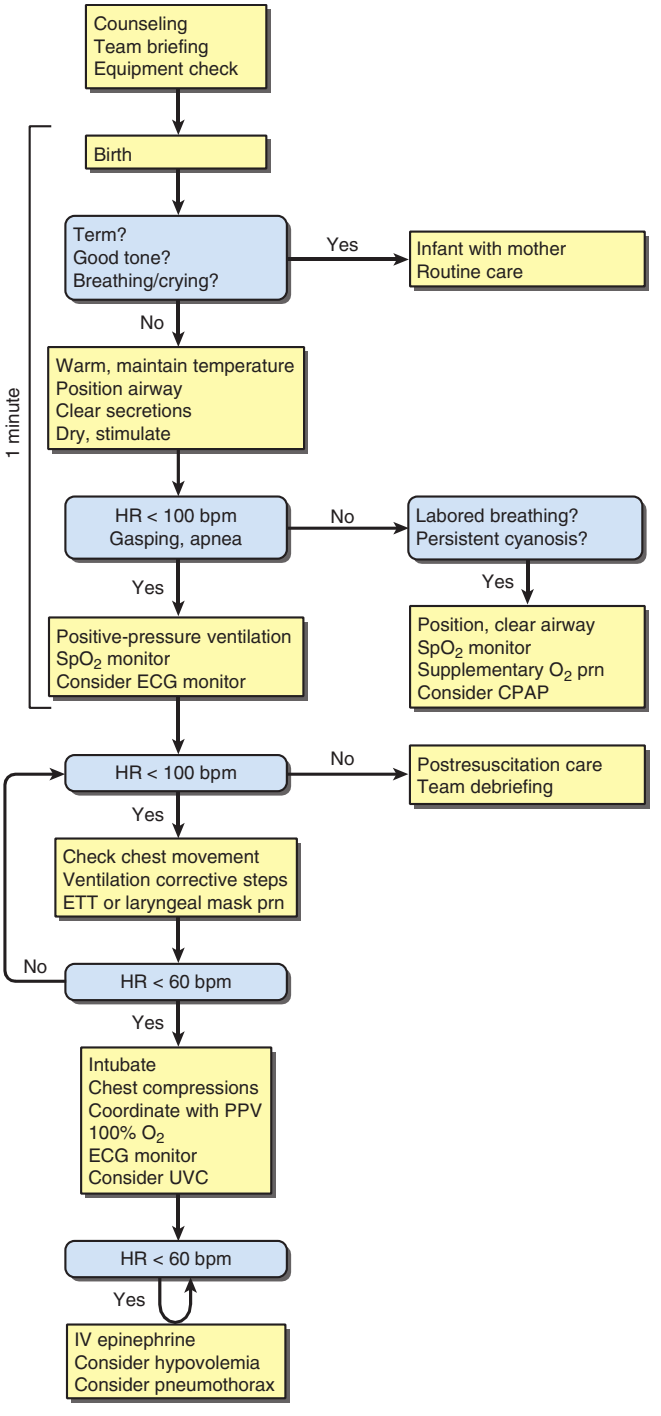


FIGURE 32-2 Algorithm for resuscitation of the newborn based on the International Liaison Committee on Resuscitation scientific review and recommended by the American Academy of Pediatrics and American Heart Association (Aziz, 2020; Wyckoff, 2020). bpm = beats per minute; CPAP = continuous positive airway pressure; ECG = electrocardiogram; ETT = endotracheal tube; HR = heart rate; IV = intravenous; PPV = positive-pressure ventilation; SpO_2 = peripheral oxygen saturation; UVC = umbilical venous catheter.

mortality. Preterm infants are particularly vulnerable, and special steps can help maintain euthermia. These are providing a warm delivery room (>25°C), covering the neonatal head with either a plastic or wool hat, applying polyethylene plastic "ponchos" or wraps to slow evaporative heat losses, using chemically

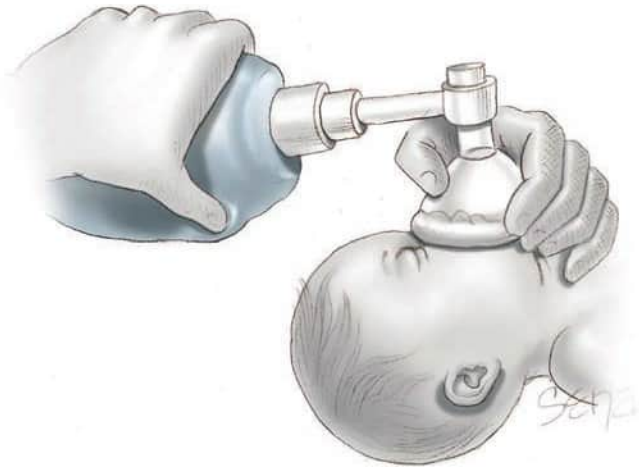


FIGURE 32-3 Correct use of bag-and-mask ventilation. The head should be in a sniffing position with the tip of the nose pointing to the ceiling. The neck should not be hyperextended.

activated thermal mattresses to reduce conductive heat loss, and administering warm, humidified respiratory gases during respiratory stabilization (Aziz, 2020; Wyckoff, 2020).

At the radiant warmer, newborns are positioned with mild neck extension to maximally open the airway. If the newborn is apneic or has copious secretions that obstruct the airway, then a bulb syringe or suction catheter can help clear the mouth and the nose. Routine intubation and suctioning of meconium-stained amnionic fluid is not recommended for the nonvigorous newborn (American College of Obstetricians and Gynecologists, 2021a; Wyckoff, 2020). Intubation and suction are reserved for suspected airway obstruction. Meconium-stained amnionic fluid is a significant risk factor for the need for advanced resuscitation. In rare circumstances, the meconium-stained fluid can obstruct the newborn's airway and necessitate intubation and tracheal suctioning (Aziz, 2020; Wyckoff, 2020).

After completion of the initial stabilization steps, persisting apnea, gasping respirations, or heart rate ≤100 beats per minute (bpm) should prompt immediate administration of positive-pressure ventilation with room air (Fig. 32-3). This should be started by 60 seconds of life, if not sooner, once the initial steps are completed.

Mask Ventilation

Assisted ventilation by facemask at a rate of 40 to 60 breaths per minute is recommended as an initial resuscitation step. Oxygen saturation is monitored by pulse oximetry. Supplemental oxygen can be given in graduated, rising percentages to maintain oxygen saturation values within a normal range. Percentage goals rise progressively with accruing minutes of life (Table 32-1) (Weiner, 2021). Adequate ventilation is best indicated by an improved heart rate. A colorimetric end-tidal carbon dioxide ($ETCO_2$) monitor that lies between the positive-pressure device and facemask serves as a helpful adjunct to detect successful gas exchange during mask ventilation.

TABLE 32-1. Oxygen Saturation Goals per Minute of Life

1 min	60–65%
2 min	65–70%
3 min	70–75%
4 min	75–80%
5 min	80–85%
10 min	85–95%

If the heart rate remains ≤100 beats per minute after 5 to 10 positive pressure breaths, and the attempted ventilation is inadequate, then further corrective steps should begin. These can be remembered by the mnemonic MR. SOPA (Table 32-2) (Weiner, 2021). The two most common problems are mask leak due to an ineffective seal and malposition of the airway (Schmölzer, 2019). Mask positioning should maintain an open mouth. This provides a superior conduit for gas transfer than the narrow-caliber nares. If the other corrective steps do not raise the heart rate, either intubation with an endotracheal tube or placement of a supraglottic airway is required.

Alternative Airway

If mask ventilation is ineffective or prolonged, an alternative airway is placed. For tracheal intubation, a laryngoscope with a straight blade—size 0 for a preterm newborn and size 1 for a term neonate—is used. Gentle cricoid pressure may be useful. An increasing heart rate and $ETCO_2$ detection after several breaths are the primary methods to confirm intubation of the trachea and not the esophagus. One can also look for symmetrical chest wall motion; auscultate for equal breath sounds, especially in the axillae; and auscultate for the absence of breath sounds or gurgling over the stomach.

Once in place, the tube is used for tracheal suctioning only for a suspected obstructed airway. Otherwise, an appropriate positive-pressure device (self-inflating bag, flow-inflating bag, or T-piece resuscitator) is attached to the endotracheal tube (Roehr, 2021). Ventilation breaths are delivered at a rate of 40 to 60 per minute with a force adequate to stabilize the heart

TABLE 32-2. Ventilation Corrective Steps (MR. SOPA)

M—Mask adjustment	Check the mask seal and reapply if needed
R—Reposition airway	Ensure the newborn is truly in the open airway position with mild neck extension
S—Suction mouth and nose	Remove obstructing secretions
O—Open the mouth	Avoid closing the mouth during efforts to achieve a good mask seal
P—Pressure increase	Increase the inflation pressure
A—Advanced airway	If all prior steps fail to achieve chest rise, then intubate or place a laryngeal mask or other supraglottic airway

rate. In term newborns, opening pressures of 30 to 40 cm H_2O typically will expand the alveoli without causing barotrauma. Once the lung is inflated, less pressure is typically needed (20 to 25 cm H_2O). For preterm neonates, pressures of 20 to 25 cm H_2O are typically used. Increases in heart rate and peripheral oxygen saturation (SpO_2) levels to acceptable ranges reflect a positive response.

Chest Compressions

Most commonly, effective ventilation is all that is required to stabilize the newborn in the delivery room. If the heart rate remains <60 bpm despite ventilation corrective steps, including placement of an endotracheal tube, chest compressions are initiated. Once the endotracheal tube is secured, compressions are done from the head of the bed rather than the side so that space is opened up for a provider to have umbilical venous access. When compressions are initiated, the oxygen concentration is increased to 100 percent. With the two-thumb compression method, hands encircle the chest, while the thumbs depress the sternum. Compressions are delivered on the lower third of the sternum at a depth sufficient to generate a palpable pulse. This is typically one third of the anterior-posterior diameter of the chest. Compared with other techniques, this method offers less provider fatigue over time, yields higher generated perfusion pressures, and lessens hand malpositioning that could cause traumatic injury (Kapadia, 2012).

A 3:1 compressions-to-ventilation ratio is recommended, and 90 compressions and 30 breaths achieve approximately 120 events each minute. Coordinated chest compressions and ventilations should continue until the spontaneous heart rate is ≥60 bpm (Wyckoff, 2020).

If the heart rate remains ≤60 bpm after adequate ventilation and chest compressions, intravenously administered epinephrine is indicated. The recommended intravenous dose is 0.01 to 0.03 mg/kg. Epinephrine may be given through the endotracheal tube if venous access has not been established, but its action is less reliable (Isayama, 2020). If given through the endotracheal tube, higher doses are employed—0.05 to 0.1 mg/kg.

Resuscitation Discontinuation

ILCOR concludes that it is reasonable to discontinue resuscitative efforts for a neonate who remains without a heartbeat despite at least 20 minutes of continuous and adequate resuscitative efforts (Wyckoff, 2020). Notably, the decision to continue or discontinue resuscitative efforts must be individualized. The time was recently lengthened due to reports of some newborns enrolled in therapeutic hypothermia trials who had a 10-minute Apgar score of 0 yet survived without disability. This suggests the need for caution in limiting resuscitation to 10 minutes (Foglia, 2020).

EVALUATION OF NEWBORN CONDITION

■ Apgar Score

The scoring system described by Dr. Virginia Apgar in 1953 remains a useful clinical tool to classify newborn health immediately after birth and to assess the effectiveness of resuscitative measures (American College of Obstetricians and Gynecologists, 2021b). During scoring, each of five easily identifiable characteristics—heart rate, respiratory effort, muscle tone, reflex irritability, and color—is assessed and assigned a value of 0, 1, or 2 (Table 32-3). In the currently recommended expanded form, concurrent resuscitation interventions also are recorded over time. The total score, based on the sum of the five components, is determined in all neonates at 1 and 5 minutes after delivery. In those with a score <7, the score may be calculated at further 5-minute intervals until a 20-minute Apgar score is assigned or resuscitation efforts are halted (Weiner, 2021).

In an analysis of more than 150,000 newborns delivered at Parkland Hospital, Casey and associates (2001b) assessed the significance of the 5-minute score for predicting survival during the first 28 days of life. They found that in term neonates, the

TABLE 32-3. 20-Minute Expanded Apgar Score

Sign	0 point	1 point	2 point	1 min	5 min	10 min	15 min	20 min
Color	Blue or pale	Acrocyanotic	Completely pink					
Heart rate	Absent	<100/min	>100/min					
Reflex irritability	No response	Grimace	Cry or active withdrawal					
Muscle tone	Limp	Some flexion	Active motion					
Respiration	Absent	Weak cry; hypoventilation	Good, crying					
			Total					
Comments:			**Resuscitation**					
			Minutes	1	5	10	15	20
			Oxygen					
			PPV/CPAP					
			ETT					
			Chest compressions					
			Epinephrine					

CPAP = continuous positive airway pressure; ETT = endotracheal tube; PPV = positive-pressure ventilation.

risk of neonatal death was approximately 1 in 5000 for those with Apgar scores of 7 to 10. This risk compares with a mortality rate of 25 percent for term newborns with 5-minute scores ≤3. Low 5-minute scores were comparably predictive of neonatal death in preterm neonates. Similarly, an analysis of more than 113,000 preterm neonates ranging from 22 to 36 weeks' gestation found that Apgar scores at 5 and 10 minutes provided prognostic information for neonatal survival rates across gestational-age strata (Cnattingius, 2020). Thus, the Apgar scoring system remains relevant for the prediction of neonatal survival.

Apgar scores alone are not predictive of hypoxic ischemic encephalopathy (HIE). However, in cohorts of babies diagnosed with HIE based on umbilical cord blood pH and standardized neurologic examinations, low 10-minute Apgar scores are significantly associated with school-age outcomes (Natarajan, 2013).

Previously, many groups established erroneous definitions of asphyxia based solely on low Apgar scores. These prompted the American College of Obstetricians and Gynecologists and American Academy of Pediatrics (2021b) to issue a series of joint opinions with important caveats regarding Apgar score limitations. Certain elements of the Apgar score are partially dependent on the physiological maturity of the newborn, and a healthy, preterm neonate may receive a low score only because of immaturity. Other influencing factors include fetal malformations, maternal medications, and infection. Thus, it is inappropriate to use an Apgar score alone to diagnose asphyxia. Moreover, the Apgar score alone cannot establish hypoxia as the cause of cerebral palsy, as discussed in Chapter 33 (p. 604).

Umbilical Cord Blood Acid–Base Studies

Blood taken from umbilical vessels may be used for acid–base studies to assess the metabolic status of the neonate. Blood collection is performed following delivery by immediately isolating a 10- to 20-cm segment of cord with two clamps placed near the neonate and another two clamps positioned nearer the placenta. The cord is then cut between the two proximal clamps and then the two distal clamps (Blickstein, 2007).

Arterial blood is drawn from the isolated cord segment into a 1- to 2-mL commercially prepared plastic syringe containing lyophilized heparin or a similar syringe that has been flushed with a heparin solution containing 1000 U/mL. Once sampling is completed, the needle is capped and the syringe transported, on ice, to the laboratory. Although efforts should be made for prompt transport, neither the pH nor partial pressure of CO_2 (P_{CO_2}) values change significantly in blood kept at room temperature for up to 60 minutes (Lynn, 2007). Mathematical models have been developed that allow reasonable prediction of birth acid–base status in properly collected cord blood samples analyzed as late as 60 hours after delivery (Chauhan, 1994). Notably, acid–base measurements can show significant variances between different analyzing devices (Mokarami, 2012).

Fetal Acid–Base Physiology

The fetus produces both carbonic and organic acids. Carbonic acid (H_2CO_3) forms from oxidative metabolism of CO_2. The fetus usually rapidly clears CO_2 through the placental circulation. If CO_2 clearance drops, carbonic acid levels rise. This often follows impaired placental exchange. When H_2CO_3 accumulates in fetal blood and organic acids do not concurrently rise, the result is *respiratory acidemia*.

In contrast, organic acids primarily include lactic and β-hydroxybutyric acids. Levels of these increase with persistent placental exchange impairment, and they result from anaerobic glycolysis. These organic acids are cleared slowly from fetal blood. When they accumulate, without a concurrent increase in H_2CO_3, the result is *metabolic acidemia*. With the development of metabolic acidemia, bicarbonate (HCO_3^-) levels drop because it is used to buffer the organic acid. A rise in H_2CO_3 concentrations accompanied by greater organic acid levels, reflected by decreased HCO_3^- levels, causes *mixed respiratory-metabolic acidemia*.

In the fetus, respiratory and metabolic acidemia and ultimately tissue acidosis are most likely part of a progressively worsening continuum. This is different from adult pathophysiology, in which distinct conditions result either in respiratory acidosis—for example, pulmonary disease, or in metabolic acidosis—for example, diabetes. In the fetus, the placenta serves as both the lungs and, to a certain degree, the kidneys. One principal cause of fetal acidemia is a drop in uteroplacental perfusion. This creates retention of CO_2, that is, respiratory acidemia, and if protracted and severe enough, yields a mixed or metabolic acidemia.

Assuming that maternal pH and blood gases are normal, the actual pH of fetal blood depends on the proportion of carbonic and organic acids and the amount of bicarbonate, which is the major buffer in blood. This can best be illustrated by the Henderson–Hasselbalch equation:

$$\text{pH} = \text{pK} + \log \frac{[\text{base}]}{[\text{acid}]} \text{ or, } \text{pH} = \text{pK} + \log \frac{HCO_3^-}{H_2CO_3}$$

For clinical purposes, HCO_3^- represents the metabolic component and is reported in mEq/L. The H_2CO_3 concentration reflects the respiratory component and is reported as the P_{CO_2} in mm Hg. Thus:

$$\text{pH} = \text{pK} + \log \frac{\text{metabolic } (HCO_3^- \text{ mEq/L})}{\text{respiratory } (P_{CO_2} \text{ mm Hg})}$$

The result of this equation is a pH value. Because pH is a logarithmic term, it does not give a linear measure of acid accumulation. For example, a change in hydrogen ion concentration associated with a fall in pH from 7.0 to 6.9 is almost twice that which is associated with a fall in pH from 7.3 to 7.2. For this reason, the change in base—termed *delta base*—offers a more linear measure of the degree of accumulation of metabolic acid (Armstrong, 2007). The delta base is a calculated number used as a measure of the change in buffering capacity of bicarbonate (HCO_3^-). The formula for calculating the base excess (BE) is as follows:

$$\text{BE} = 0.02786 \times P_{CO_2} \times 10^{(\text{pH} - 6.1)} \times 13.77 \times \text{pH} - 124.58$$

Shown in Figure 32-4 is a nomogram from which these can be calculated if only two parameters are known. For example, the HCO_3^- concentration declines with a metabolic acidemia as it is consumed to maintain a normal pH. A base deficit develops when the HCO_3^- concentration drops below normal levels, and a

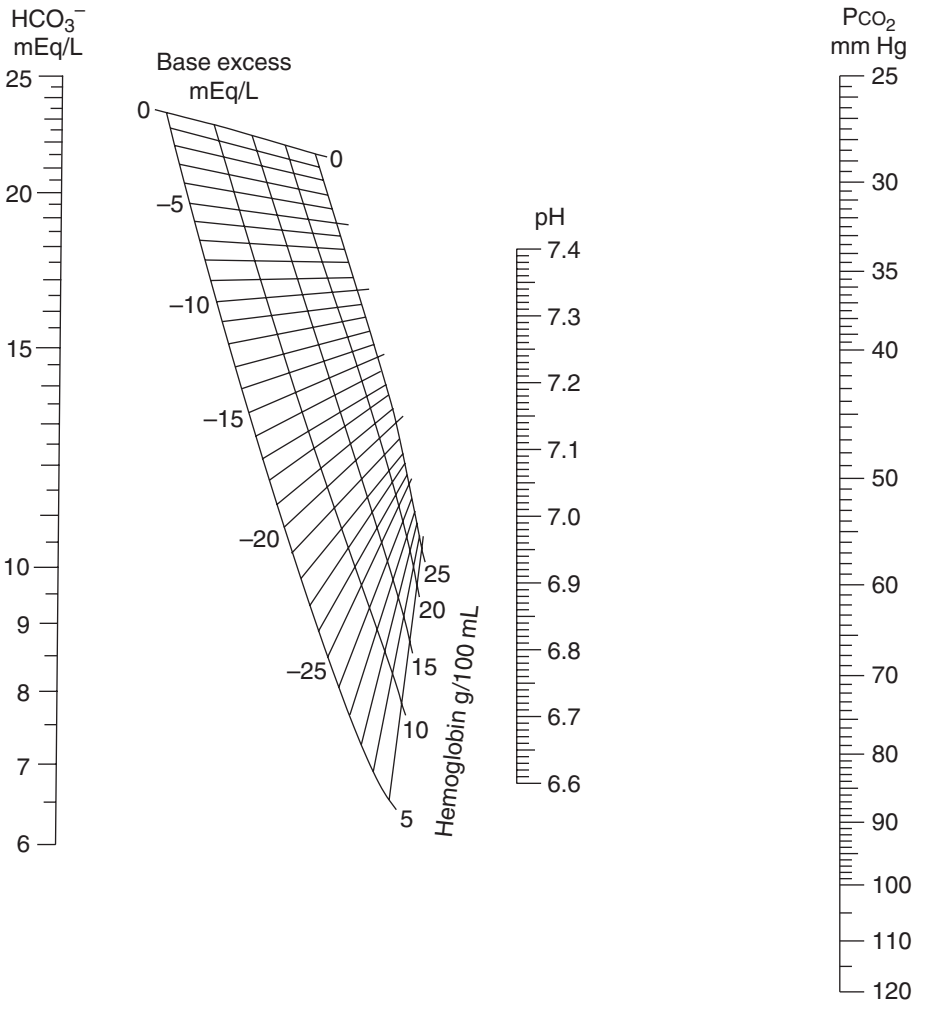


FIGURE 32-4 Nomogram for determining the delta base. (Reproduced with permission from Siggaard-Anderson O: Blood acid–base alignment nomogram. Scand J Clin Lab Invest. 1963;15:211–7.)

base excess occurs when HCO_3^- values are above normal. Importantly, a mixed respiratory–metabolic acidemia with a large base deficit and a low HCO_3^-, for example 12 mmol/L, is more often associated with a depressed neonate than is a mixed acidemia with a minimal base deficit and a more nearly normal HCO_3^- level.

Clinical Significance of Acidemia

Fetal oxygenation and pH generally decline during the course of normal labor. Normal umbilical cord blood pH and blood gas values at delivery in term newborns are summarized in Table 32-4. Similar values have been reported for preterm neonates (Ramin, 1989; Skiold, 2017). The lower limits of normal pH in the newborn range from 7.05 to 7.16 for newborns 28 to 42 weeks' gestation at birth, with some variation based on gestational age (Skiold, 2017). Thus, these values should be considered to define neonatal acidemia. Even so, most fetuses will tolerate intrapartum acidemia with a pH as low as 7.00 without incurring neurological impairment (American College of Obstetricians and Gynecologists, 2014; Lee, 2020). That said, in a study of newborns with

TABLE 32-4. Umbilical Cord Blood pH and Blood Gas Values in Normal Term Newborns

Values	Ramin, 1989[a] Spontaneous Delivery n = 1292[c]	Riley, 1993[b] Spontaneous Delivery n = 3522[c]	Kotaska, 2010[b] Spontaneous Delivery n = 303[d]	Kotaska, 2010[e] Cesarean Delivery n = 189[d]
Arterial Blood				
pH	7.28 (0.07)	7.27 (0.069)	7.26 (7.01–7.39)	7.3 (7.05–7.39)
Pco_2 (mm Hg)	49.9 (14.2)	50.3 (11.1)	51 (30.9–85.8)	54 (37.5–79.5)
HCO_3^- (mEq/L)	23.1 (2.8)	22.0 (3.6)	—	—
Base excess (mEq/L)	−3.6 (2.8)	−2.7 (2.8)	—	—
Venous Blood				
pH	—	7.34 (0.063)	7.31 (7.06–7.44)	7.34 (7.10–7.42)
Pco_2 (mm Hg)	—	40.7 (7.9)	41 (24.9–70.9)	44 (29.1–70.2)
HCO_3^- (mEq/L)	—	21.4 (2.5)	—	—
Base excess (mEq/L)	—	−2.4 (2)	—	—

[a]Newborns of selected women with uncomplicated vaginal deliveries.
[b]Newborns of unselected women with vaginal deliveries.
[c]Data shown as mean (SD).
[d]Data shown as range with 2.5 or 97.5 percentile.
[e]Cesarean delivery—labor not stated.
From Centers for Disease Control and Prevention, 2012; Watson, 2006.

a pH <7.0 from Parkland Hospital, the incidences of neonatal deaths—8 percent, intensive care admissions—39 percent, intubations—14 percent, and seizures—13 percent, were notable (Goldaber, 1991). In a study of more than 51,000 term newborns, the incidence of neonatal encephalopathy in those with a birth pH <7.0 was 3 percent (Yeh, 2012). Even those who had normal 5-minute Apgar scores but who had an arterial cord pH values <7.0 experienced a higher risk of morbidity. This included respiratory distress, neonatal intensive care unit admission, and sepsis (Sabol, 2016). Faster acidemia resolution after birth is associated with better outcome (Casey, 2001a).

Respiratory Acidemia

Acute interruption in placental gas exchange is accompanied by subsequent CO_2 retention and respiratory acidemia. The most common antecedent factor is transient umbilical cord compression. Generally, respiratory acidemia is not harmful to the fetus (Low, 1994).

The degree to which pH is affected by P_{CO_2}—the respiratory component of the acidosis—can be calculated. First, the upper normal neonatal P_{CO_2} value of about 50 mm Hg is subtracted from the cord blood gas P_{CO_2} value. Each additional 10 mm Hg P_{CO_2} increment will lower the pH by 0.08 units (Eisenberg, 1987). Thus, in a mixed respiratory–metabolic acidemia, the benign respiratory component can be calculated. As an example, acute cord prolapse during labor prompts cesarean delivery of a neonate 20 minutes later. The umbilical artery blood gas pH was 6.95 and the P_{CO_2} was 90 mm Hg. The degree to which the cord compression and subsequent impairment of CO_2 exchange affected the pH is calculated using the relationship given earlier and shown below.

$$90 \text{ mm Hg} - 50 \text{ mm Hg} = 40 \text{ mm Hg excess } CO_2$$

$$\text{To correct pH: } (40 \div 10) \times 0.08 = 0.32;\ 6.95 + 0.32 = 7.27$$

Thus, the pH before cord prolapse was approximately 7.27, well within normal limits. Thus, the low pH resulted from respiratory acidosis.

Metabolic Acidemia

The fetus begins to develop metabolic acidemia when oxygen deprivation is sufficiently long and severe to require anaerobic metabolism for cellular energy needs. Low and associates (1997) defined fetal acidosis as a base deficit ≥12 mmol/L, and severe fetal acidosis as a base deficit ≥16 mmol/L. In the Parkland study of more than 150,000 newborns cited earlier, metabolic acidemia was defined using umbilical cord blood gas thresholds that were two standard deviations below the mean (Casey, 2001b). Thus, metabolic acidemia was an umbilical artery blood pH <7.00 accompanied by a P_{CO_2} ≤76.3 mm Hg, with higher values indicating a respiratory component; HCO_3^- concentration ≤17.7 mmol/L; and base deficit ≥10.3 mEq/L. From the standpoint of *possible* neurological injury, the American College of Obstetricians and Gynecologists (2014) defines metabolic acidosis as umbilical arterial pH <7.0 and a base deficit ≥12 mmol/L.

Metabolic acidemia is associated with a high rate of multiorgan dysfunction. In rare cases, such hypoxia-induced metabolic acidemia may be so severe that it causes subsequent hypoxic ischemic encephalopathy (Chap. 33, p. 601). Severe metabolic acidosis is poorly predictive of subsequent neurological impairment in the term neonate (Cahill, 2017). In fact, a fetus without such acidemia cannot by definition have suffered recent hypoxic-induced injury. In preterm infants, newborn acid–base status is more closely linked to intraventricular hemorrhage, periventricular leukomalacia, and poorer long-term neurological outcomes (Baalbaki, 2021; Morgan, 2017).

Associations between metabolic acidemia, low Apgar scores, and neonatal death have been described in term and preterm newborns (Morgan, 2015). Regarding term neonates, the risk of neonatal death was more than 3200-fold greater in term neonates with metabolic acidemia and 5-minute scores ≤3 compared with those with a 5-minute Apgar score ≥7 (Casey, 2001b).

Recommendations for Cord Blood Gas Determinations

In some centers, cord gas analysis is performed in all neonates at birth (Morgan, 2015; Sabol, 2016). Cost-effectiveness analysis for universal cord blood gas measurement suggests benefit and potential cost savings (White, 2016). It seems reasonable to obtain cord blood gas determinations for intrapartum cases of cesarean delivery for fetal compromise, abnormal fetal heart rate tracing, fever, and low 5-minute Apgar score. Multifetal gestation and severely growth-restricted fetuses are others.

Although umbilical cord acid–base blood determinations are poorly predictive of either immediate or long-term adverse neurological outcome, they provide the most objective evidence of the fetal metabolic status at birth.

PREVENTIVE CARE

Eye Infection Prophylaxis

Ophthalmia neonatorum is mucopurulent conjunctivitis of newborns. Gonococcal and chlamydial infections are among the most common causes (American Academy of Pediatrics, 2021b).

Neisseria gonorrhoeae infection acquired at birth was a common cause of childhood blindness in the past. Gonococcal prophylaxis is now mandatory for all neonates in most states (American Academy of Pediatrics, 2017a). For *prophylaxis* soon after delivery, 0.5-percent erythromycin ophthalmic ointment is recommended (U.S. Preventive Services Task Force, 2019).

For a neonate born to a mother with untreated gonorrhea, *treatment* of presumptive neonatal gonococcal conjunctivitis is a single ceftriaxone dose, 25 to 50 mg/kg, intravenously or intramuscularly, not to exceed 125 mg intramuscularly (American Academy of Pediatrics, 2021b). Before treatment, neonatal testing for both gonococcal and chlamydia infections should be obtained.

With *chlamydial conjunctivitis*, adequate neonatal prophylaxis is challenging. Ideally, prenatal screening and treatment for *Chlamydia trachomatis* obviates conjunctival infection (Hammerschlag, 2011) (Chap. 68, p. 1212). In neonates delivered vaginally of mothers with an active chlamydial infection, 30 to 50 percent will develop conjunctivitis (Zikic, 2018).

Prophylactic topical eye treatments do not reliably reduce the incidence of chlamydial conjunctivitis.

Conjunctivitis in a newborn up to age 3 months should prompt consideration for chlamydial infection (Moore, 2015). Treatment for neonatal chlamydial conjunctivitis is oral erythromycin base or ethylsuccinate, 50 mg/kg/d given daily and divided into four doses for 14 days. Another is oral azithromycin, 20 mg/kg given as a single daily dose for 3 days. A second course may be required since the efficacy of erythromycin therapy approximates only 80 percent. Posttreatment follow-up of these infants is recommended (American Academy of Pediatrics, 2021b).

Hepatitis B Immunization

Routine immunization with thimerosal-free vaccine against hepatitis B within the first 24 hours of life is standard practice for all medically stable newborns with birthweights >2000 g (American Academy of Pediatrics, 2017b). If the mother is seropositive for hepatitis B surface antigen, the neonate is also passively immunized with hepatitis B immune globulin. For high-risk or even all seropositive women during pregnancy, some advocate treatment with antiviral nucleoside or nucleotide analogues to minimize fetal transmission (Dunkelberg, 2014) (Chap. 58, p. 1038).

Vitamin K

Supplemental vitamin K injection will prevent vitamin K deficiency bleeding of the newborn (Chap. 33, p. 606). A single intramuscular dose of vitamin K, 0.5 to 1 mg, is given within 1 hour of birth (American Academy of Pediatrics, 2017a).

COVID-19

The novel SARS-CoV-2 virus is very contagious, spreads person to person, and can cause severe morbidity or mortality. Thus, birth attendants at the delivery of a mother with COVID-19 should implement airborne and contact isolation precautions to protect themselves during potentially aerosolizing resuscitation procedures (Edelson, 2020).

National data suggest that approximately 2 percent of newborns of women who test positive for SARS-CoV-2 near delivery have also tested positive in the first 24 to 96 hours of life (American Academy of Pediatrics, 2021a). Newborn death directly attributable to perinatal infection with SARS-CoV-2 is rare in the United States. However, evidence suggests that symptomatic maternal infection at delivery is associated with increased risks of preterm birth and perinatal morbidity (Chap. 67, p. 1188).

Infected mothers should wear a mask while holding their newborn. A mother who is acutely ill with COVID-19 may be unable to care for her neonate and may need temporary separation until she improves. Mothers who are infected but who are not acutely ill can room-in with their well newborn but should maintain a reasonable distance from their babies when possible. Breastfeeding while wearing a mask and maintaining good hand hygiene is suitable (American College of Obstetricians and Gynecologists, 2020b). The newborn should be tested at least once for SARS-CoV-2 prior to discharge (American Academy of Pediatrics, 2021a).

Newborn Screening

Mass-screening tests are available for 35 newborn conditions, and these are recommended by the Advisory Committee on Heritable Disorders in Newborns and Children (2018). Shown in Table 32-5, many are mandated by various state laws. Most states require that all tests in the core panel be performed. Supplemental conditions—*secondary conditions*—are listed on the Advisory Committee's website. Some states require some of these in addition to their mandated core panel. Each practitioner should be familiar with their individual state requirements, which are available at: babysfirsttest.org/newborn-screening/states.

TABLE 32-5. Newborn Screening Core Panel

Organic Acid Metabolism	Fatty Acid Metabolism	Amino Acid Metabolism	Others
Isovaleric acidemia	Medium-chain acyl-CoA dehydrogenase deficiency	Phenylketonuria	Biotinidase deficiency
Propionic acidemia	Very long-chain acyl-CoA dehydrogenase deficiency	Maple syrup urine disease	Galactosemia
Glutaric acidemia type I	Long-chain 3-OH acyl-CoA dehydrogenase deficiency	Homocystinuria	Hearing loss
β-Ketothiolase deficiency	Trifunctional protein deficiency	Citrullinemia, type I	Cystic fibrosis
3-Hydroxy-3-methylglutaric aciduria	Carnitine uptake defect	Argininosuccinic	Critical congenital heart disease
Holocarboxylase synthase deficiency	**Endocrine Disorders**	Tyrosinemia, type I	Severe combined immunodeficiency
3-Methylcrotonyl-CoA carboxylase deficiency	Congenital hypothyroidism	**Hemoglobin Disorders**	Glycogen storage disease, type II
Methylmalonic acidemia (methylmalonyl-CoA mutase)	Congenital adrenal hyperplasia	SS disease	Mucopolysaccharidosis, type 1
Methylmalonic acidemia (cobalamin disorder)		S-β-thalassemia	X-linked adrenoleukodystrophy
		SC disease	Spinal muscular atrophy

From Advisory Committee on Heritable Disorders in Newborns and Children, 2018; Watson, 2006.

ROUTINE NEWBORN CARE

Gestational Age Estimation

Newborn gestational age can be estimated very soon after delivery. The relationship between gestational age and birthweight can identify neonates at risk for complications. For example, neonates who are either small or large for gestational age are at greater risk for hypoglycemia and polycythemia, and measurements of blood glucose and hematocrit are indicated.

Care of Skin and Umbilical Cord

All excess vernix, blood, and meconium is gently wiped off after delivery while keeping the newborn warm. Any remaining vernix is readily absorbed and disappears within 24 hours. The first bath is postponed until the neonate's temperature is stable.

Aseptic precautions are observed in the immediate care of the cord. The American Academy of Pediatrics (2017a) has concluded that keeping the cord dry is sufficient care. The umbilical cord begins to lose water from its Wharton jelly shortly after birth. Within 24 hours, the cord stump loses its characteristic bluish-white, moist appearance and soon becomes dry and black. Within several days to weeks, the stump sloughs and leaves a small, granulating wound, which after healing forms the umbilicus. Separation usually takes place within the first 2 weeks. The umbilical cord dries more quickly and separates more readily when exposed to air (López-Medina, 2020). Thus, a dressing is not recommended.

In resource-poor countries, local antimicrobial prophylaxis is reasonable (Salam, 2014). The World Health Organization (2014) recommends cleansing with chlorhexidine in situations in which hygienic conditions are poor or infection rates are high.

Despite precautions, a serious umbilical infection—*omphalitis*—sometimes develops. The most likely offending organisms are *Staphylococcus aureus*, group A and B streptococcus, and gram-negative rods such as *Escherichia coli* (Stewart, 2016). Typical signs of cellulitis and stump discharge usually aid diagnosis. Mild erythema and some bleeding at the stump site with cord detachment is common, but some cases present with no outward signs.

Feeding and Weight Loss

Exclusive breastfeeding is preferred for the newborn's first 6 months. In 2020, 84 percent of U.S. newborns were initially breastfed, 58 percent were still nursing at 6 months, and 35 percent at 1 year (Centers for Disease Control and Prevention, 2020). In many hospitals, breastfeeding begins in the delivery room. Most term newborns thrive best when fed 8 to 12 times daily for approximately 15 minutes each episode. Preterm or growth-restricted newborns require feedings at shorter intervals. Breastfeeding is discussed further in Chapter 36 (p. 639).

Because most neonates actually receive little nutriment for the first 3 or 4 days of life, they progressively lose weight until the flow of maternal milk is established or other feeding is instituted. Preterm neonates lose relatively more weight and regain their birthweight more slowly. Conversely, growth-restricted but otherwise healthy newborns regain their initial weight more quickly than those born preterm. With proper nourishment, birthweight of term newborns usually is regained by 10 days.

Stools and Urine

For the first 2 or 3 days after birth, the colon contains soft, brown-green meconium. This consists of desquamated epithelial cells from the intestinal tract, mucus, epidermal cells, and lanugo (fetal hair) that have been swallowed along with amnionic fluid. The characteristic color results from bile pigments. During fetal life and for a few hours after birth, the intestinal contents are sterile, but bacteria quickly colonize the bowel contents.

Meconium stooling is seen in 90 percent of newborns within the first 24 hours and in most of the rest within 36 hours. Usually, newborns first void shortly after birth but may not until the second day. Meconium and urine passage indicates patency of the gastrointestinal and urinary tracts, respectively. Failure of the newborn to stool or urinate after these times suggests a congenital defect, such as Hirschsprung disease, imperforate anus, or posterior urethral valve. After the third or fourth day, as a result of milk ingestion, meconium is replaced by light-yellow, softer, homogeneous feces.

Neonatal Hyperbilirubinemia

Between the second and fifth day of life approximately one third of all neonates develop physiological jaundice of the newborn. It has special significance considering most hospitals have policies for early discharge. Guidelines regarding standard phototherapy equipment and monitoring, as well as treatment recommendations per gestational age, hour of life, and risk factors are used (American Academy of Pediatrics, 2017a). Hyperbilirubinemia is discussed further in Chapter 33 (p. 606).

Male Circumcision

Indications

Neonatal circumcision of male newborns has been a controversial topic in the United States for at least 35 years. Even so, scientific evidence supports several medical benefits that include prevention of phimosis, paraphimosis, and balanoposthitis. Circumcision also lowers the incidence of penile cancer and of cervical cancer among their sexual partners. The Centers for Disease Control and Prevention (2011) estimates that the newborn male circumcision rate has declined over the past decades in the United States, and rates vary widely by region. From a national database, the overall circumcision rate decreased from 57 percent in 2003 to 52 percent in 2016 (Jacobson, 2021).

The American Academy of Pediatrics Task Force on Circumcision (2012) concluded that health benefits of newborn male circumcision outweigh the risks. Specific benefits include prevention of urinary tract infections, penile cancer, and transmission of some sexually transmitted infections, including HIV (American Academy of Pediatrics, 2017a). Thus, access to the procedure is justified for families who choose it. The Task Force stopped short of recommending circumcision for *all* newborns.

Surgical Technique

Circumcision is performed only in a healthy neonate. Other contraindications include any genital abnormalities such as hypospadias and a family history of a bleeding disorder, unless excluded in the newborn.

The Task Force (2012) recommends procedural analgesia. Various pain relief techniques include lidocaine-prilocaine topical cream, local analgesia infiltration, dorsal penile nerve block, or ring block. The dorsal penile nerve block or the ring block is superior to topical analgesia. The use of a pacifier dipped in sucrose is a useful adjunct to these methods (Rossi 2021).

After appropriate penile cleansing, the ring block places a wheal of 1-percent lidocaine at the base of the penis and then advances the needle in a 180-degree arc around the base of the penis. The needle is advanced first to one side and then to the other to achieve a circumferential ring of analgesia. The maximum dose of lidocaine is 1.0 mL. *No vasoactive compounds such as epinephrine should ever be added to a local analgesic agent for circumcision.*

The most commonly used instruments are shown in Figure 32-5 and are Gomco and Mogen clamps and the Plastibell device. Compared with the Gomco procedure, Kaufman and colleagues (2002) reported that the Mogen technique required less time to perform and was associated with less apparent discomfort for the newborn. Regardless of the method used, the goal is to remove enough shaft skin and inner preputial epithelium so that the glans is exposed sufficiently to prevent phimosis. Suitable technique ensures that: (1) the amount of external skin to be removed must be accurately estimated, (2) the preputial orifice must be dilated to visualize the glans and ensure that it is normal, (3) the inner preputial epithelium must be freed from the glans epithelium, and (4) the circumcision device must be left in place long enough to produce hemostasis before excising the prepuce (Omole, 2020).

The risks for bleeding, infection, and hematoma formation are low. Unusual complications include distal glans amputation, acquisition of HIV infection or other sexually transmitted infection, meatal stenosis, penile denudation, penile destruction with electrosurgical coagulation, subsequent epidermal inclusion cyst and urethrocutaneous fistula, and ischemia following the inappropriate use of lidocaine with epinephrine (El Bcheraoui, 2014; Pippi-Salle, 2013; Omole, 2020).

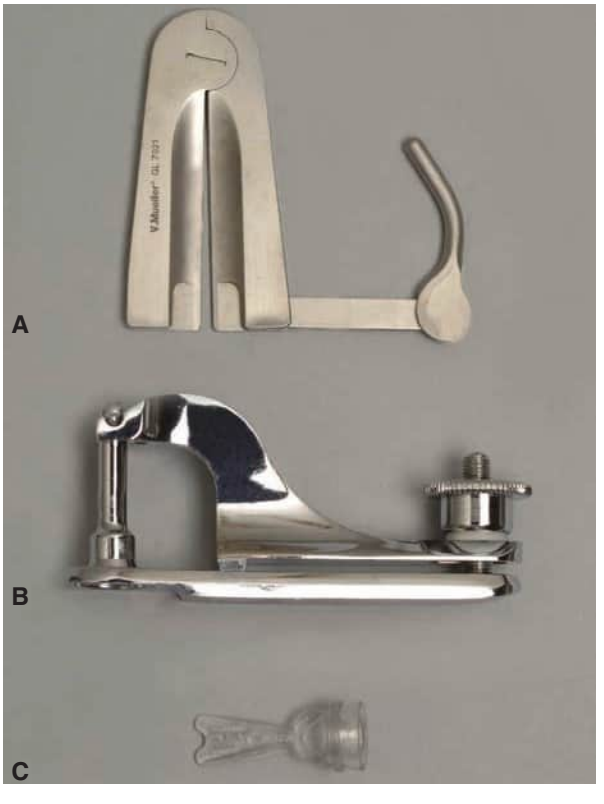


FIGURE 32-5 Three different tools used for circumcision. **A.** Mogen clamp. The arms of the clamp open to a 3-mm maximum width. **B.** Gomco clamp, assembled. **C.** Plastibell device.

Rooming In and Hospital Discharge

Hospital *rooming in* places newborns in their mothers' rooms instead of central nurseries. This practice attempts to make all phases of childbearing as natural as possible. It aims to foster early mother-child relationships and establish effective breast feeding practices. By 24 hours, the mother is generally fully ambulatory. Thereafter, she can usually provide routine care for herself and her newborn.

Traditionally, the newborn is discharged with its mother, and in most cases, maternal stay has determined that of the neonate. From 1970 to the mid-1990s, average maternal postpartum length of stay declined steadily, and many mothers were discharged before 48 hours. The World Health Organization (2014) cites a minimal stay of only 24 hours. Although it is clear that most newborns can be safely discharged within 48 hours, this is not uniformly true. When Belgium recently reduced postpartum stays by 1 day, rates of neonatal readmission for jaundice and dehydration increased (Plusquin, 2020). Using Washington state data, Malkin and coworkers (2000) found that the 28-day mortality rate was increased fourfold in newborns discharged within 30 hours of birth, and the 1-year mortality rate grew twofold. Safe discharge for late-preterm newborns has special concerns (Whyte, 2012).

Because of the increased scrutiny regarding short hospital stays, federal legislation—*The Newborns' and Mothers' Health Protection Act of 1996*—was enacted to prohibit insurers from restricting hospital stays for mothers and newborns to less than 2 days for vaginal delivery or 4 days for cesarean delivery. In an analysis of more than 662,000 births in California, Datar and Sood (2006) found that readmission rates declined by 9, 12, and 20 percent, respectively, at 1, 2, and 3 years after the legislation was implemented.

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CHAPTER 33

Complications of the Term Newborn

Term newborns are susceptible to various illnesses and injuries. In many instances, clinical manifestations of these disorders are extensions of pathological effects already incurred by the fetus. A common example is the newborn who is depressed and acidotic because of intrapartum septicemia. Susceptibility varies depending upon gestational age, and those more common in term newborns are considered here. Those more frequent in preterm neonates are discussed in Chapter 34. Specific disorders that are the direct consequence of maternal diseases are discussed in pertinent chapters.

RESPIRATORY DISTRESS

At the time of delivery, the newborn must convert rapidly to air breathing as described in Chapter 32 (p. 586). With inspiration, alveoli expand, lung fluid is cleared, and surfactant prevents alveolar collapse. Interference with these functions can create respiratory insufficiency. The neonate demonstrates hypoxemia and compensatory tachypnea, nasal flaring, chest wall retractions, and grunting. In preterm neonates, this is often caused by lung immaturity and insufficient surfactant—*respiratory distress syndrome (RDS)*, which is discussed in Chapter 34 (p. 615).

As fetuses approach term, surfactant deficiency as a cause of respiratory distress diminishes. The leading causes in term newborns are transient tachypnea of the newborn (TTN), meconium aspiration syndrome, pneumonia, and pneumothorax. Less common etiologies are RDS, persistent pulmonary hypertension, acid/base disturbances, central nervous system (CNS) insults, and congenital chest, respiratory tract, CNS, or cardiac anomalies (Alhassen, 2021).

Following birth, successful neonatal transition to air breathing may be delayed. With longer delays, evaluations to identify the cause of respiratory distress are warranted. The initial neonatal evaluation includes chest radiographs. Complete blood count or C-reactive protein levels and blood cultures are obtained to identify infection. Arterial blood gas assessments can define respiratory status and direct oxygenation care.

In general, treatment of respiratory distress is supportive with oxygen therapy provided as needed. Depending on the etiology and severity, continuous positive airway pressure (CPAP) or mechanical ventilation may be needed. Nutritional intake may be oral, gavage, or intravenous depending on the degree of neonatal tachypnea. High respiratory rates can limit effective breastfeeding and raise aspiration risk.

Transient Tachypnea of the Newborn

TTN is benign, self-limited, and stems from slow clearance of fetal lung fluid after birth. Neonates of any gestational age can be affected. However, delivery before 39 weeks' gestation raises risk, and rates vary inversely with gestational age. Other risk factors are cesarean delivery without labor, male gender, perinatal asphyxia, and large- or small-for-gestational-age birthweight. Maternal gestational diabetes or asthma are others.

TTN is a diagnosis of exclusion. Thus, the evaluation outlined in the last section excludes pathological sources.

Treatment is supportive with oxygen therapy as needed. Most TTN cases resolve within 48 hours.

Respiratory Distress Syndrome

This condition stems from surfactant deficiency and has a relatively low incidence at term (Berthelot-Ricou, 2012). Risks include male gender, white race, and maternal diabetes (Anadkat, 2012; Li, 2019). Less frequently, rare mutations in genes that code for surfactant protein synthesis may contribute. Four are *surfactant protein B*, *surfactant protein C*, *adenosine triphosphate (ATP)-binding cassette subfamily A member 3 (ABCA3)*, and *thyroid transcription factor 1* genes (Liszewski, 2017). Regardless of etiology, when surfactant secretion is diminished, the pulmonary pathophysiology, clinical course, and management are similar to that for preterm infants. Treatment includes CPAP or mechanical ventilation and potentially surfactant replacement either through an endotracheal tube or by less invasive surfactant techniques (Chap. 34, p. 616). Bacterial pneumonia, especially related to group B *Streptococcus* in a newborn is often clinically and radiographically indistinguishable from RDS. Thus, empirical antibiotics are often added to respiratory management. The prognosis in term newborns with RDS largely depends on the cause, severity, and response to treatment.

Antenatal maternal corticosteroid treatment is employed for threatened preterm birth and described in Chapter 45 (p. 802). In late-preterm fetuses 34 to 37 weeks' gestation, this therapy also enhances surfactant synthesis (Gyamfi-Bannerman, 2016). At Parkland Hospital, corticosteroids are not given in the late-preterm period for this indication. Neonatal hypoglycemia is a concern with such treatment, and long-term effects are unknown. However, data indicate that hypoglycemia, if promptly treated, creates no adverse sequelae (McKinlay, 2015).

Meconium Aspiration Syndrome

The physiology of meconium passage and amnionic fluid contamination is considered in Chapter 24 (p. 458). In some instances, inhalation of meconium-stained fluid at or near delivery causes acute airway obstruction, chemical pneumonitis, surfactant dysfunction or inactivation, and pulmonary hypertension (Vain, 2017). If severe, hypoxemia may lead to neonatal death or long-term neurological sequelae in survivors.

Meconium-stained fluid in labor is common. Fortunately, severe aspiration leading to overt respiratory failure is much less frequent. In one study, the incidence of severe disease was 4 cases per 1000 newborn hospital discharges, and rates rise progressively from 37 to 43 weeks' gestation (Thornton, 2019). Mortality rates depend on severity.

Fetal morbidity is more often associated with thicker meconium content. Presumably, in most cases, amnionic fluid is ample to dilute the meconium to permit prompt clearance by normal fetal physiological mechanisms. Meconium aspiration syndrome still occasionally develops with light staining. Many newborns are affected after a normal labor and uncomplicated delivery. However, some associated obstetrical factors include postterm pregnancy and fetal-growth restriction. These fetuses are at highest risk because diminished amnionic fluid and labor with cord compression or uteroplacental insufficiency are often comorbid. These can enhance the likelihood of meconium passage that is thick and undiluted (Leveno, 1984).

Prevention

Previously, aspiration was thought to be stimulated by fetal hypoxic episodes, and fetal heart rate tracing abnormalities were used to identify fetuses at greatest risk during labor. Unfortunately, this was found to be an unreliable predictor (Dooley, 1985). As another potential prevention, oropharyngeal suctioning at the perineum was standard care for a time. However, this was abandoned when evidence failed to support a reduction in meconium aspiration syndrome incidence or severity (American College of Obstetricians and Gynecologists, 2021b; Vain, 2004). From other studies, endotracheal intubation and suctioning for both vigorous and nonvigorous meconium-stained neonates provides no benefit and is no longer recommended as a routine (Trevisanuto, 2020; Wiswell, 2000; Wyckoff, 2020). Because neonates born through meconium may need effective positive pressure ventilation for stabilization, it is still critical that pediatric providers attend such deliveries (Aziz, 2020).

Intrapartum amnioinfusion has been used successfully in laboring women with diminished amnionic fluid volume to help resolve frequent variable fetal heart rate decelerations (Chap. 24, p. 459). Earlier, it was also studied as a preventive measure in labors complicated by meconium staining. This practice fails to lower rates of meconium aspiration syndrome in settings with standard peripartum surveillance (Hofmeyr, 2014). A trial was conducted with almost 2000 women at 36 weeks' gestation or later and in whom labor was complicated by thick meconium (Fraser, 2005). The perinatal death rate with and without amnioinfusion was 0.05 percent in both groups. Rates of moderate or severe meconium aspiration also were not significantly different in those with (4.4 percent) and without (3.1 percent) amnioinfusion. Last, cesarean delivery rates were similar—32 versus 29 percent, respectively.

Treatment

Ventilatory support including CPAP, intubation, and mechanical ventilation is carried out as needed (Pandita, 2018). Because some aspects of meconium aspiration syndrome are caused by surfactant deficiency, replacement therapy is beneficial (Natarajan, 2016a). In a review of randomized trials, authors found that surfactant replacement may reduce the need for extracorporeal membrane oxygenation (ECMO) but did not lower the mortality rate (El Shahed, 2014). Inhaled corticosteroids may partially ameliorate the severity of meconium aspiration syndrome, but neither inhaled or systemic corticosteroids consistently improve critical outcomes (Garg, 2016; Yeung, 2021). Newborns with meconium aspiration syndrome and pulmonary hypertension are often treated with inhaled nitric oxide, which reduces rates of death and need for ECMO (Vain, 2017). ECMO therapy is reserved for neonates who remain poorly oxygenated despite maximal ventilatory assistance (Hirakawa, 2017). The proportion that requires ECMO treatment varies. From the California Perinatal Quality Care Collaborative, 0.35 percent of more than 5100 cases of meconium aspiration syndrome required

ECMO treatment. The associated mortality rate was 5.3 percent (Kalra, 2020).

NEONATAL ENCEPHALOPATHY AND CEREBRAL PALSY

Few events evoke more apprehension in parents and obstetricians than the specter of "brain injury," which immediately prompts concerns for disabling cerebral palsy and intellectual disability. Although most brain disorders or injuries are less profound, history has helped to perpetuate the more dismal outlook. In his first edition of this textbook, Williams (1903) limited discussions of brain injury to those sustained from birth trauma. When later editions introduced the concept that *asphyxia neonatorum* was another cause of cerebral palsy, this too was linked to traumatic birth. Even as brain damage caused by traumatic delivery became uncommon during the ensuing decades, the belief—albeit erroneous—was that intrapartum events caused most neurological disability. This was a major reason for the escalating cesarean delivery rate beginning in the 1970s. Unfortunately, because the genesis of cerebral palsy occurs long before labor in most cases, cesarean delivery did little to mitigate cerebral palsy risks. Cerebral palsy rates have remained the same for 50 years despite a sixfold rise in cesarean birth rates (MacLennan, 2015).

These realizations stimulated scientific investigations to determine the etiopathogenesis of fetal brain disorders, including those leading to cerebral palsy. Seminal observations, including those of Nelson and Ellenberg (1984, 1985, 1986a), are discussed subsequently. These investigators are appropriately credited with proving that these neurological disorders are due to complex multifactorial processes caused by a combination of genetic, physiological, environmental, and obstetrical factors. Importantly, these studies showed that few neurological disorders are associated with peripartum events. However, continuing international interest was garnered to codify the potential role of intrapartum events. In 2000, a task force of the American College of Obstetricians and Gynecologists was appointed to study neonatal encephalopathy and cerebral palsy. The multispecialty coalition reviewed data and provided criteria to define various neonatal brain disorders. Their findings were promulgated by the American Academy of Pediatrics and American College of Obstetricians and Gynecologists (2003).

Ten years later, a second task force updated the findings (American College of Obstetricians and Gynecologists, 2014a). The 2014 Task Force findings are more circumspect in contrast to the earlier ones. Specifically, more limitations are cited in identifying cause(s) of peripartum *hypoxic-ischemic encephalopathy (HIE)* compared with other etiologies of neonatal encephalopathy. The 2014 Task Force recommends multidimensional assessment of each affected infant. They add the caveat that no one strategy is infallible, and thus no single strategy will achieve 100-percent certainty in attributing a cause to neonatal encephalopathy.

Neonatal Encephalopathy

The 2014 Task Force defined neonatal encephalopathy as a syndrome of neurological dysfunction identified in the earliest days of life in neonates born at ≥35 weeks' gestation. It is manifested by seizures or subnormal levels of consciousness and is often accompanied by difficulty with initiating and maintaining respiration and by depressed tone and reflexes. The incidence of encephalopathy has been cited to be 1 to 2 cases per 1000 term liveborn neonates, and it is much more frequent in preterm newborns (Ensing, 2015; Laptook, 2016; Novak, 2018; Ravichandran, 2020). The 2014 Task Force concluded that many etiologies may lead to encephalopathy and cerebral palsy, however, it focused on HIE and causes that were thought to be incurred intrapartum. To identify affected infants, a thorough evaluation is necessary and includes maternal history, obstetrical antecedents, intrapartum factors, placental pathology, and newborn course. These are complemented by laboratory and neuroimaging findings.

Three clinically defined levels categorize encephalopathy. *Mild encephalopathy* is characterized by hyperalertness, irritability, jitteriness, and hypertonia and hypotonia. *Moderate encephalopathy* shows lethargy, abnormal tone, and occasional seizures. *Severe encephalopathy* is manifest by coma, multiple seizures, and recurrent apnea.

The 2014 Task Force also concluded that of the several forms of cerebral palsy, only the *spastic quadriplegic* type can result from acute peripartum ischemia. Other forms—*hemiparetic* or *hemiplegic cerebral palsy, spastic diplegia,* and *ataxia*—are unlikely to result from an intrapartum event. Purely dyskinetic or ataxic cerebral palsy, especially when accompanied by a learning disorder, usually has a genetic origin (Nelson, 2015).

Criteria for Hypoxic-Ischemic Encephalopathy

The 2014 Task Force radically revised the 2003 criteria used to define an acute peripartum event that is consistent with HIE and neonatal encephalopathy. These are outlined in Table 33-1 and are considered with the following caveats (American College of Obstetricians and Gynecologists, 2014b).

First, *Apgar scores* that are low at 5 and 10 minutes are associated with greater risk for neurological impairment. Low scores stem from many causes, and most of these infants will not develop cerebral palsy. With a 5-minute Apgar ≥7, it is unlikely that peripartum HIE caused cerebral palsy.

Acid-base study results define a second HIE criterion. Low pH and high base deficit levels raise the likelihood that neonatal encephalopathy was caused by HIE. Decreasing pH levels form a continuum of increasing risk, but most acidemic neonates will be neurologically normal (Lee, 2020b). A cord artery pH ≥7.2 is very unlikely to be associated with HIE.

Magnetic resonance (MR) imaging or *MR spectroscopy (MRS)* is the best modality with which to visualize findings consistent with HIE. The 2014 Task Force concluded that cranial sonography and computed tomography (CT) lack sensitivity in the term newborn. Normal imaging findings after the first 24 hours of life, however, effectively exclude a hypoxic-ischemic cause of encephalopathy. MR imaging between 24 and 96 hours may be more sensitive for the timing of peripartum cerebral injury, and MR imaging at 7 to 21 days following birth is the best technique to delineate the full extent of cerebral injury.

Last, *multisystem involvement* of injury is consistent with HIE. These include renal, gastrointestinal, hepatic, or cardiac

TABLE 33-1. Findings Consistent with an Acute Peripartum or Intrapartum Event Leading to Hypoxic-Ischemic Encephalopathy

Neonatal Findings
Apgar score: <5 at 5 and 10 minutes
Umbilical arterial acidemia: pH <7.0 and/or base deficit ≥12 mmol/L
Neuroimaging evidence of acute brain injury: MR imaging or MRS consistent with HIE
Multisystem involvement consistent with HIE
Type and Timing of Contributing Factors
Sentinel hypoxic or ischemic event occurring immediately before or during delivery
Fetal heart rate monitor patterns consistent with an acute peripartum or intrapartum event

HIE = hypoxic-ischemic encephalopathy; MR = magnetic resonance; MRS = magnetic resonance spectroscopy.

injury; hematological abnormalities; or combinations of these. The severity of neurological injury does not necessarily correlate with injuries to these other systems.

The 2014 Task Force also found that certain contributing factors may be consistent with an acute peripartum event. Of these, *sentinel events* are considered adverse obstetrical events that may lead to catastrophic clinical outcomes. Examples include ruptured uterus, severe placental abruption, cord prolapse, and amnionic fluid embolism. Martinez-Biarge and associates (2012) studied almost 58,000 deliveries and identified 192 cases with one of these sentinel events. Of these 192 fetus/newborns, 6 percent died intrapartum or in the early neonatal period, and 10 percent developed neonatal encephalopathy. Other risk factors for neonatal acidosis include prior or emergent cesarean delivery, maternal age ≥35 years, maternal obesity, thick meconium, chorioamnionitis, and general anesthesia (Johansson, 2018; Johnson, 2014; Nelson, 2014).

Differentiating an *abnormal fetal heart rate (FHR) tracing* on presentation versus one that develops subsequently also was emphasized by the 2014 Task Force. A category 1 or 2 FHR tracing associated with Apgar scores ≥7 at 5 minutes, normal cord gases (±1 SD), or both are not consistent with an acute HIE event (Graham, 2014). An FHR pattern at the time of presentation with persistently minimal or absent variability and lacking accelerations, with duration ≥60 minutes, and even without decelerations is suggestive of an already compromised fetus (Chap. 24, p. 450). The 2014 Task Force further recommended that with these findings present, if fetal well-being cannot be established, the woman should be evaluated for the method and timing of delivery.

Prevention

In term newborns, one of the best-studied interventions for neonatal HIE is postnatally induced hypothermia. Cooling initiated within the first 6 hours of life to a level of 33.5°C for 72 hours reduces death and moderate to severe neurological disability in term newborns (Jacobs, 2013; Natarajan, 2016b). One metaanalysis of more than 1500 neonates concluded that hypothermia improves survival rates and neurodevelopment by 24 months of age (Jacobs, 2013). This neuroprotection extends to childhood (Azzopardi, 2014; Guillet, 2012; Shankaran, 2012). MR imaging studies have demonstrated a slowing of diffusional abnormalities and fewer infarctions with hypothermia (Bednarek, 2012; Natarajan, 2016b). Longer or deeper cooling does not offer additional protection compared with standard cooling (Shankaran, 2017).

Importantly, hospitals should develop plans for timely transfer of encephalopathic newborns to a cooling center for evaluation and possible treatment. A trial of "late" hypothermia, with cooling initiated after 6 hours of life, showed some benefit. However, brain protection was not as robust as with cooling initiated in the first 6 hours (Laptook, 2017).

Since therapeutic hypothermia is not completely protective, adjuvant therapies are being explored. In preclinical HIE models, erythropoietin has both early and late beneficial effects. These include antiapoptosis and antiinflammatory effects and greater neurogenesis, oligodendrogenesis, and angiogenesis (McAdams, 2016). One metaanalysis of small clinical trials evaluating this therapy for neuroprophylaxis reports some reductions in cognitive impairment and cerebral palsy rates (Razak, 2019). A large national trial has completed enrollment and is in the follow-up phase (Juul, 2018). Other adjuvant therapies under investigation are allopurinol, xenon, melatonin, and stem cell therapies (McAdams, 2016).

■ Cerebral Palsy

This term refers to a group of nonprogressive disorders of movement or posture caused by abnormal development or damage to brain centers for motor control. Cerebral palsy is further classified by the type of neurological dysfunction—spastic, dyskinetic, or ataxic—and by the number and distribution of limbs involved—quadriplegia, diplegia, hemiplegia, or monoplegia. Together, the major types are *spastic quadriplegia*—the most common—which has a strong association with mental retardation and seizure disorders; *diplegia,* which is common in preterm or low-birthweight neonates; *hemiplegia; choreoathetoid types;* and *mixed varieties.* Although epilepsy and intellectual disability frequently accompany cerebral palsy, these two disorders seldom are associated with perinatal asphyxia in the absence of cerebral palsy.

Incidence and Epidemiological Correlates

According to the Centers for Disease Control and Prevention (2021), the prevalence of cerebral palsy in the United States

approximates 3 cases in 1000 children. *It is crucial to emphasize that this rate is derived from all children—including those born preterm.* Because of the remarkably greater survival rates of the latter currently, and despite the elevated cesarean delivery rate, the overall rate of cerebral palsy has remained essentially unchanged (Fig. 33-1). For example, neonates born at 23 to 27 weeks' gestation in a Swedish birth cohort had a cerebral palsy incidence of 105 cases per 1000 infants alive at 1 year (Hafström, 2018). Similar findings have been reported for Australian births (Smithers-Sheedy, 2016). In absolute numbers, term newborns constitute half of cerebral palsy cases because preterm births are proportionately far fewer. It is again emphasized that most studies of cerebral palsy rates have not made distinctions between term and preterm neonates.

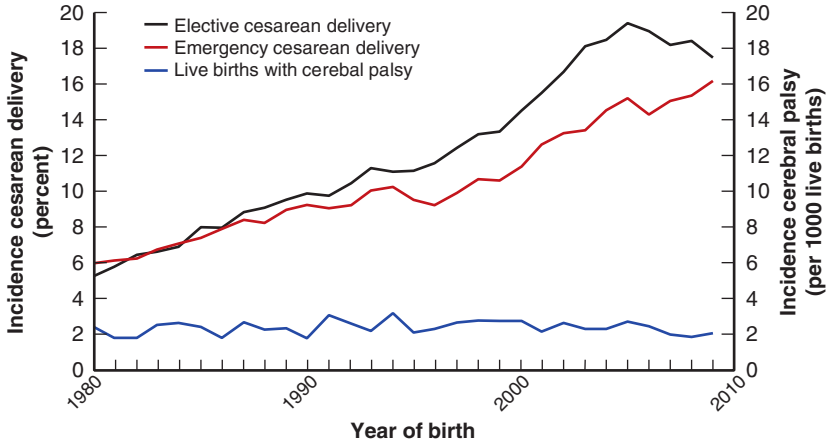

FIGURE 33-1 Elective and emergency cesarean deliveries and live births with cerebral palsy. (Reproduced with permission from Nelson KB, Blair E: Prenatal factors in singletons with cerebral palsy born at or near term, N Engl J Med. 2015 Sep 3;373(10):946–953.)

As noted earlier, Nelson and Ellenberg (1984, 1985, 1986a) made many fundamental observations concerning cerebral palsy. Their initial studies emanated from data from the Collaborative Perinatal Project. This included children from almost 54,000 pregnancies who were followed until age 7. They found that the most frequently associated risk factors for cerebral palsy were: (1) evidence of genetic abnormalities such as maternal mental retardation or fetal congenital malformations; (2) birthweight <2000 g; (3) birth before 32 weeks; and (4) perinatal infection. They also found that obstetrical complications were not strongly predictive, and only a fifth of affected children had markers of perinatal asphyxia. *For the first time, solid evidence supported that the cause of most cases of cerebral palsy was unknown, and importantly, only a small proportion stemmed from neonatal HIE.* Equally importantly, no foreseeable single intervention would likely prevent a large proportion of cases.

Numerous studies have since confirmed many of these findings and have identified an imposing list of other risk factors (Table 33-2). As expected, preterm birth continues to be the single most important risk (Nelson, 2015). Small-for-gestational-age neonates also are at higher risk. In one study, cerebral palsy was due to antepartum factors in more than 90 percent of growth-restricted newborns (Stoknes, 2012).

Many other placental and neonatal risk factors are associated with neurodevelopmental abnormalities (MacLennan, 2015). Some placental factors are discussed further in Chapter 6 (p. 111). One example is the substantively greater risk from chorioamnionitis (Shevell, 2014; Shi, 2017). Of neonatal causes, one is arterial ischemic stroke, which may be associated with inherited fetal thrombophilias (Harteman, 2013; Wanenaar, 2018). Additionally, newborns with isolated congenital heart lesions have an elevated risk for microcephaly, possibly due to chronic fetal hypoxemia (Barbu, 2009). Other miscellaneous etiologies of cerebral palsy include fetal anemia, twin-twin transfusion syndrome, intrauterine transfusions, and fetal alcohol syndrome (DeJong, 2012; Nelson, 2015; O'Leary, 2012; Rossi, 2011; Schou, 2019).

Apart from these causes, intrapartum hypoxemia was linked to only a few cases of cerebral palsy by the National Collaborative Perinatal Project. The contribution of HIE to subsequent neurological disorders was discussed earlier. The 2003 Task Force applied these criteria to more contemporaneous outcomes and determined that only 1.6 cases of cerebral palsy per 10,000 deliveries are attributable solely to intrapartum hypoxia.

TABLE 33-2. Perinatal Risk Factors Reported to Be Increased in Children with Cerebral Palsy

Risk Factors	Risk Ratio	95% CI
Hydramnios	6.9	1.0–49.3
Placental abruption	7.6	2.7–21.1
Interval between pregnancies <3 mo or >3 yr	3.7	1.0–4.4
Spontaneous preterm labor	3.4	1.7–6.7
Preterm delivery at 23–27 weeks	78.9	56.5–110
Breech or face presentation, transverse lie	3.8	1.6–9.1
Severe birth defect	5.6	8.1–30.0
Nonsevere birth defect	6.1	3.1–11.8
Time to cry >5 minutes	9.0	4.3–18.8
Obesity	1.2–2	1.1–2.8
Low placental weight	3.6	1.5–8.4
Placental infarction	2.5	1.2–5.3
Chorioamnionitis		
Clinical	2.4	1.5–3.8
Histological	1.8	1.2–2.9
Others[a]	—	—

[a]Includes respiratory distress syndrome, meconium aspiration, emergent cesarean or operative vaginal delivery, hypoglycemia, gestational hypertension, hypotension, advanced maternal age, genetic factors, twins, thrombotic states, nighttime delivery, seizures, fetal-growth restriction, male gender, and nulliparity.
CI = confidence interval.
From Ahlin, 2013; Blair, 2011; McIntyre, 2013; Moster, 2008; Nelson, 2015; O'Callaghan, 2011; Shatrov, 2010; Takenouchi, 2012; Torfs, 1990; Villamor, 2017; Wu, 2012.

This finding is supported by a study of nearly 1000 infants in which fetal-growth restriction and birth defects recognized by age 6 years were more substantial contributors to cerebral palsy and neonatal death than potentially asphyxial birth events and inflammation (McIntyre, 2013).

Intrapartum Fetal Heart Rate Monitoring

Despite persistent attempts to validate continuous intrapartum electronic FHR monitoring as effective to prevent adverse perinatal outcomes, evidence does not support its ability to predict or reduce cerebral palsy risk (Alfirevic, 2017). Moreover, no specific FHR patterns is predictive of cerebral palsy, and no relationship has been found between the clinician's response to abnormal patterns and neurological outcome. Efforts using computer-assisted analysis of FHR tracings have not enhanced predictions (Alfirevic, 2017; INFANT Collaborative Group, 2017). Indeed, an abnormal heart rate pattern in fetuses that ultimately develop cerebral palsy may reflect a preexisting neurological abnormality (Phelan, 1994). Because of these studies, the American College of Obstetricians and Gynecologists (2019a; 2021a) concludes that electronic FHR monitoring does not reduce the incidence of long-term neurological impairment.

Apgar Scores

In general, 1- and 5-minute Apgar scores are poor predictors of long-term neurological impairment (American College of Obstetricians and Gynecologists, 2021c). However, if the 5-minute Apgar score is ≤3, neonatal death or the risk of neurological sequelae rises substantially (Chen, 2020; Nelson, 1984). In a Swedish study, 5 percent of such children subsequently required special schooling (Stuart, 2011). In a Scottish study, the incidence of these low Apgar scores was 0.3 percent in more than 750,000 children who were born at term and were in national school census records. Low Apgar score was strongly associated in a dose-dependent manner with the need for additional educational support in later life, after adjusting for confounding factors. The strongest association was for the support of physical and motor impairments and was followed by visual, hearing, and cognitive impairments (Tweed, 2016).

Persistence past 5 minutes of these extremely low scores correlates strongly with a higher risk for neurological morbidity and death (Foglia, 2020). This of course is not absolute, and the 2003 Task Force cited a 10-percent risk for cerebral palsy for neonates with 10-minute scores of 0 to 3. For 15-minute scores ≤2, the cited mortality rate was 53 percent, and cerebral palsy rate was 36 percent. For 20-minute scores ≤2, the mortality rate was 60 percent, and cerebral palsy rate was 57 percent. Outcomes from a Norwegian population study of neonates who were born from low-risk pregnancies and who had low 5-minute Apgar scores are shown in Table 33-3 (Moster, 2001).

Umbilical Cord Blood Gas Studies

Objective evidence of metabolic acidosis, that is, cord arterial blood pH <7.0 and base deficit ≥12 mmol/L, is a risk factor for encephalopathy and for cerebral palsy (p. 601). The risk accrues as acidosis worsens. From one review of 51 studies, low pH in arterial umbilical cord blood correlates with greater risk for neonatal encephalopathy and cerebral palsy (Malin, 2010). When used alone, however, these determinations are not accurate in predicting long-term neurological sequelae (Yeh, 2012).

TABLE 33-3. Comparison of Mortality and Morbidity in Norwegian Infants Weighing >2500 g According to 5-Minute Apgar Scores

Outcome	Apgar 0–3 (%)	Apgar 7–10 (%)	Relative Risk (95% CI)
Number	292	233, 500	
Mortality rates			
Neonatal	16.5	0.05	386 (270–552)
Infant	19.2	0.3	76 (56–103)
1–8 yr	3	0.2	18 (8–39)
Morbidity rates			
Cerebral palsy	6.8	0.09	81 (48–128)
Mental retardation	1.3	0.1	9 (3–29)
Other neurological	4.2	0.5	9 (5–17)
Non-neurological	3.4	2.0	2 (0.8–5.5)

CI = confidence interval.

Data from several studies corroborate that a pH <7.0 is the threshold for clinically significant acidemia (Gilstrap, 1989; Goldaber, 1991). The likelihood of neonatal death grows as the cord artery pH falls to ≤7.0. Casey and colleagues (2001) reported that when the pH was ≤6.8, the neonatal mortality rate rose 1400-fold. When the cord pH was ≤7.0 *and* the 5-minute Apgar score was 0 to 3, the risk of neonatal death rose 3200-fold.

In a study from Oxford, the rate of adverse neurological outcomes was 0.36 percent with pH <7.1 and was 3 percent with pH <7.0 (Yeh, 2012). A systematic review that includes 12 studies suggests that cord blood lactate levels also help predict neonatal outcomes (Allanson, 2017).

Nucleated Red Blood Cells and Lymphocytes

Both immature red cells and lymphocytes enter the circulation of term newborns in response to hypoxia or hemorrhage. During the past two decades, quantification of these cells has been proposed as a measure of hypoxia, but not all studies support this premise (Boskabadi, 2017; Silva, 2006; Walsh, 2011, 2013).

Neuroimaging Studies in Encephalopathy and Cerebral Palsy

Various neuroimaging techniques have provided important insight into the etiology and evolution of perinatal HIE and later cerebral palsy. Findings vary by fetal age, and the preterm neonatal brain responds differently to an ischemic episode than that of a term newborn. Other factors include insult severity and duration and restoration of cerebrovascular hypoperfusion. *Thus, precise timing of an injury with neuroimaging studies is not a realistic goal.* Moreover, the grade of neonatal encephalopathy, that is, mild, moderate, or severe, does not correlate with MR imaging findings (Walsh, 2017).

Neuroimaging in the Neonatal Period

The 2014 Task Force concluded that for term newborns, imaging studies are helpful in timing an injury, but they provide only a time window that is imprecise. The 2014 Task Force reported that these head imaging techniques provide the following information:

1. Neonatal sonography findings are generally normal on the day of birth. With injury, the thalami and basal ganglia become increasingly echogenic beginning at approximately 24 hours. This progresses over 2 to 3 days and persists for 5 to 7 days.
2. CT images are usually normal the first day in term newborns. With injury, the thalami or basal ganglia show decreased density beginning at approximately 24 hours, and this persists for 5 to 7 days.
3. MR imaging will detect some abnormalities on the first day. Within 24 hours, MR imaging may show restricted water diffusion that peaks at approximately 5 days and disappears within 2 weeks. T1- and T2-weighted images display variable abnormalities, which have an onset from less than 24 hours to several days. In a study of 175 term neonates with acute encephalopathy, MR imaging that showed basal ganglia lesions accurately predicted motor impairment at 2 years of age (Martinez-Biarge, 2012).

Neuroimaging in Older Children with Cerebral Palsy

Imaging studies performed in children diagnosed with cerebral palsy frequently show abnormal findings. Wu and associates (2006) used CT or MR imaging to study 273 children who were born after 36 weeks' gestation and who were later diagnosed with cerebral palsy. Although a third of these imaging studies were normal, focal arterial infarction was seen in 22 percent; brain malformations in 14 percent; and periventricular white-matter injuries in 12 percent. In another study of 351 children with cerebral palsy, of whom approximately half were born near term, MR imaging findings were abnormal in 88 percent (Bax, 2006). One MR imaging study found pathological findings in 84 percent of children with spastic quadriplegia (Robinson, 2008). Remember, the 2014 Task Force concluded that this neurological lesion correlated with neonatal encephalopathy.

Imaging techniques in older children also help define the timing of fetal or perinatal cerebral injury. Due to concerns regarding the radiation exposure of CT scans, MR imaging is more often used. Wiklund and coworkers (1991a,b) studied 83 children between ages 5 and 16 years who were born at term and who developed hemiplegic cerebral palsy. Nearly 75 percent had abnormal CT findings, and these investigators concluded that more than half had CT changes that suggested a *prenatal injury.* Approximately 20 percent were attributed to a *perinatal injury.*

■ Intellectual Disability and Seizure Disorders

These both frequently accompany cerebral palsy. However, when either manifests alone, it is seldom caused by perinatal hypoxia (Nelson, 1984, 1986a, 2015). Severe mental disability has a prevalence of 3 cases per 1000 children, and its most frequent causes are chromosomal, gene mutation, and other congenital malformations. Last, preterm birth also is associated with these (Hientz, 2018).

The major predictors of seizure disorders are fetal malformations—cerebral and noncerebral; family history of seizures; and neonatal seizures (Nelson, 1986b; Pisani, 2015). Neonatal encephalopathy causes a small proportion of seizure disorders. Reports from the Neonatal Research Network and other studies conclude that increasing severity of encephalopathy correlates best with seizures (Glass, 2011; Kwon, 2011).

Autism Spectrum Disorders

According to the Centers for Disease Control and Prevention, the frequency of autism spectrum disorders is 15 cases per 1000 8-year-old children (Christensen, 2016). Although these may be associated with maternal metabolic conditions, none has been linked convincingly to peripartum events (Krakowiak, 2012).

NEONATAL ABSTINENCE SYNDROME

This is a drug-withdrawal syndrome that most commonly follows in-utero exposure to maternal opioids. It also can complicate exposure to alcohol or benzodiazepines. The syndrome shows hypertonia, autonomic instability, irritability, poor sucking reflex, and seizures (Finnegan, 1975). Its incidence has risen six- to sevenfold during the past decade, coincidental with growing opioid use. For example, 4 percent of all neonatal intensive care unit days in 2013 were attributed to care of these affected newborns (Tolia, 2015).

Care includes close observation, and pharmacotherapy is usually given. In addition to morphine and methadone, other treatment may include phenobarbital, benzodiazepines, and clonidine (Tolia, 2015). More recently, buprenorphine compared with morphine was reported to result in shorter lengths of treatment and hospital stays (Kraft, 2017; Lee, 2019). Consensus is lacking regarding the most effective regimen. The American College of Obstetricians and Gynecologists and the American Society of Addiction Medicine (2019c) have taken the lead in screening, intervention, and treatment of opioid use disorders in pregnant women (Chap. 64, p. 1150).

HEMATOLOGICAL DISORDERS

Obstetricians should be familiar with a few neonatal disorders of erythrocytes, platelets, and coagulation. Many of these manifest in the fetus and persist in the newborn.

■ Anemia

After 35 weeks' gestation, the mean cord hemoglobin concentration approximates 17 g/dL, and values below 14 g/dL are considered abnormal. In newborns, delayed umbilical cord clamping raises hemoglobin levels at birth and improves iron stores in the first several months. A review of nearly 9200 late-preterm and term deliveries found delayed cord clamping was associated with a mean neonatal hemoglobin rise of 1.2 g/dL at birth (Gomersall, 2021). However, rates of infant anemia at 6 months were similar in groups with or without delayed cord clamping. Moreover, this practice raises the incidence of hyperbilirubinemia that

requires phototherapy but does not prolong hospital stay. Discussed further in Chapter 27 (p. 500), the American College of Obstetricians and Gynecologists (2020) recommends a 30- to 60-second delay in cord clamping in all healthy newborns.

Significant neonatal anemia may predate or follow delivery. First, neonatal anemia may reflect an extension of antenatal fetal anemia. General etiological groups are immune-medicated red cell destruction, aneuploidy, hematology-related genetic defects, fetomaternal hemorrhage, fetal infection, and placental abnormalities such as chorioangioma or twin anastomotic defects.

Second, at delivery, acute anemia with hypovolemia can follow laceration of the placenta, fetal vessel, or umbilical cord. Intracranial or extracranial injury or trauma to fetal intraabdominal organs also can cause hemorrhage with acute anemia (Malec, 2020).

Polycythemia

Neonatal polycythemia can be associated with chronic or acute fetal hypoxia, twin anemia-polycythemia syndrome, maternal diabetes or hypertension, placental- and fetal-growth restriction, aneuploidy, and delayed cord clamping. When the hematocrit rises above 65, blood viscosity markedly increases. Routine neonatal screening is not recommended in newborns without symptoms (Remon, 2011). Frequent signs are hypotonia, a ruddy complexion (plethora), respiratory distress with cyanosis, jitteriness, or hypoglycemia. Because of the shorter life span of macrocytic fetal erythrocytes, hyperbilirubinemia commonly follows. Associated blood hyperviscosity can lead to end-organ damage and neurodevelopmental harm. Isovolemic partial exchange transfusion (PET) with saline can lower the hematocrit and improve symptoms, however, it is not neuroprotective and has associated complications (Dempsey, 2006). From limited data, PET is often reserved for neonates with acute symptoms or hypoglycemia (Hopewell, 2011).

Hyperbilirubinemia

Excessive serum bilirubin levels can be neurotoxic for newborns. In fetuses, hepatic maturation is incomplete, and some unconjugated bilirubin is cleared by placental transfer to be conjugated and excreted by the mother. After delivery, clearance relies on neonatal hepatic function, and thus varying degrees of neonatal hyperbilirubinemia arise. Even in the mature newborn, serum bilirubin levels usually increase for 3 to 4 days to reach up to 10 mg/dL. After this, concentrations usually fall rapidly. In approximately 15 percent of term newborns, bilirubin levels cause jaundice. Of risks, polycythemia, hemolysis such as from ABO incompatibility or glucose-6-phosphate dehydrogenase deficiency, and extravasation of blood such as from a cephalohematoma all raise bilirubin burden. Decreased bilirubin clearance is seen with prematurity.

With excessive serum bilirubin levels, toxicity has two forms. *Acute bilirubin encephalopathy* develops in the first days of life and may cause hypotonia, poor feeding, lethargy, and abnormal auditory-evoked responses. Immediate recognition and treatment will usually mitigate progressive neurotoxicity.

The chronic form is termed *kernicterus*. With this, profound neuronal degeneration follows bilirubin deposition and staining of the basal ganglia and hippocampus. Survivors have spasticity, muscular incoordination, and varying degrees of mental deficiencies. Continuing hemolysis is a risk factor for kernicterus (El Houchi, 2017; Vandborg, 2012).

Initial prevention emphasizes effective breastfeeding to avoid neonatal dehydration. Surveillance for jaundiced skin is recommended at the same time other newborn vital signs are obtained. Moreover, prior to hospital discharge, universal screening of total serum bilirubin assessment from blood or more commonly by transcutaneous bilirubinometry is done (Maisels, 2009). The latter is a handheld meter that directs light into the skin and measures the intensity of specific returned wavelengths.

Once diagnosed, various forms of phototherapy are used to treat neonatal hyperbilirubinemia. These "bili-lights" emit a spectrum of 460 to 490 nm, which augments bilirubin oxidation to enhance its renal clearance and lower serum levels. Sunlight filtered to remove ultraviolet light can be used in resource-poor countries (Slusher, 2015). Light that penetrates the skin also raises peripheral blood flow, which further enhances photo-oxidation.

For term newborns, the American Academy of Pediatrics and the American College of Obstetricians and Gynecologists (2017) stress early detection and prompt phototherapy to prevent bilirubin encephalopathy. Despite these measures, bilirubin encephalopathy persists, and this is somewhat related to early hospital discharges (Kuzniewicz, 2014). In the United States, hospitalizations for kernicterus in term newborns were 5 cases per 100,000 in 1988 (Burke, 2009). Since then, this rate has dropped to 0.4 to 2.7 cases per 100,000 births (Watchko, 2013). Legislation to minimize brief postpartum hospital stays may be contributory (Chap. 36, p. 645).

Vitamin K Deficiency Bleeding

Newborns are vitamin K deficient due to insufficient antenatal liver stores, limited synthesis in an initially sterile gut, and low vitamin K content in breast milk. *Vitamin K deficiency bleeding (VKDB)* describes spontaneous internal or external bleeding, and its onset is grouped as early, classic, or late onset. Most cases result from abnormally low levels of the vitamin K–dependent clotting factors. Early onset is within the first 24 hours, and one cause is maternal vitamin K deficiency. Classic hemorrhagic disease is usually apparent between days 2 and 7 of life in neonates not given vitamin K prophylaxis at delivery. Delayed hemorrhage may occur at 2 to 12 weeks in exclusively breastfed infants.

The American Academy of Pediatrics and the American College of Obstetricians and Gynecologists (2017) recommend routine prophylaxis with a single, intramuscular, 0.5- to 1-mg dose of vitamin K_1 (phytonadione). Oral administration is less effective, and maternal vitamin K administration results in very little transport to the fetus (Sankar, 2016). Evidence does not support initial links with vitamin K and childhood leukemia (Fear, 2003; Roman, 2002).

Hemorrhagic disease of the newborn includes VKDB but also bleeding from other etiologies. These include congenital clotting factor deficiency, disseminated intravascular coagulopathy, birth trauma, and thrombocytopenia.

Thrombocytopenia

Abnormally low platelet concentrations in term newborns are often categorized as *early onset*, within the first 72 hours, and *late onset* thereafter. In the term neonate, causes include immune disorders, infections, inherited platelet defects, or congenital syndromes (American College of Obstetricians and Gynecologists, 2019b; Cremer, 2016). Of immunologic sources, neonatal thrombocytopenia stemming from alloimmunization or from maternal idiopathic thrombocytopenic purpura are described in Chapter 18 (p. 359). Neonatal lupus syndrome can also show thrombocytopenia (Chap. 62, p. 1113). With all these, antiplatelet IgG transferred to the fetus may cause accelerated platelet destruction.

Alternatively, thrombocytopenia can be an extension of fetal infection with B19 parvovirus, cytomegalovirus, toxoplasmosis, and others discussed in Chapters 67 and 68. Neonatal thrombocytopenia has been reported with maternal antiretroviral therapy for human immunodeficiency virus (HIV) infection (Smith, 2016). Term newborns with sepsis can have accelerated platelet consumption (Eissa, 2013). Last, inherited platelet disorders are described in Chapter 59 (p. 1059).

NEWBORN INJURIES

Incidence

Birth injury can complicate any term delivery, and from population studies, its incidence approximates 2 percent of deliveries (Linder, 2012; Sauber-Schatz, 2010). Imprecision in these numbers may stem from lumping of major and minor injuries and trauma definitions. In one population study from Washington State, the rate of neonatal birth trauma declined by 14 percent and from 5.3 events per 1000 live births in 2004 to 4.5 in 2013 (Wen, 2017). Major injury rates were highest with forceps or vacuum delivery and substantially lower for all caesarean delivery categories.

Cranial Injuries

The fetal head has considerable plasticity and can undergo appreciable molding during labor. However, traumatic head injuries can occur and result in bony fracture or in intracranial or extracranial hemorrhage. With intra- and extracranial hemorrhages, anatomical location defines their classification (Table 33-4).

Intracranial Hemorrhage

Most aspects of neonatal intracranial hemorrhage are related to gestational age. Of the categories shown in Table 33-4, the term newborn may suffer subdural and intracerebral hemorrhages most often. Intraventricular, subarachnoid, or cerebellar hemorrhages are more frequent in the preterm neonate. In those born preterm, blood pressure instability, hypoxia, and ischemia are prominent causes and described in Chapter 34 (p. 618). In term neonates, birth trauma is the most frequent etiology. Other uncommon causes or contributors include acquired or congenital fetal coagulopathy, vascular anomaly, tumor, genetic mutation, and infection (Tan, 2018). *Importantly, in some newborns, intracranial hemorrhage may follow an apparently uneventful vaginal delivery, and no cause is found.*

Term newborns with intracranial hemorrhage may initially display seizures, apnea or tachypnea, poor feeding, and temperature instability (Ou-Yang, 2010). Imaging options are

TABLE 33-4. Major Types of Cranial Hemorrhage

Type	Collection Site	Associations in Term Neonates	Clinical Outcomes
INTRACRANIAL			
Epidural	Between periosteum and dura mater	Difficult or prolonged birth Idiopathic	Usually good
Subdural	Between dura and arachnoid mater		
Subarachnoid	Between arachnoid and pia mater		
Intraventricular	Ventricles (lateral, 3rd, or 4th)	Birth trauma, hypoxia, or coagulation dysfunction	Variable; worse with high IVH grade and thalamic source
Intracerebral	Cerebral parenchyma	Coagulation dysfunction, vascular anomalies, intrapartum factors	Variable; affected by size, location, or comorbid hydrocephalus
Intracerebellar	Cerebellar parenchyma	Abnormal FHR, OVD, resuscitation required	Variable; affected by size and comorbid lesions
EXTRACRANIAL			
Cephalohematoma	Subperiosteal	OVD, especially VAD Dystocia	Good; risk of anemia or hyperbilirubinemia
Subgaleal	Between galea aponeurotica and periosteum	OVD, especially VAD Dystocia	Variable; worse with associated acidosis, hypovolemia, and comorbid lesions

OVD = operative vaginal delivery; VAD = vacuum-assisted delivery.

sonography or CT, but MR imaging is often preferred. With most lesions, treatment is supportive and nonsurgical. However, acute hydrocephalus, rising intracranial pressure, or mass effects are infrequent complications that can prompt surgery (Tan, 2018).

Names of intracranial lesions reflect anatomy. First, the meninges forms from the dura, arachnoid, and pia mater, and the dura mater is the external layer. *Subdural hemorrhage* collects between the dura and arachnoid mater. Prolonged and difficult delivery can produce cranial molding, dural stretch, and tearing of bridging veins in the subdural space (Towner, 1999; Hong, 2018). Asymptomatic subdural hemorrhage can also accompany uneventful vaginal or cesarean delivery (Rooks, 2008). In asymptomatic newborns, prognosis is good (Zamora, 2021). Poorer outcome may attend those with comorbid conditions or lesions (Hong, 2018).

Less commonly, *subarachnoid hemorrhage* collects between the arachnoid and pia mater. Rarely, *epidural hemorrhage* collects outside the dura mater and beneath the periosteum. In both these hemorrhage types, risks, mechanisms, and recovery are similar to subdural hemorrhage (Hong, 2018; Shah, 2016).

Intraventricular hemorrhage is less common in term than preterm newborns. Described in Chapter 34 (p. 618), the vascular germinal matrix is a vulnerable site for preterm neonates but has mainly regressed by term. Instead, the choroid plexus, thalamus, or residual germinal matrix are bleeding sources at term. Etiology can include birth trauma, hypoxia, or coagulation dysfunction. Additional rare causes are listed in this section's first paragraph. However, in small case series, one to two thirds had no identified antecedent (Roland, 1990; Wu, 2003). Prognosis varies, and worse outcomes are associated with advanced hemorrhage grade or thalamic hemorrhage (Kaur, 2020).

Intracerebral hemorrhage or *neonatal hemorrhagic stroke* is uncommon at term. Risk factors are coagulation defects, vascular anomalies, and intrapartum factors that include FHR abnormalities and low Apgar scores. Trauma is less often implicated (Cole, 2017).

Intracerebellar hemorrhage is infrequent in the term newborn. In one series, associated factors were FHR abnormalities, operative vaginal delivery, emergent cesarean delivery, and delivery-room resuscitation (Limperopoulos, 2009). Prognosis with both intracerebral and intracerebellar hemorrhages is affected by lesion size, presence of additional hemorrhage sites, and associated hydrocephalus or elevated intracranial pressure.

Extracranial Hemorrhage

These blood collections accumulate outside the calvarium (see Table 33-4). From its most superficial surface inward, the scalp consists of skin, subcutaneous tissue, galea aponeurotica, subgaleal space, and calvarium periosteum (Fig. 33-2). The galea aponeurotica is dense fibrous tissue, whereas the subgaleal space contains loose, fibroareolar tissue. Traversing across the subgaleal space are *emissary veins*, which connect the dural sinuses inside the skull with superficial scalp veins.

Caput succedaneum is soft-tissue edema of the scalp. It forms from repetitive contractions that press the head against an unyielding cervix. The caput is maximal at birth, rapidly grows smaller, and usually disappears within hours or days.

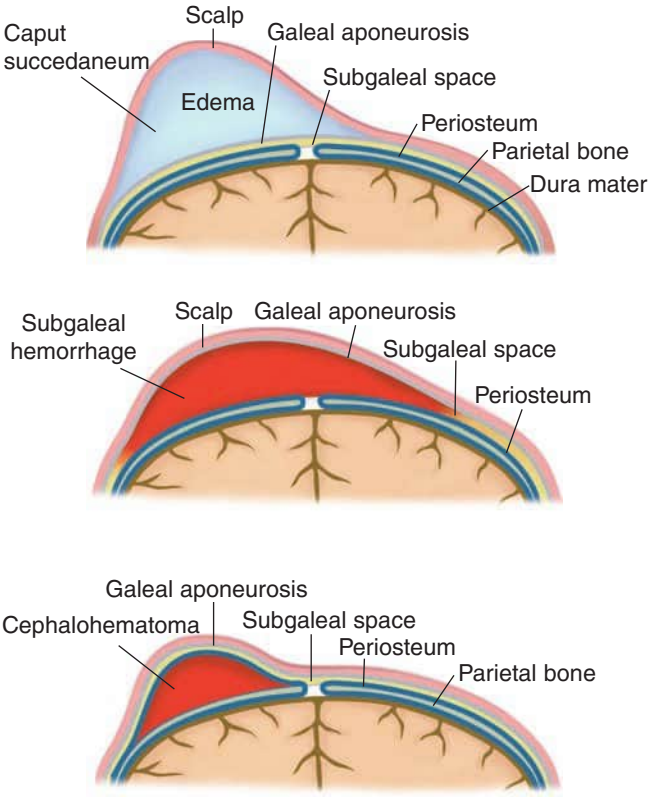

FIGURE 33-2 Schematic of extracranial lesions in the neonate that include caput succedaneum, subgaleal hemorrhage, and cephalohematoma.

Cephalohematoma is a cranial subperiosteal hematoma. It has an incidence of 1 percent and makes up a large percentage of birth injuries (Werner, 2011; Kekki, 2020). It usually develops in the setting of dystocia or operative vaginal delivery. Vacuum-assisted births have a greater association than births by forceps or cesarean delivery (Alexander, 2006; Werner, 2011). Cephalohematoma develops from shearing forces during labor and delivery, which lacerate the emissary or diploic veins. Fortunately, the densely adhered periosteum impedes rapid enlargement and limits final hematoma size. Hemorrhage can be over one or both parietal bones, but collections do not cross suture lines. A cephalohematoma may not be apparent until hours after delivery, when bleeding is sufficient to raise the periosteum. After it is identified, it often grows larger and persists for weeks or even months, and bleeding may cause anemia or hyperbilirubinemia. Outcomes are good in the absence of additional injuries. Rare hematoma complications are infection or calcification (Kandemirli, 2020; Zimmermann, 2016).

Subgaleal hemorrhage is rare and results from emissary vein laceration and bleeding between the galea aponeurotica and the skull periosteum. Both the galea aponeurotica and subgaleal space span across the occipital, parietal, and frontal bones. Because of its loose areolar tissue and large surface area, significant blood volumes can collect in this potential space and may extend from the neck to the orbits and laterally to the temporal fascia above the ears (Modanlou, 2016). Resulting hypovolemia

can lead to shock and significant morbidity, and cited mortality rates approximate 15 percent (El Dib, 2019; Lee, 2018; Swanson, 2011). Other findings are seizures, enlarging head circumference, and respiratory distress. The subgaleal hemorrhage rate is 0.05 percent with spontaneous birth but is ten times greater with vacuum-assisted delivery (Colditz, 2015). The most frequent associate is operative vaginal delivery, especially with vacuum devices, but cases can follow spontaneous vaginal or cesarean delivery (Christensen, 2011).

In general, diagnosis of extracranial lesions begins with head ultrasound (Bansal, 2018). This may be sufficient for cephalohematomas. CT or MR imaging may benefit those with subgaleal hemorrhage to exclude comorbid cranial injuries.

Skull Fractures

These are rare but are especially worrisome because of their association with intracranial hemorrhage. The incidence of birth-related skull fractures approximates 1 case per 100,000 births (Högberg, 2020). Operative vaginal delivery is an associated factor (Dupuis, 2005). However, cases can also attend spontaneous or cesarean delivery (Fig. 33-3) (Dolivet, 2018; Merhar, 2016). In these, fracture may result from tight skull compression against the bony pelvis, by hand pressure used by the surgeon to lift the head at cesarean delivery, or from transvaginally applied upward hand pressure by an assistant. Fractures are diagnosed with radiographs or CT. Depending on type, a fracture may be managed expectantly or require surgery. Prognosis is mainly influenced by comorbid intra- or extracranial injuries.

Spinal Cord Injury

Overstretch of the spinal cord and its associated hemorrhage and edema are rare. The cervical spine is most often injured, and excessive traction, rotation, or hyperextension during shoulder dystocia manipulations, breech vaginal delivery, and operative vaginal delivery are implicated (Lee, 2020a; Menticoglou, 1995). Upper cervical spinal cord injury is often fatal, and survivors can be quadriplegic (Lee, 2020a). Immediate treatment has included ventilator support coupled with corticosteroids or therapeutic hypothermia.

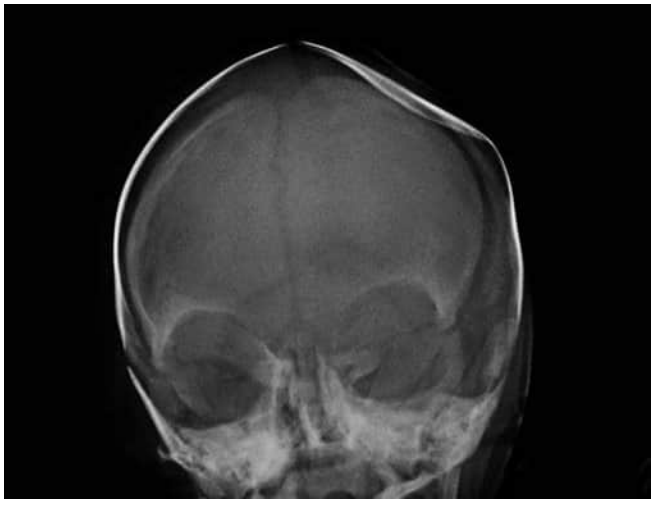

FIGURE 33-3 Depressed skull fracture evident immediately after cesarean delivery. Labor had progressed, and the head was deep in the pelvis. Dislodgment of the head from the birth canal was performed by an assistant using manual pressure upward through the vagina. (Reproduced with permission from Dr. Kimberly M. Spoonts.)

Peripheral Nerve Injuries

Brachial Plexopathy

Injury can involve a single nerve or can affect a nerve root, plexus, or trunk. Trauma to the brachial plexus is infrequent. In one database study, the rate was 1 case per 1000 term births in the United States. The incidence was 1.3 per 1000 vaginal deliveries and 0.2 per 1000 cesarean deliveries (Chen, 2021). Shoulder dystocia, labor dystocia, and breech delivery are risks (Johnson, 2020).

With plexopathy, the injury damages the nerve roots that supply the brachial plexus—$C_{5–8}$ and T_1. With hemorrhage and edema, axonal function may be temporarily impaired, but the recovery chances are good. However, with avulsion, the prognosis for complete recovery is poor. Damage to the $C_{5–6}$ nerve roots can cause *Erb palsy*. Injuries with breech delivery are normally of this type, whereas the more extensive and persistent lesions can follow difficult cephalic deliveries. The latter are more often forceps or vacuum-assisted vaginal deliveries (Wilson, 2016). The $C_{5–6}$ roots join to form the upper trunk of the plexus, and injury leads to paralysis of the deltoid, infraspinatus, and flexor muscles of the forearm. The affected arm is held straight and internally rotated, the elbow is extended, and the wrist and fingers flexed. Finger function usually is retained.

Damage to the C_8-T_1 roots supplying the lower plexus results in *Klumpke palsy,* in which the hand is flaccid. With total involvement of all brachial plexus nerve roots, flaccidity of the arm and hand results. Rarely, with severe injury, phrenic nerve damage can cause ipsilateral diaphragm paralysis, or injury to sympathetic nerve fibers can cause *Horner syndrome*, which manifests as ptosis, miosis, and anhidrosis (Rizeq, 2020). Clavicle or humeral fracture can be comorbid, and clinical concern may prompt chest radiography. MR imaging may be obtained with concern for nerve avulsion (Govindan, 2019).

Because of the importance of brachial plexopathy, the American College of Obstetricians and Gynecologists (2014b) convened a task force to review extant studies. This Task Force concluded that shoulder dystocia cannot be accurately predicted, but in most cases, axonal death does not occur and the prognosis is good. Lindqvist and associates (2012) reported complete recovery in 86 percent of children with $C_{5–6}$ trauma, which was the most common injury, and in 38 percent of those with $C_{5–7}$ damage. However, those with global $C_{5–8}$–T_1 injuries always had permanent disability.

Early physical therapy is initiated to prevent contractures or joint deformity. Maintaining passive joint motion, promoting extremity use, strengthening affected muscles, and providing compensatory techniques are goals (Smith, 2018). Severe injuries may require surgical exploration and nerve reconstruction, usually at 3 to 6 months (Vuillermin, 2016; Wilson, 2016).

FIGURE 33-4 Left facial nerve injury. Classically, the eye fails to close tightly, the labionasal fold is lost, and the mouth pulls to the unaffected side during crying. This was almost completely resolved two days after delivery.

Facial Paralysis

The facial nerve can be injured as it emerges from the stylomastoid foramen, and this may cause facial paralysis (Fig. 33-4). From one series, the incidence was 0.3 cases per 1000 term births (Al Tawil, 2010). Of these vaginal births, forceps were used in one fourth, and three fourths followed spontaneous birth. Pressure from the forceps blade or the bony pelvis, respectively, are suggested injury mechanisms. It can follow cesarean delivery (Alexander, 2006). Spontaneous recovery within a few days is the rule, however, permanent paralysis has been described (Al Tawil, 2010).

Fractures

Most long-bone fractures follow difficult deliveries, however, this is not always the case. At minimum, palpation of the clavicles and long bones is indicated for all newborns after a difficult delivery. Overlying crepitation or irregularity will prompt radiography.

Clavicular fractures are common, unpredictable, and unavoidable complications of normal birth (Ahn, 2015; Roberts, 1995). Their incidence approximates 5 cases in 1000 live births (Kekki, 2020; Linder, 2012). Rates are tenfold higher with vaginal birth than with cesarean delivery (Ahn, 2015). With vaginal birth, shoulder dystocia is an association (Högberg, 2020). With cesarean delivery, greater birth weight is a factor (Choi, 2017).

Humeral fractures and *femoral fractures* are rare. For the humerus, associated settings are breech delivery or posterior arm delivery during shoulder dystocia release (Rietberg, 2003; von Heideken, 2020). Those of the femur are usually associated with breech presentation. Because most breech-presenting fetuses now undergo cesarean delivery, most of these fractures are associated with this mode (Kancherla, 2012). As potential prevention for both fracture types, careful splinting of the bone along its long axis and avoiding perpendicular forces during extraction are encouraged.

Last, *rib fractures* are rare at term. In one series, none was associated with cardiopulmonary resuscitation (Högberg, 2020). Instead, compression forces to the chest during difficult birth or shoulder dystocia are implicated (van Rijn, 2009).

Soft Tissue Injury

Conceivably, any fetal organ or part could be injured with either vaginal or cesarean delivery. Intraabdominal hemorrhage is rare and most often stems from the liver, spleen, or adrenal glands, which are disproportionally large in the newborn. Risks are difficult delivery, especially those presenting breech; cardiac resuscitation; macrosomia; or pathologic enlargement of the involved organ (Schullinger, 1993). Retroperitoneal bleeding with these may manifest as bruising of the flanks, umbilicus, groin, upper thigh, or scrotum (Akin 2011; Heyman, 2011; Raveenthiran, 2008). Pale skin, distended abdomen, and falling hematocrit reflect associated hypovolemia. Treatment involves hemodynamic resuscitation and control of bleeding.

Congenital Deformity Injuries

In *congenital torticollis*, one sternocleidomastoid muscle fails to elongate sufficiently. The head gradually turns toward the side of the injury. Its etiology is unclear. Some cases are associated with breech presentation, operative vaginal birth, or difficult delivery. However, many follow uncomplicated birth, and intrauterine positioning, genetics, and ischemia are some suggested theories (Hardgrib, 2017; Sargent, 2019). Early physical therapy is recommended (Kaplan, 2018).

With *congenital deformations*, a normally developed fetal structure becomes deformed usually by restrictive intrauterine mechanical forces. Common factors are chronic oligohydramnios, multifetal gestation, or abnormally shaped or small uterine cavity. Some mechanical deformations include *talipes equinovarus* (clubfoot) and *oligohydramnios sequence* (Hall, 2014; Society for Maternal-Fetal Medicine, 2019). The latter may lead to pulmonary hypoplasia and deformations of the head, face, skin, and limbs. This sequence and talipes can also be associated with genetic abnormalities or malformations and are discussed in Chapters 14 and 15 (p. 260 and 303).

Last, *congenital hip dislocation* is strongly associated with an in-utero breech presentation (Yang, 2019). Physical examination screening for all newborns is recommended. Treatment may include observation or bracing (Shaw, 2016).

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CHAPTER 34

The Preterm Newborn

At the time of this textbook's first edition in 1903, preterm delivery was often followed by neonatal death. However, subsequent scientific innovation has advanced the threshold of viability to 22 to 24 weeks' gestation (Watkins, 2020). Moreover, the overall survival rate for preterm neonates <29 weeks' gestation approaches 80 percent (Travers 2018). Still, the preterm newborn is susceptible to many serious medical complications both early and later in life (Table 34-1).

The complications of prematurity can be serious, and this is reflected in overall neonatal mortality rates. In 2018, two thirds of all infant deaths in the United States were in the 10 percent born before 37 weeks (Ely, 2020; Hamilton, 2021). Fortunately, rates of preterm birth have declined from approximately 12 percent in 2007 to 10 percent in 2020. The rate of early preterm births (<34 weeks' gestation) declined from 2.77 to 2.69 percent, which is the lowest level reported since 2007 (Hamilton, 2021).

RESPIRATORY DISTRESS SYNDROME

The seminal complication of the preterm newborn is *respiratory distress syndrome (RDS)*. This results from immature lungs that are unable to sustain necessary oxygenation due to surfactant deficiency. The resulting hypoxia can be associated with pulmonary hypertension and neurologic damage such as cerebral palsy. In addition, hyperoxia, a side effect of RDS treatment, contributes to other preterm morbidities including bronchopulmonary dysplasia, necrotizing enterocolitis, periventricular leukomalacia, and retinopathy of prematurity.

Etiopathogenesis

To provide blood gas exchange immediately following delivery, the lungs must rapidly fill with air while being cleared of fluid. Concurrently, pulmonary arterial blood flow must rise. Although some of the fluid is expelled as the chest is compressed during vaginal delivery, most is absorbed through the pulmonary lymphatics via complex mechanisms described in Chapter 32 (p. 586). Sufficient surfactant, synthesized by type II pneumocytes, is essential to stabilize the air-expanded alveoli. This lipoprotein lowers surface tension and thereby prevents lung collapse during expiration (Chap. 7, p. 131). If surfactant is inadequate, hyaline membranes form in the distal bronchioles and alveoli, and RDS develops. Although

TABLE 34-1. Complications of Prematurity

Respiratory distress syndrome (RDS)
Bronchopulmonary dysplasia (BPD)
Pneumothorax
Pneumonia/sepsis
Patent ductus arteriosus (PDA)
Necrotizing enterocolitis (NEC)
Retinopathy of prematurity (ROP)
Intraventricular hemorrhage (IVH)
Periventricular leukomalacia (PVL)
Cerebral palsy (CP)
Neurodevelopmental Impairment (NDI)

RDS is generally a disease of preterm neonates, it can develop in term newborns, especially with sepsis, pneumonia, or meconium aspiration. In these cases, surfactant can be inactivated by inflammation and/or the presence of meconium (Chap. 33, p. 600).

With inadequate surfactant, alveoli are unstable and collapse with the low pressures of end expiration. Pneumocyte nutrition is compromised by hypoxia and systemic hypotension. Partial persistence of the fetal circulation may lead to pulmonary hypertension and a relative right-to-left shunt. Eventually, alveolar cells undergo ischemic necrosis. When oxygen therapy is initiated, the pulmonary vascular bed dilates, and the shunt reverses. Protein-filled fluid leaks into the alveolar ducts, and the cells lining the ducts slough. Hyaline membranes composed of fibrin-rich protein and cellular debris line the dilated alveoli and terminal bronchioles. The epithelium underlying the membrane becomes necrotic. At autopsy, with histological staining of lung tissue with hematoxylin-eosin, these membranes appear amorphous and eosinophilic, like hyaline cartilage. Because of this, respiratory distress syndrome is also termed *hyaline membrane disease*.

Clinical Course

In typical RDS, tachypnea develops, the chest wall retracts, and expiration is accompanied by nostril flaring and by grunting—in an attempt to provide a positive end-expiratory pressure to prevent lung collapse. Shunting of blood through nonventilated lung contributes to hypoxemia and to metabolic and respiratory acidosis. Poor peripheral circulation and systemic hypotension may be evident. The typical chest radiograph shows a diffuse reticulogranular infiltrate and an air-filled tracheobronchial tree—*air bronchograms* (Fig. 34-1).

Respiratory insufficiency can also be caused by sepsis, pneumonia, meconium aspiration, pneumothorax, persistent fetal circulation, heart failure, and congenital malformations involving thoracic structures, such as diaphragmatic hernia (Chap. 33, p. 599). Common mutations in surfactant protein production and the phospholipid transporter (ABCA3) are rare causes of RDS (Singh, 2021).

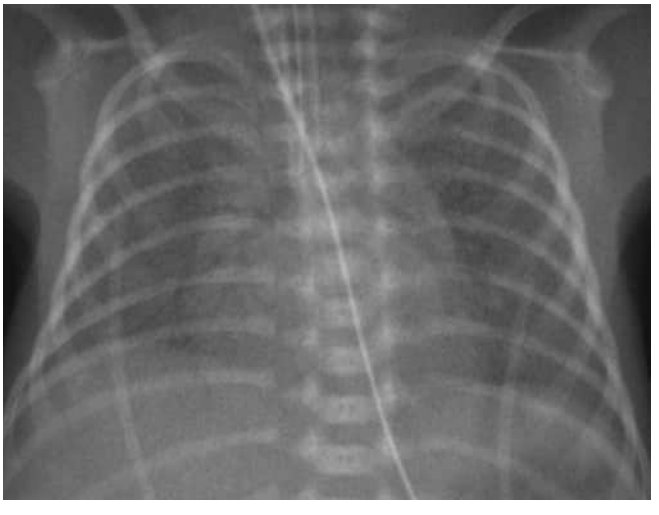

FIGURE 34-1 Chest radiograph of a preterm newborn with moderate respiratory distress syndrome. Note the diffuse granularity throughout the lungs and mild, central, air bronchograms. The lungs are only eight ribs expanded despite mechanical ventilation.

Treatment

An important factor influencing survival is neonatal intensive care. Although hypoxemia prompts application of supplemental oxygen, excess oxygen can damage the pulmonary epithelium, retina, and other immature tissues. Despite this, advances in mechanical ventilation technology have improved neonatal survival rates. For example, *continuous positive airway pressure (CPAP)* prevents the collapse of unstable alveoli. This allows high concentrations of inspired oxygen to be reduced, thereby minimizing its toxicity. To help limit the need for tracheal intubation and intermittent positive-pressure ventilation, CPAP has been studied in well-designed trials (Morley, 2008; SUPPORT Study Group, 2010b). An initial CPAP strategy coupled with subsequent selective surfactant use is a beneficial alternative to immediate intubation and surfactant for neonates of extremely early gestational age (Wyckoff, 2020). Less-invasive surfactant administration techniques allow surfactant delivery while maintaining the preterm newborn on CPAP. Such methods reduce the need for intubation and mechanical ventilation in the first 72 hours and decrease rates of death or bronchopulmonary dysplasia (Abdel-Latif, 2021).

Mechanical ventilation has undoubtedly improved survival rates, but it is an important factor in the genesis of chronic lung disease of prematurity—*bronchopulmonary dysplasia (BPD)*. Namely, mechanical ventilation places a newborn at risk for barotrauma and volutrauma. Moreover, hyperoxia can create reactive oxygen species that trigger inflammation. Infection also can be contributory. In affected newborns, alveolar and pulmonary vascular development is disrupted, leading to hypoxia, hypercarbia, and chronic oxygen dependence. It can also affect adult lung function (Thébaud, 2019). BPD remains the most frequent complication of extreme preterm birth (Stoll, 2015).

High-frequency oscillatory ventilation is an alternative to conventional mechanical ventilation for preterm newborns. However, benefits and risks vary considerably between studies (Cools, 2015). Similarly, thus far, the evidence for *high-frequency jet ventilation* is not superior to conventional ventilation for this population (Rojas-Reyes, 2015).

In the past, ventilator-dependent preterm neonates were often treated with *glucocorticoids* to prevent and treat BPD. This differs from antenatal use, described in the next sections. The American Academy of Pediatrics now recommends against routine neonatal corticosteroid use because of limited benefits and greater rates of impaired motor and cognitive function and school performance in exposed newborns (Watterberg, 2010). The risk of adverse neurodevelopment is highest if dexamethasone is given to preterm newborns at low risk of BPD. Attempts have been made to identify the highest-risk neonates for whom the benefits would exceed the risks (Cuna, 2018). Different types of corticosteroids, with various timing and administration routes, have been studied. Current trials are focused on corticosteroids, mixed with surfactant, delivered intratracheally directly to the lung. This approach may avoid some systemic adverse effects of corticosteroids (Cheong, 2019).

In other efforts to prevent BPD, early animal studies demonstrated significant improvements in lung function with weeks of *inhaled nitric oxide* (McCurnin, 2005). Despite initial enthusiasm, clinical trials failed to demonstrate a consistent benefit (Greenough, 2020). A National Institutes of Health (NIH) consensus statement concluded that the available data do not support its use to prevent or treat BPD (Cole, 2011).

Caffeine has been used widely to treat apnea of prematurity, but it also has bronchodilatory effects. One large randomized trial of caffeine versus placebo showed lower BPD rates, improved neurodevelopmental outcomes during early childhood, and good evidence of safety up to 11 years (Schmidt, 2006, 2012, 2017). This therapy is now widely used for newborns weighing ≤1250 g.

The antioxidant *vitamin A* is necessary for normal lung growth and the integrity of respiratory tract epithelial cells. Preterm newborns have low vitamin A levels at birth, and this is associated with a greater risk of developing BPD. Randomized trials support the use of vitamin A to modestly reduce BPD rates for very-low-birthweight neonates weighing <1500 g (Darlow, 2016). Unfortunately, production shortages have limited the use of vitamin A prophylaxis in the past decade.

Surfactant Prophylaxis and Rescue Therapy

Surfactant replacement was established decades ago as an effective and safe therapy for RDS. Surfactant improves mortality rates, reduces the need for ventilation, and improves short-term outcomes for low-birth-weight neonates (Hentschel, 2020). It is standard therapy for newborn RDS (American Academy of Pediatrics, 2017).

Exogenous surfactant products are most commonly delivered via endotracheal tube to help treat RDS. They contain biological or animal surfactants such as bovine—*Survanta*, calf—*Infasurf*, or porcine—*Curosurf*. One Cochrane review found that animal-derived surfactants led to better outcomes than synthetic ones, which do not contain important surfactant proteins (Ardell, 2015). Currently, no synthetic surfactants are available, yet newer ones are in testing (Hentschel, 2020).

For rescue surfactant therapy, less invasive methods of delivery to spontaneously breathing preterm neonates have been developed. These include surfactant application into the pharynx, surfactant nebulization, and application via laryngeal mask (Hentschel, 2020). Administration of surfactant via a thin catheter while maintaining the newborn on CPAP is associated with reduced risk of death or BPD, lower intubation rate in the first 72 hours, reduced incidence of major complications, and a reduced in-hospital mortality rate compared with administration via an endotracheal tube (Abdel-Latif, 2021).

Surfactant has been used for *prophylaxis* of preterm, at-risk newborns. Given together, antenatal corticosteroids and postnatal surfactant result in an even greater reduction in the overall death rate. However, randomized trials indicate that in populations with high use of antenatal corticosteroids and routine use of CPAP in the delivery room, prophylactic surfactant is no longer beneficial and is associated with greater risk of death or BPD (Rojas-Reyes, 2012; Sardesai, 2017).

Prevention

Antenatal Corticosteroids

More than two decades ago, the NIH (2000) concluded that a single course of antenatal corticosteroid therapy reduces RDS and intraventricular hemorrhage rates in preterm neonates born between 24 and 34 weeks' gestation (p. 619). The American College of Obstetricians and Gynecologists (2020a) considers all women at risk for preterm birth in this gestational-age range to be potential candidates for therapy. It also may be *considered* for pregnant women starting at 23 weeks' gestation who are at risk of preterm delivery within 7 days. For the periviable fetus, other management guidelines are listed in Table 45-4 (p. 786). Administration of corticosteroids for pregnant women during the periviable period who are at risk of preterm delivery within 7 days should be linked to a family's decision regarding resuscitation and should be considered in that context. Thus, as survival at even earlier gestations improves, the threshold for administration may decrease as well.

Administration of antenatal corticosteroids to women at risk for late-preterm delivery (34 to 36 weeks' gestation) reduces the rate of neonatal respiratory complications (Gyamfi-Bannerman, 2016). *Consideration* of a single course of betamethasone for women at risk for late-preterm delivery is supported by the American College of Obstetricians and Gynecologists (2020a). Based on data presented in Chapter 45 (p. 802), at Parkland Hospital, this is not currently our practice.

Amniocentesis to Assess Fetal Lung Maturity

Amniocentesis to assess fetal lung maturity was used previously to predict the neonatal risk for RDS. However, this use of amniocentesis to guide delivery decisions in any clinical situation of pregnancy is not currently supported or recommended (American College of Obstetricians and Gynecologists, 2021a,b).

NECROTIZING ENTEROCOLITIS

This newborn bowel disorder has clinical findings that include abdominal distention, emesis, ileus, bilious gastric aspirates, and bloody stools. Often, radiological images show *pneumatosis intestinalis*, which is bowel wall gas derived from invading bacteria (Fig. 34-2). Other classic imaging findings include hepatobiliary gas and pneumoperitoneum. Bowel perforation necessitates prompt resection.

Necrotizing enterocolitis (NEC) is seen primarily in low-birthweight newborns but occasionally in mature neonates. Hypothesized causes include perinatal hypotension, hypoxia, sepsis, umbilical catheterization, exchange transfusions, blood transfusions, and the feeding of cow milk and hypertonic solutions (Neu, 2011). The pathophysiology is thought to be multifactorial, and genetic disposition, intestinal immaturity, imbalance in microvascular tone, abnormal microbial colonization in the intestine, exposure to enteral feeds, and highly immunoreactive intestinal mucosa play potential roles (Bazacliu, 2019; Neu, 2011).

Medical treatment includes abdominal decompression, bowel rest, broad-spectrum antibiotics, and parenteral nutrition. Surgery

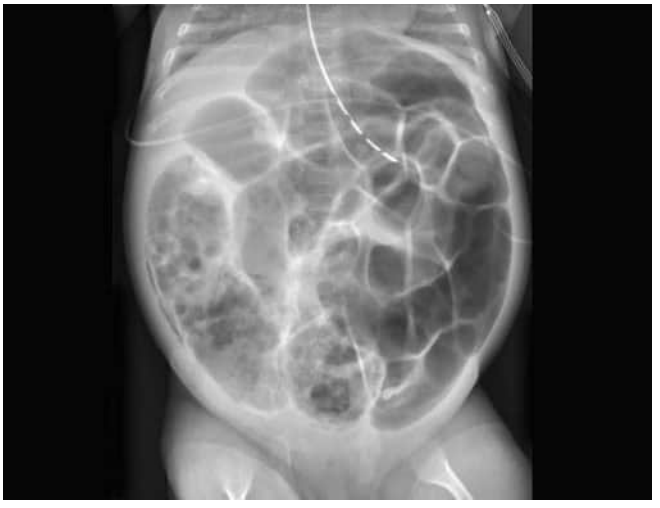

FIGURE 34-2 Abdominal radiograph of a preterm newborn with necrotizing enterocolitis. Note the distended air-filled loops of large and small bowel. Significant pneumatosis intestinalis, which is intramural bowel gas, is visualized within the right lower quadrant and within the pelvis. Not seen here, an associated finding is air in the portal veins of the liver.

is reserved for neonates with intestinal perforation or deteriorating clinical or biochemical status. Possible surgical procedures include drain placement, exploratory laparotomy with resection of diseased bowel, or enterostomy with creation of a stoma (Neu, 2011).

RETINOPATHY OF PREMATURITY

By 1950, this condition, formerly known as *retrolental fibroplasia,* became the largest single cause of blindness in this country. After the discovery that the disease resulted from hyperoxemia, its frequency declined but began to rise again with the increasing survival rates of extremely preterm newborns.

Normally, the fetal retina vascularizes centrifugally from the optic nerve starting at approximately the fourth month, and this continues until shortly after birth. During vascularization, excessive oxygen induces severe retinal vasoconstriction, which leads to endothelial damage and vessel obliteration. This is followed by subsequent aberrant neovascularization, in which the new vessels penetrate the retina and extend into the vitreous. Here, they are prone to leak proteins or to burst and bleed. Adhesions can form to detach the retina. Vascular endothelial growth factor (VEGF) contributes to normal angiogenesis and is upregulated during retinopathy of prematurity (ROP) development (Hellström, 2019). This understanding has opened new avenues of treatment with anti-VEGF therapies.

The precise levels of hyperoxemia that can be sustained without causing ROP are unknown. After birth, there is a "relative" hyperoxia compared with in-utero oxygen content, even in newborns not exposed to higher inspired oxygen concentrations. To better understand the oxygen saturation threshold necessary to minimize ROP without raising rates of other adverse outcomes, the Neonatal Research Network performed a randomized trial of oxygenation in 1316 neonates born between 24 and 27 weeks' gestation (SUPPORT Study Group, 2010a). The two target ranges of oxygen saturation were 85 to 89 percent in one arm and 91 to 95 percent in the other arm. These targets were both commonly employed in neonatal intensive care units. Death before discharge occurred significantly more frequently in the lower-oxygen saturation group—20 versus 16 percent. However, severe ROP among survivors developed significantly less often in the lower-oxygen saturation group—8.6 versus 17.9 percent.

BRAIN DISORDERS

Central nervous system injury usually creates different neuroanatomical sequelae in preterm newborns compared with those at term (Chap. 33, p. 607). In preterm neonates, cerebral lesions detected by neuroimaging include intraventricular hemorrhage, cerebellar hemorrhage, periventricular hemorrhagic infarction, cystic periventricular leukomalacia, and diffuse white matter injury. All of these are strongly associated with adverse neurodevelopmental outcomes (Kwon, 2014).

Cranial sonography remains the preferred approach for detecting frequently occurring brain abnormalities and acute events in the preterm neonate. It is readily available and reliable for detecting common abnormalities and monitoring brain growth. Because cystic injuries may take 2 to 5 weeks to evolve, serial scans are obtained during this time. In those whose findings are transient and resolve in the neonatal period, prognosis is improved compared with infants whose lesions remain and evolve. At the same time, however, between 4 and 10 percent of prematurely born children may develop cerebral palsy (CP) in the absence of lesions. Put another way, 90 to 96 percent of preterm newborns with CP have cerebral lesions that are detectable using cranial sonography.

Intracranial Hemorrhage

There are five major categories of intracranial hemorrhage in the neonate (Table 33-4, p. 607) (Volpe, 2016). *Primary subarachnoid hemorrhage* is more common in those born preterm and is frequently benign. *Cerebellar hemorrhage* is also more frequent in preterm neonates and is increasingly recognized as a cause of serious sequelae. *Intraventricular hemorrhage (IVH)* is almost exclusively seen in preterm newborns, is relatively common, and can have serious effects (Hintz, 2015, 2018). *Subdural hemorrhages* are more frequent in term newborns and can be serious (Chap. 33, p. 608). *Miscellaneous intraparenchymal hemorrhage* is also more frequent in those born at term and is of variable concern.

Intraventricular Hemorrhage

The germinal matrix is a highly cellular and vascular region of the developing brain located beneath the lateral ventricles. In preterm neonates, the germinal matrix capillary network is fragile for several reasons. First, the subependymal germinal matrix provides poor support for the vessels coursing through it. Second, venous anatomy in this region causes stasis and congestion, which makes vessels susceptible to bursting if intravascular pressure rises. Third, vascular autoregulation is impaired in the preterm neonate (Verhagen, 2014; Volpe, 2016).

If fragile capillaries in the germinal matrix rupture, blood escapes into the ventricular system—*intraventricular hemorrhage (IVH)*. This may dilate the ventricle, which then can obstruct venous drainage of the surrounding tissue. As a result, venous infarction and hemorrhage, termed *periventricular hemorrhagic infarction*, may follow.

Risk of severe IVH is inversely related to gestational age (Stoll, 2015). IVH is a serious complication of preterm neonates born before 32 weeks and is particularly frequent in those born before 27 weeks. The germinal matrix involutes between 34 and 36 weeks' gestation. Thus, IVH is infrequent after that period of brain development (Guillot, 2020). Most hemorrhages develop within 72 hours of birth (Hand, 2020). Because IVH usually is recognized within 3 days of delivery, its genesis is sometimes erroneously attributed to birth events. It is important to realize that *prelabor* IVH also can occur (Dunbar, 2021).

The pathogenesis of IVH is multifactorial and includes hypoxic-ischemic events, carbon dioxide elevations, anatomical factors, blood pressure instability, coagulopathy, genetic factors, and many others (Gilard, 2020; Leijser, 2019). Moreover, preterm birth is frequently associated with infection, which further predisposes to endothelial activation, platelet adherence, and thrombi (Villamor-Martinez, 2018). Respiratory distress and mechanical ventilation are commonly associated factors (Leijser, 2019).

Almost half of hemorrhages are clinically silent. Most small germinal matrix hemorrhages and those confined to the cerebral ventricles resolve without impairment. But, nearly half do show some sign of neurological impairment (Leijser, 2019). Survivors of extensive periventricular/intraventricular hemorrhage can have major neurodevelopmental handicaps (Mukerji, 2015). Large lesions can result in hydrocephalus or in degenerated cystic areas termed *periventricular leukomalacia (PVL)*, discussed later. Importantly, the extent of PVL correlates with CP risk (Dorner, 2018).

Incidence and Severity

IVH incidences vary according to gestational age at birth. Severe IVH rates have declined (Handley, 2018; Yeo, 2020). From the Neonatal Research Network, the incidence from 1993 to 2012 for neonates <29 weeks' gestation dropped from 19 to 13 percent (Stoll, 2015). In 2012, the incidence ranged from 11 percent in those born at 23 weeks to only 5 percent for those born at 28 weeks.

The severity of IVH can be assessed by neuroimaging studies. Papile and coworkers (1978) devised the most widely used grading scheme to quantify the lesion extent and estimate prognosis. Since the initial report, the Papile classification has been modified (Hand, 2020):

- *Grade I*—hemorrhage is limited to the germinal matrix
- *Grade II*—IVH occupies 10 to 50 percent of the ventricular area
- *Grade III*—hemorrhage with >50 percent of the ventricular area involved
- *Parenchymal hemorrhage (previously called Grade IV)*—most likely attributable to hemorrhagic venous infarction rather than extension of IVH into the parenchyma.

Antenatal Corticosteroids

If given at least 48 hours before delivery, corticosteroids prevent or reduce the incidence of severe IVH (Battarbee, 2020). A Consensus Development Conference of the NIH (1994) concluded that such therapy reduced rates of mortality, RDS, and IVH in preterm neonates born between 24 and 32 weeks' gestation. A second consensus statement by the NIH (2000) recommended that repeated courses of corticosteroids not be given (Chap. 45, p. 803).

Subsequently, the Maternal–Fetal Medicine Units Network reported that repeated corticosteroid courses were associated with some improved preterm neonatal outcomes, but also with reduced birthweight and increased risk for fetal-growth restriction (Wapner, 2006). Surveillance of this cohort through age 2 to 3 years found that children exposed to repeated versus single-dose corticosteroid courses did not differ significantly in physical or neurocognitive measures (Wapner, 2007). It was worrisome, however, that infants exposed to multiple courses had a nonsignificant 5.7-fold relative risk of CP.

At the same time, the 2-year follow-up of the Australian Collaborative Trial was reported by Crowther and coworkers (2007). In more than 1100 newborns, the incidence of CP was almost identical—4.2 versus 4.8 percent—in those given repeated versus single-course corticosteroids, respectively. More recently, it was reported that for those born before 28 weeks' gestation, if 10 days or more had passed since betamethasone administration, the incidence of severe IVH was higher (Liebowitz, 2016). This is not a consistent finding in all studies (Battarbee, 2020).

The most recent recommendations from the American College of Obstetricians and Gynecologists (2020a) are for a single course of corticosteroids for pregnant women between $24^{0/7}$ weeks and $33^{6/7}$ weeks' gestation who are at risk for preterm delivery. They further note that those given their initial course more than 14 days prior and who have imminent risk of preterm delivery may receive a second "rescue" course.

Other Preventive Methods

Although antenatal *magnesium sulfate* for those at risk for preterm delivery does not reduce the incidence of IVH, it does offer protection from neurodevelopmental impairment (Shepherd, 2018). The American College of Obstetricians and Gynecologists (2020b) recommends its use for this indication, as discussed further in Chapter 45 (p. 803). Antenatal *vitamin K* and *phenobarbital* and postnatal phenobarbital have not consistently reduced the incidence of IVH in studies (Crowther, 2010a,b; Smit, 2013). Although *vitamin E* reduced IVH rates, the associated risk for sepsis was increased (Brion, 2003). Metaanalyses of the many randomized trials of postnatal *indomethacin* and other prostaglandin inhibitors show inconsistent results regarding reductions in IVH rates (Fowlie, 2010; Mitra, 2018). None has shown improvements in neurodevelopmental impairment.

The benefits of cesarean delivery compared with vaginal birth to lower IVH rates remains controversial. One metaanalysis reported that cesarean delivery for very-low-birthweight neonates had no effect on rates of severe IVH but did reduce

overall IVH rates (Barzilay, 2016). The benefits of cesarean delivery to lower IVH rates in breech and growth-restricted fetuses are unclear from current observational data (Baalbaki, 2018). Prospective trials are needed.

Delayed umbilical cord clamping compared to immediate cord clamping has been reported to reduce the risk for any grade of IVH in preterm newborns but has not reduced rates of severe IVH (Rabe, 2019; Seidler, 2021). In preterm neonates, deferred cord clamping may also raise hemoglobin and hematocrit levels and improve survival rates (Seidler, 2021). Cord milking is associated with higher rates of severe IVH in neonates <28 weeks' gestation and should be avoided (Katheria, 2019; Wyckoff, 2020).

Periventricular Leukomalacia

This histological description refers to cystic areas deep in brain white matter that develop after hemorrhagic or ischemic infarction. Tissue ischemia leads to regional necrosis. Because brain tissue does not regenerate and the preterm neonate has minimal gliosis, these irreversibly damaged areas appear as echolucent cysts in neuroimaging studies. Generally, they require at least 2 weeks to form but may develop as late as 4 months after the initial insult. Thus, their presence at birth may help to determine the timing of an inciting event.

CEREBRAL PALSY

This group of conditions is characterized by chronic movement or posture abnormalities that are cerebral in origin, arise early in life, and are nonprogressive (Nelson, 2003). Epilepsy and mental retardation frequently accompany CP. Its cause differs in preterm and term neonates, and the latter is described in Chapter 33 (p. 602).

CP is commonly classified by the type of neurological dysfunction—spastic, dyskinetic, or ataxic—and by the number and distribution of limbs involved—quadriplegia, diplegia, hemiplegia, or monoplegia.

- *Spastic quadriplegia* has a strong association with developmental retardation and epilepsy. Spastic quadriplegia is the most severe form of spastic CP and affects all four limbs, the trunk, and the face.
- *Spastic diplegia* is common in preterm or low-birthweight neonates. In this CP type, muscle stiffness is mainly in the legs, and the arms are less or not involved. Affected persons might have difficulty walking because tight extremity muscles cause their legs to pull together, turn inward, and cross at the knees.
- *Spastic hemiplegia* affects only one side of a person's body, and the arm is affected usually more than the leg.
- *Dyskinetic CP* includes *athetoid, choreoathetoid, and dystonic cerebral* forms. Poor control of hand, arm, feet, and leg movements make sitting and walking difficult. Movements may be slow and writhing or rapid and jerky.
- *Ataxic CP* manifests as problems with balance and coordination.
- *Mixed CP* manifests with symptoms of more than one CP type. The most common type is spastic–dyskinetic CP (National Institute of Neurological Disorders and Stroke, 2020).

Incidence

According to the Centers for Disease Control and Prevention (2020a), the prevalence of CP in the United States approximates 3 cases in 1000 children. Hafström and coworkers (2018) reported the 6-year follow-up of all babies born at gestational ages <28 weeks in Sweden from 2004 to 2007. The CP rate overall was 10.5 percent, and no linear association was found between gestational age at birth and CP rates in this cohort.

Risks

Intraventricular Hemorrhage

Various clinical and pathological data link CP with associated severe IVH (grade III or IV) and resulting PVL. Low-grade IVH is generally considered benign, but it is associated with higher rates of CP in school-aged children born extremely preterm (Hollebrandse, 2021). Higher IVH grades are associated with even greater rates.

Ischemia

Preterm newborns are susceptible to brain ischemia and PVL. This is in part due to immature cerebral vasculature and an immature cerebrovascular autoregulation system that is pressure passive. In response to systemic hypotension, preterm infants cannot increase cerebral perfusion to border-zone regions of the brain supplied by the immature penetrating cerebral vasculature (Novak, 2018). This triggers a cascade of events caused by hypoxia–ischemia that results in pyramidal tract damage, which can cause spastic diplegia.

Perinatal Infection/Inflammation

PVL is associated with infection and inflammation. In one study of 753 neonates born between 24 and 32 weeks' gestation, 9 percent developed PVL (Zupan, 1996). Those born before 28 weeks, those who had inflammatory events during the last days to weeks before delivery, and those who had both were at highest risk. In another study, PVL was strongly associated with prolonged membrane rupture, chorioamnionitis, and neonatal hypotension (Perlman, 1996). Bailis and coworkers (2008) reported that chronic—and not acute—placental inflammation was associated with PVL. In another study of 3094 singletons born before 33 weeks' gestation, 15 percent had evidence of clinical chorioamnionitis (Soraisham, 2009). Compared with noninfected infants, cases complicated by infection had significantly higher rates of IVH—22 versus 12 percent.

Fetal infection may be a key element in the pathway between preterm birth and CP (Burd, 2012; Leviton, 2010, Novack, 2018). As discussed in Chapter 45 (p. 789), chorioamnionitis is a major cause of spontaneous preterm delivery. In the pathway proposed in Figure 34-3, antenatal reproductive tract infection evokes the production of cytokines such as tumor necrosis factor (TNF) and interleukins 1, 6, and 8. These in turn stimulate prostaglandin production and preterm labor. Preterm fetal intracranial blood vessels are susceptible to rupture and damage, and the cytokines that stimulate preterm labor also have direct toxic effects on oligodendrocytes and myelin. Vessel rupture, tissue hypoxia, and cytokine-mediated

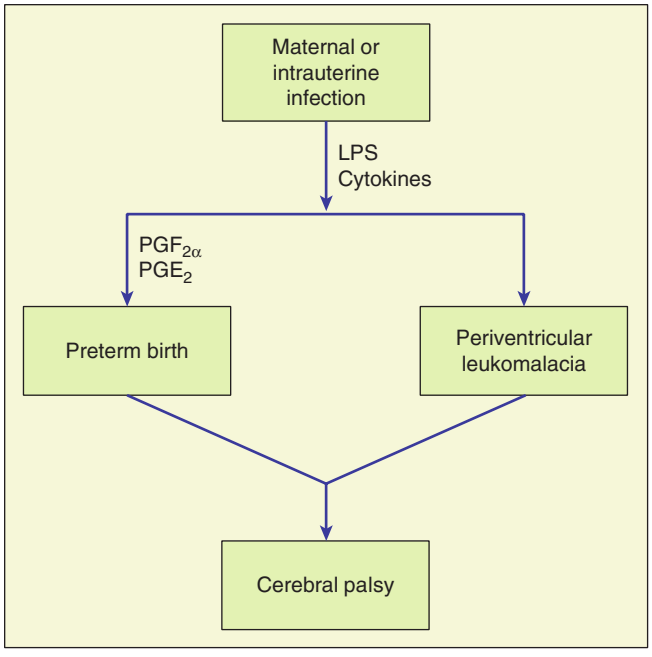

FIGURE 34-3 Schematic representation of the hypothesized pathway between maternal or intrauterine infection and preterm birth or periventricular leukomalacia. Both potentially lead to cerebral palsy. LPS = lipopolysaccharide; PG = prostaglandin.

damage result in massive neuronal cell death. Glutamate is released, which stimulates membrane receptors to allow excess calcium to enter the neurons. High intracellular calcium levels are toxic to white matter, and glutamate may be directly toxic to oligodendrocytes (Khwaja, 2008). Inflammation induced by the activation of microglia and macrophages with the production and release of proinflammatory cytokines, chemokines, proteases, complement factors, excitotoxic amino acids, reactive oxygen species, and nitric oxide further exacerbates secondary brain injury (Novack, 2018).

Many studies show that infection and cytokines can directly damage the immature brain (Chau, 2014; Yoon, 1997a). TNF and interleukin 6 were more frequently found in the brains of infants who died with PVL (Yoon, 1997b). Cytokines are strongly linked to white matter lesions even when organisms cannot be demonstrated (Yoon, 2000).

■ Prevention—Neuroprotection

The benefits of antenatal magnesium sulfate and corticosteroids are well described (Gentle, 2020). Another potential neuroprotective therapy is *erythropoiesis-stimulating agents (ESAs)* such as erythropoietin and darbepoetin. In addition to stimulating erythropoiesis, ESAs protect the developing brain in animal models (Wassink, 2017). One recent metaanalysis found decreased rates of IVH and PVL in preterm neonates treated with ESAs soon after birth. The effects on neurodevelopmental impairment are unclear (Ohlsson, 2020). In one large trial, early high-dose erythropoietin compared with placebo did not lower the risk of severe neurodevelopmental impairment or death at age 2 years (Juul, 2020). A large trial of the longer-acting darbepoetin has completed enrollment and is in the follow-up phase (clinicaltrials.gov/ct2/show/NCT01471015). Last, discussed in Chapter 33 (p. 602) for neonates >36 weeks, induced hypothermia for neuroprotection is not recommended for preterm newborns. This stems from their different pattern of gray and white matter injury and their greater susceptibility to cold stress. The exact gestational age for which therapeutic cooling for hypoxic-ischemic encephalopathy (HIE) would provide more benefit than harm is unknown. A trial of cooling for neonates born at $33^{0/7}$ to $35^{6/7}$ weeks' gestation with moderate/severe HIE has completed enrollment and is in the follow-up phase.

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CHAPTER 35

Stillbirth

Perinatal mortality combines fetal and neonatal deaths and is one measure of healthcare quality before, during, and after delivery. Fetal mortality data from the National Vital Statistics system are usually presented for fetal deaths after the 20-week threshold. Using this threshold, the numbers of fetal deaths in the United States in 2013 slightly surpassed numbers of neonatal deaths when considering fetal deaths beyond 20 weeks (Fig. 35-1) (MacDorman, 2015a).

DEFINITIONS

As discussed in Chapter 1 (p. 3), the current definition of fetal death adopted in the United States by the National Center for Health Statistics is based on one recommended by the World Health Organization (MacDorman, 2015a). It states that "*Fetal death means death prior to complete expulsion or extraction from the mother of a product of human conception irrespective of the duration of pregnancy and which is not an induced termination of pregnancy. The death is indicated by the fact that after such expulsion or extraction, the fetus does not breathe or show any other evidence of life such as beating of the heart, pulsation of the umbilical cord, or definite movement of voluntary muscles. Heartbeats are to be distinguished from transient cardiac contractions; respirations are to be distinguished from fleeting respiratory efforts or gasps.*"

Reporting requirements for fetal deaths in the United States are determined by each state, and thus criteria differ. Most states mandate reporting of deaths of fetuses that are 20 weeks' gestation or older or have a minimum birthweight of 350 g, which roughly equates to that at 20 weeks—or a combination of both. However, evidence shows that not all required fetal deaths are reported, especially at earlier gestational ages (MacDorman, 2015a).

Similarly, comparisons of rates among countries are limited by incomplete fetal death data. Internationally, less than 5 percent of neonatal deaths have formalized documentation (Lawn, 2016). Further, comparative analyses using birthweight versus gestational age among countries yield discordant results. In the

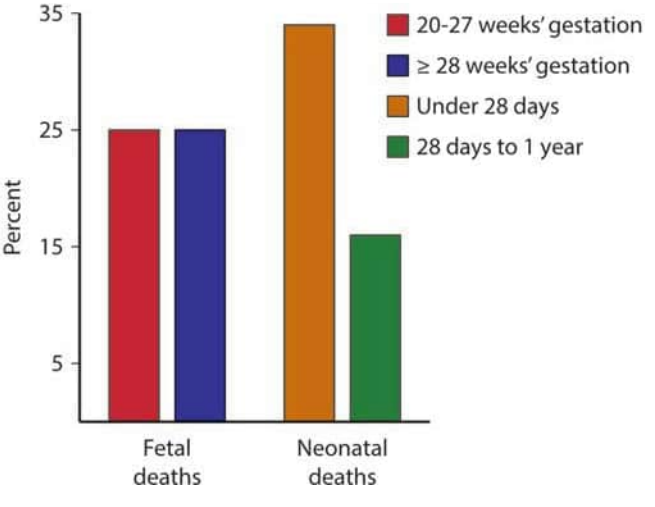

FIGURE 35-1 Distribution of fetal and neonatal deaths in the United States, 2013. (Data from MacDorman, 2015a.)

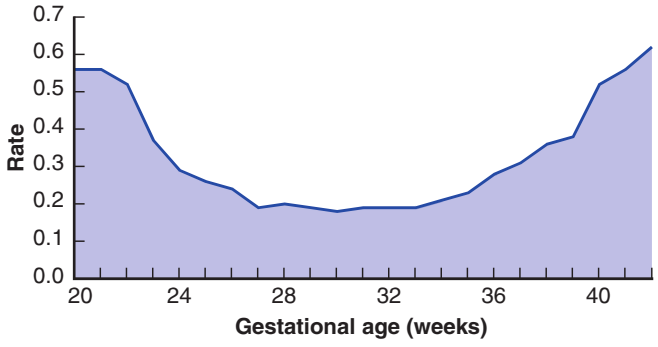

FIGURE 35-2 National Vital Statistics Report: fetal mortality rate per 1000 births by weeks' gestation. (Data from MacDorman, 2015a.)

United States, if stillbirth were defined by a birthweight ≥500 g, the stillbirth rate would be reduced by 40 percent compared with a 20-week-age defined cohort (Blencowe, 2016).

Three fetal mortality epochs are generally recognized. *Early* describes deaths before 20 completed weeks' gestation; *intermediate* for those between 20 and 27 weeks; and *late* for those ≥28 weeks. The fetal mortality rate in each epoch has changed little since 2006. As shown in Figure 35-2, fetal death rates are highest at the earliest and latest gestational ages, which suggests etiological differences.

ETIOLOGIES

To ascertain stillbirth causes in racially and geographically diverse populations in the United States, the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) organized the Stillbirth Collaborative Research Network Writing Group (2011b). The group examined reasons for death at 20 weeks' gestation or later between 2006 and 2008 in 59 tertiary care and community hospitals in five states. Standardized evaluations included autopsy, placental histology, and testing of maternal or fetal blood/tissues, including fetal karyotyping. Evaluations were performed in 500 women with 512 stillbirths. Of these losses, 83 percent were before labor. Causes were divided into eight categories (Table 35-1). These categories were then classified as probable, possible, or unknown causes. As an example, diabetes was considered a *probable cause* if the fetus had diabetic embryopathy with lethal anomalies or if the mother had diabetic ketoacidosis. It was a *possible cause* if the mother had poor glycemic control and the fetus had abnormal growth. A probable or possible source was identified in 76 percent of cases. This proportion is similar to that from Australia using a comparable national audit tool (Lehner, 2019).

This Network study is unprecedented in the United States for several reasons. It was a population-based cohort of stillbirths, in which all underwent systematic and thorough evaluation. Each assigned cause of fetal death is reasonably straightforward and comprehensible except for "placental abnormalities." This category contains uteroplacental insufficiency and a few other less clearly defined placental entities. This aside, the leading reasons for fetal death were obstetrical and primarily included abruption, multifetal gestation complications, and spontaneous labor or ruptured membranes before viability. Structural anomaly was another (Son, 2021a). This study also illustrated that systematic evaluation may identify a likely cause in approximately three fourths of stillbirths. This high rate emphasizes the importance of standardized evaluation. However, a Cochrane database study concluded that evidence specifically from randomized trials to support specific tests for stillbirth evaluation was lacking (Wojcieszek, 2018b).

RISK FACTORS

Many factors are associated with an increased stillbirth risk (Table 35-2). Major associations include sociodemographic factors such as non-Hispanic black women, who have higher incidences of hypertension, diabetes, placental abruption, and preterm premature rupture of membranes (Healy, 2006). Other common associations are maternal age at either end of the spectrum, obesity, preeclampsia, diabetes, substance use, and late-term pregnancy (American College of Obstetricians and Gynecologists, 2020; Page, 2018). Multifetal pregnancies, especially monochorionic gestations, are high risk (Korlesky, 2019). Women with prior adverse pregnancy outcomes—such as stillbirth, preterm birth, or growth restriction—also carry an increased risk (Reddy, 2010; Varner, 2014). Pregnancies complicated by current fetal-growth restriction are particularly vulnerable because of their associations with hypertension, diabetes,

TABLE 35-1. Causes of 512 Stillbirths in the Stillbirth Collaborative Research Network Study

Cause	Percent	Examples
Obstetrical complications	29	Placental abruption, multifetal gestation, ruptured membranes at 20–24 weeks
Placental abnormalities	24	Uteroplacental insufficiency, maternal vascular disorders
Fetal malformations	14	Major structural abnormalities and/or genetic abnormalities
Infection	13	Involving the fetus or placenta
Umbilical cord abnormalities	10	Prolapse, stricture, thrombosis
Hypertensive disorders	9	Preeclampsia, chronic hypertension
Medical complications	8	Diabetes, antiphospholipid antibody syndrome
Undetermined	24	Not applicable

Percentages are rounded and total more than 100 percent because some stillbirths had more than one cause.
Overall, a probable or possible cause was identified in 76 percent of stillbirths.

TABLE 35-2. Maternal Risk Factors and Estimated Stillbirth Rate

Condition	Estimated Rate (per 1000 births)
All pregnancies	6.4
Low-risk pregnancies	4.0–5.5
Hypertensive disorders	
Chronic hypertension	6–25
Preeclampsia	
Nonsevere	9–51
Severe	12–29
Diabetes: insulin requiring	6–35
SLE	40–150
Renal disease	15–200
Thyroid disease	12–20
Cholestasis of pregnancy	12–30
Smoking >10 cigarettes	10–15
Obesity	
BMI 25–29.9 kg/m^2	12–15
BMI >30	13–18
Education (<12 yr vs ≥12 yr)	10–13
Fetal-growth restriction	10–47
Prior fetal-growth restriction	12–30
Late-term pregnancy	14–40
Oligohydramnios	14
Antiphospholipid syndrome	NS
Prior stillbirth	9–20
Multifetal gestation	
Twins	12
Triplets	34
Maternal age	
35–39 yr	11–14
≥49 yr	11–21
Black women (versus white)	12–14

BMI = body mass index; NS = not stated; SLE = systemic lupus erythematosus.
Adapted from American College of Obstetricians and Gynecologists, 2020; Fretts, 2005; Malacova, 2018; Muglu, 2019; Rosenstein, 2014.

fetal infection, autoimmune disorders, and chronic renal disease (Brackett, 2020; Silver, 2018). Recently, the SARS-CoV-2 pandemic has posed both direct and indirect risks for adverse perinatal outcomes. Data are mixed as to whether rates of stillbirth have been higher during the pandemic (Khalil, 2020; Srivastava, 2021; Simon, 2021; Son, 2021b). Some suggest greater risks in low-source countries (Leisher, 2021). Although with recognized limitations, these findings merit further investigation regarding perinatal care during this pandemic (Hu, 2021; Rasmussen, 2020). In 245 gravidas with SARS-CoV-2 infection at Parkland Hospital, the stillbirth rate was not increased compared with that in gravidas with negative test results during the same period.

To help lower stillbirth rates, two major studies assessed whether risk factors could be identified either before or shortly after pregnancy confirmation. In the first, Reddy and colleagues (2010) analyzed data from the NICHD Consortium on Safe Labor. Briefly, the pregnancy outcomes of 206,969 women delivered between 2002 and 2008 at 19 hospitals in the United States were analyzed. When stillbirths were apportioned according to gestational age, most occurred primarily at term. These investigators concluded that their results did not support routine antenatal surveillance for any demographic risk factors.

The second analysis of risk factors was included in the Stillbirth Collaborative Research Network study described earlier (2011a). The validity of stillbirth prediction was assessed based on risks identified in early pregnancy. They found that pregnancy factors known at the start of pregnancy accounted for only a small proportion of stillbirth risk. Indeed, except for prior stillbirth or pregnancy loss from causes such as preterm birth or fetal-growth restriction, other risks had limited predictive value. Prior stillbirth as a risk for recurrence has been emphasized by others (Lamont, 2015; Sharma, 2006). Specifically, the stillbirth risk was fivefold higher in women with a prior stillbirth. From another report, prior preterm birth, fetal-growth restriction, preeclampsia, and placental abruption were strongly associated with subsequent stillbirth (Rasmussen, 2009).

EVALUATION OF THE STILLBORN FETUS

Clinical Examination

Determining the cause of fetal death aids maternal coping, helps assuage perceived guilt, permits more accurate counseling regarding recurrence risk, and may prompt intervention to prevent a recurrent outcome. Identification of inherited syndromes also assists other family members. Important tests include autopsy, chromosomal analysis, and pathological examination of the placenta, cord, and chorioamnionic membranes (Pinar, 2014). Page and coworkers (2017) found placental pathology and fetal autopsy to be the most useful.

Clinically, the fetal weight, head circumference, and length and the placental weight are measured (Fig. 35-3). Photographs are taken of the extremities and palms. Frontal plus profile views of the whole fetus and face also are obtained. A full radiograph of the fetus—a *fetogram*—may be performed (American College of Obstetricians and Gynecologists, 2020). Postnatal magnetic resonance (MR) imaging, radiographs, or sonography may be especially important if parents decline a full autopsy (McPherson, 2017; Shruthi, 2018). Findings are documented in the medical record, and relevant ante- and intrapartum events are delineated.

The reported incidence of fetal anomalies varies. For example, Faye-Petersen and colleagues (1999) reported that if autopsy and chromosomal studies are performed, up to 35 percent of stillborn fetuses were discovered to have major structural anomalies. Approximately 20 percent had dysmorphic features or skeletal anomalies, and 8 percent had chromosomal abnormalities (Pauli, 1994; Saller, 1995). As shown in Table 35-1, however, the incidence of structural anomalies in the Stillbirth Collaborative Research Network (2011b) was only 14 percent.

Laboratory Evaluation

In the absence of anatomical dysmorphology, up to 5 percent of stillborn fetuses will have a chromosomal abnormality (Korteweg, 2008). Previously, karyotyping all stillborn fetuses

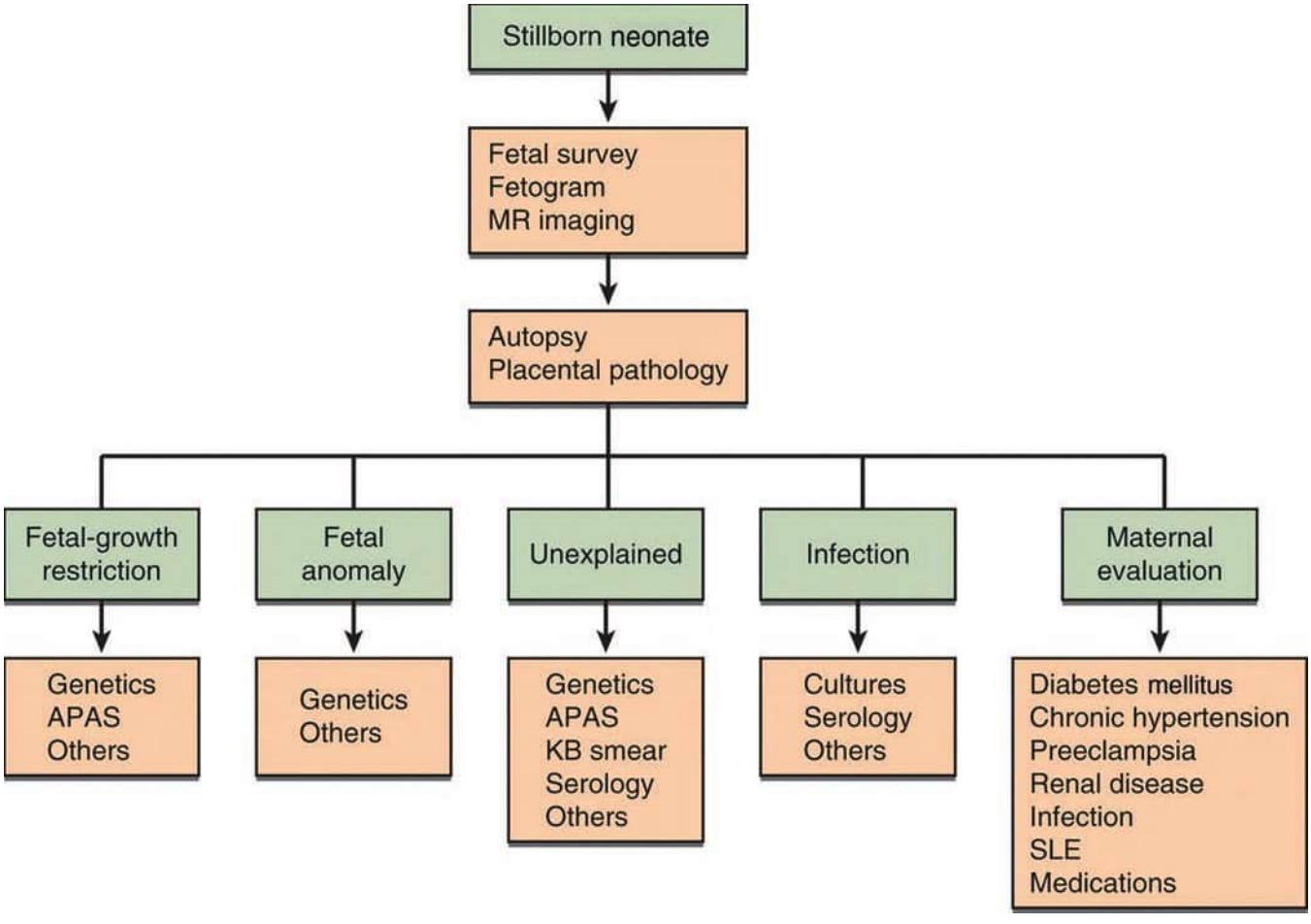

FIGURE 35-3 Flow chart for stillbirth evaluation. APAS = antiphospholipid antibody syndrome; KB = Kleihauer-Betke; MR = magnetic resonance; SLE = systemic lupus erythematosus. (From American College of Obstetricians and Gynecologists, 2020; Page, 2017, 2018.)

was standard practice, but whole-genome sequencing—such as with *chromosomal microarray analysis (CMA)*—is now recommended for stillborns (American College of Obstetricians and Gynecologists, 2020; Holmes, 2018; Martinez-Portilla, 2019). Described further in Chapter 16 (p. 325), this technique does not require dividing cells. This is especially helpful because culturing of macerated fetal tissue is frequently unsuccessful (Reddy, 2012).

Looking to the future, Stanley and associates (2020) evaluated exome sequencing in 246 unexplained stillbirths to search for disease-causing variants in the coding region of the genome. These investigators found that 8.5 percent of stillbirths with a normal chromosomal microarray and without probable maternal or obstetrical causes were probably attributable to mendelian disorders. These findings suggest that a portion of stillbirth cases is caused by pathological variants in genes known to underlie disorders in infants and adults. In addition, a similar number of cases are caused by loss-of-function variants in genes that are critical to in-utero survival but not currently known to be associated with stillbirth. Thus, the full phenotypic spectrum of many known mendelian disorders is not fully understood without the inclusion of cases resulting in stillbirth (Wojcik, 2020).

To take fetal samples, a provider must obtain appropriate parental consent. Any type of fetal or placental tissue or amnionic fluid can be submitted for genetic testing using CMA (American College of Obstetricians and Gynecologists, 2018). Contamination with maternal tissue or blood is ideally avoided. Specimens are collected by sterile technique and kept at room temperature. If fetal blood cannot be withdrawn from the umbilical cord or heart, at least one of the following can be sent for testing: (1) placental block measuring 1 × 1 cm taken below the cord insertion site in a specimen not fixed in formalin; (2) 1.5-cm-long umbilical cord segment; or (3) internal fetal tissue sample from the costochondral junction, fascia lata, or patella. Tissue is washed with sterile saline and suspended in Ringer solution, or sterile cytogenetic medium. Formalin or alcohol kills viable cells.

If conventional karyotyping is the only test available and the death is recent, amnionic fluid can be obtained by amniocentesis. This is particularly valuable if delivery is not expected imminently. As such, these cells provide a greater likelihood of cell growth and eventual results compared with tissue harvested after delivery.

Maternal blood is obtained for Kleihauer-Betke staining; for antiphospholipid antibody and lupus anticoagulant testing if indicated; and for serum glucose measurement to exclude overt diabetes (Silver, 2013). Testing for syphilis is reasonable if no prior screen has been performed, if the patient has exposure risk factors, or if patient, fetus, or placenta show suggestive findings, described in Chapter 68 (p. 1208) (Page, 2017).

Although some have recommended routine evaluation of heritable thrombophilias, no evidence supports the clinical

efficiency of screening in an unselected population. Silver and colleagues (2016) found that most maternal and fetal thrombophilias were not associated with stillbirth and recommended against routine testing. This is echoed by the American College of Obstetricians and Gynecologists and the Society for Maternal-Fetal Medicine (2020).

Placental Examination

Gross and microscopical examination of the placenta, membranes, and cord by a perinatal pathologist is ideal. Numerous maternal and fetal disorders can be identified. Cord knotting and placental microvascular abnormalities are examples and discussed in Chapter 6 (p. 107). Implicated infections are described in Chapters 67 and 68.

Autopsy

Parents are encouraged to allow a full autopsy, which is more likely to yield valuable data. Pinar and coworkers (2012) provide the autopsy protocol used by the Stillbirth Collaborative Research Network. An analysis of 400 consecutive fetal deaths in Wales showed that autopsy altered the presumed cause of death in 13 percent and provided new data in another 26 percent (Cartlidge, 1995). Other investigators have found that autopsy results changed the recurrence risk estimates and parental counseling in 25 to 50 percent of cases (Faye-Petersen, 1999; Silver, 2007). Miller and associates (2016) reported that placental examination with autopsy altered future medical management in 45 percent of cases. Limited autopsy protocols can also yield valuable information. Of components, external examination combined with photography, radiography, MR imaging, bacterial cultures, and selective use of chromosomal and histopathological studies often aids determination.

According to one survey, most hospitals do not audit stillbirths (Goldenberg, 2013). In other centers, including ours, maternal records and autopsy findings are reviewed monthly by a stillbirth committee composed of obstetricians, maternal-fetal medicine specialists, neonatologists, geneticists, and perinatal pathologists. If possible, the cause of death is assigned from available evidence. Most importantly, parents are then contacted and offered counseling regarding the cause of death, the potential recurrence risk, and possible strategies to avoid recurrence (Page, 2020).

PERINATAL CARE

Fetal death is psychologically traumatic for a woman and her family. Further stressors include an interval of more than 24 hours between the diagnosis of fetal death and labor induction; not seeing her neonate for as long as she desires; having no tokens of remembrance; and poor communication with caregivers (Heazell, 2016; Siassakos, 2018). Seeing and holding a stillborn neonate assists parental psychological well-being (Kingdon, 2015). Unfortunately, few obstetrical providers receive formal training in perinatal bereavement care (Nuzum, 2014). At Parkland Hospital, care is coordinated through a dedicated nursing team affiliated with labor and delivery. Intervention includes time with the neonate, keepsake items, photographs, chaplaincy consultation, and bereavement support information. These principles dovetail with the recent global consensus recommendations for bereavement care (Shakespeare, 2020). A woman experiencing a stillbirth or early miscarriage is at increased risk for depression and posttraumatic stress disorder and should be closely monitored (Nelson, 2013) (Chap. 64, p. 1145).

Distinct from stillbirth, fetuses with life-limiting conditions and short survival also merit special consideration. Conceptually, *perinatal palliative care* provides obstetrical and neonatal care to maximize the comfort and quality of life for these newborns (American College of Obstetricians and Gynecologists, 2019). Components of this care include review of the diagnosis, creation of a birth plan, bereavement counseling, and consultation with neonatal services. This care is typically provided by a team that is able to offer medical, psychological, and spiritual support. During planning, parents' values, goals, and fears are a focus.

PRIOR STILLBIRTH

The woman with a prior stillbirth has a substantial risk for a recurrence (see Table 35-2). Preterm or growth-restricted stillborn fetuses magnify this risk (Malacova, 2018). In one cohort of 43 women with a recurrent stillbirth, most fetuses died before 28 weeks' gestation (Fig. 35-4) (Whitham, 2020).

An outlined approach for women with a prior stillbirth is shown in Table 35-3. Importantly, these recommendations are based primarily on limited or inconsistent scientific evidence or on expert opinions. Few studies address management of affected women (Wojcieszek, 2018a).

Very few risk factors for stillbirth are modifiable (Whitham, 2020). Intuitively some such as hypertension or diabetes warrant disease-specific prevention strategies. Women with a prior fetal death due to placental insufficiency also are at increased risk for subsequent adverse perinatal outcomes (Monari, 2016). According to Reddy (2007), almost half of fetal deaths are associated with growth restriction, and thus sonographic anatomical assessment beginning at midpregnancy is recommended. This is followed by serial growth studies beginning at 28 weeks. Detection of growth restriction may lead to

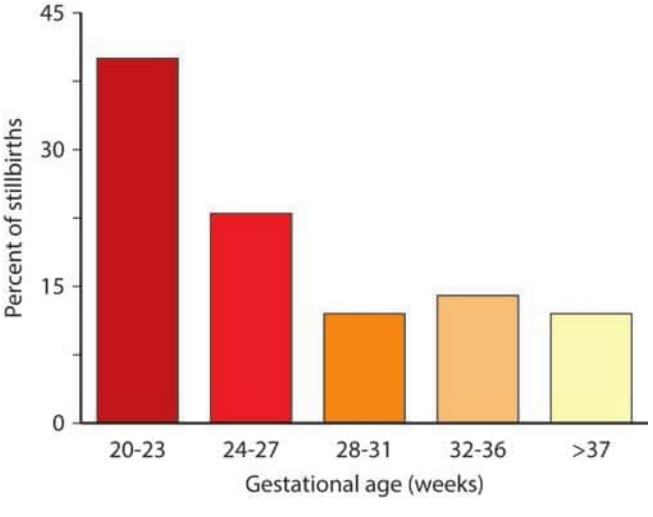

FIGURE 35-4 Stillbirth Collaborative Research Network: gestational age distribution of recurrent stillbirths.

TABLE 35-3. Management of Subsequent Pregnancy after Stillbirth

Preconceptional or Initial Prenatal Visit
Detailed medical and obstetrical history
Review evaluation of prior stillbirth
Determination of recurrence risk
Discuss recurrence of comorbid obstetrical complications
Smoking cessation
Preconceptional weight loss in obese women
Genetic counseling if familial genetic condition exists
Diabetes screen
Screen for antiphospholipid antibodies
Reassurance

First Trimester
Dating sonography
First-trimester screen: PAPP-A, hCG, cfDNA, NT
Reassurance

Second Trimester
Sonographic anatomy survey at 18–20 weeks' gestation
Maternal serum screening (quadruple) *or* single-marker AFP if first-trimester screening elected
Possible uterine artery Doppler studies at 22–24 weeks
Reassurance

Third Trimester
Sonographic screening for fetal-growth restriction, starting at 28 weeks
Kick counts starting at 28 weeks
Antepartum fetal surveillance starting at 32 weeks *or* 1–2 weeks earlier than prior stillbirth
Reassurance

Delivery
Labor induction at 39 weeks
Delivery before 39 weeks for obstetrical indications

AFP = alpha-fetoprotein; cfDNA = cell-free DNA; hCG = human chorionic gonadotropin; NT = nuchal translucency; PAPP–A = pregnancy-associated plasma protein-A.
Adapted from American College of Obstetricians and Gynecologists, 2020; Reddy, 2007.

iatrogenic prematurity and its associated long-term childhood consequences but to fewer intrauterine deaths (Andreasen, 2021).

Weeks and associates (1995) evaluated fetal biophysical testing in 300 women whose only indication was prior stillbirth. There was one subsequent stillbirth, and only three fetuses had abnormal testing results before 32 weeks. Notably, the gestational age of the prior stillborn fetus did not relate to the incidence or timing of abnormal test results or fetal jeopardy in the subsequent pregnancy. These investigators concluded that antepartum surveillance should begin at 32 weeks' gestation or later in the otherwise healthy woman with a history of stillbirth. The American College of Obstetricians and Gynecologists and the Society for Maternal-Fetal Medicine (2020) support this, with the caveat that it increases the iatrogenic preterm delivery rate. Although fetal movement counting strategies are routinely employed and described in Chapter 20 (p. 384), few data guide its use in clinical practice for those with a prior stillbirth (Mangesi, 2015). Unless other indications intervene, delivery at 39 weeks' gestation is recommended. This timing minimizes fetal mortality rates, although the degree of risk reduction may be greater for older women (Page, 2013). Labor induction is suitable, and cesarean delivery is reserved for those with a contraindication to induction.

CHANGES IN STILLBIRTH RATES

As noted, following declines through 2011, the United States fetal mortality rate has changed little (Middleton, 2018). Interpretation of these rates in the context of changing healthcare strategies has spawned debate. One example is the trend against nonmedically indicated deliveries before 39 weeks' gestation and its subsequent effect on term stillbirth rates (Middleton, 2018). This practice's value for neonatal outcome is described in Chapter 26 (p. 486). To analyze whether implementation of this 39-week rule has altered the term stillbirth rate, data from 45 states and the District of Columbia were examined (Nicholson, 2016). The proportion of births before 39 weeks progressively declined from 2007 and 2013, but the term stillbirth rate increased. This suggests that the 39-week rule may cause unintended harm. One review of studies with 15 million pregnancies showed that the prospective risk of stillbirth rose from 0.11 per 1000 births at 37 weeks to 3.18 per 1000 births at 42 weeks (Muglu, 2019).

MacDorman and associates (2015b) also evaluated trends in stillbirth rates by gestational ages in the United States between 2006 and 2012. They used a "traditional stillbirth rate," which was calculated using a denominator composed of the live-birth number *plus* the stillbirth number at a given gestational age. They found increased rates at 24 to 27, 34 to 36, and 38 weeks' gestation. Alternatively, no differences were found in "prospective stillbirth rates." These rates were calculated using a denominator composed of the number of women who are pregnant at a given gestational age for weeks 21 through 42. The discrepancies in stillbirth rates appear to primarily derive from the decline in the birth numbers in the preterm and early-term gestational ages.

In sum, implementation of the 39-week rule has reduced the number of elective births before 39 weeks' gestation, although an unintended consequence may be an increase in term stillbirths—especially among women with medical complications. The importance of induction before 39 weeks in pregnant women with complications to prevent stillbirth is underscored by Little and colleagues (2015). These authors performed a retrospective multistate analysis of early-term deliveries—$37^{0/7}$ to $38^{6/7}$ weeks—from 2005 to 2011. They noted a decline in the number of early-term deliveries during this time but not a significant change in the term stillbirth rates. There was, however, a 25-percent rise in the rate of term, singleton stillbirths among women with diabetes, and this was attributed to clinicians misapplying early-term delivery policies to high-risk women. Undoubtedly, continued surveillance of stillbirth rates is warranted for both high- and low-risk pregnancies at the state and national level.

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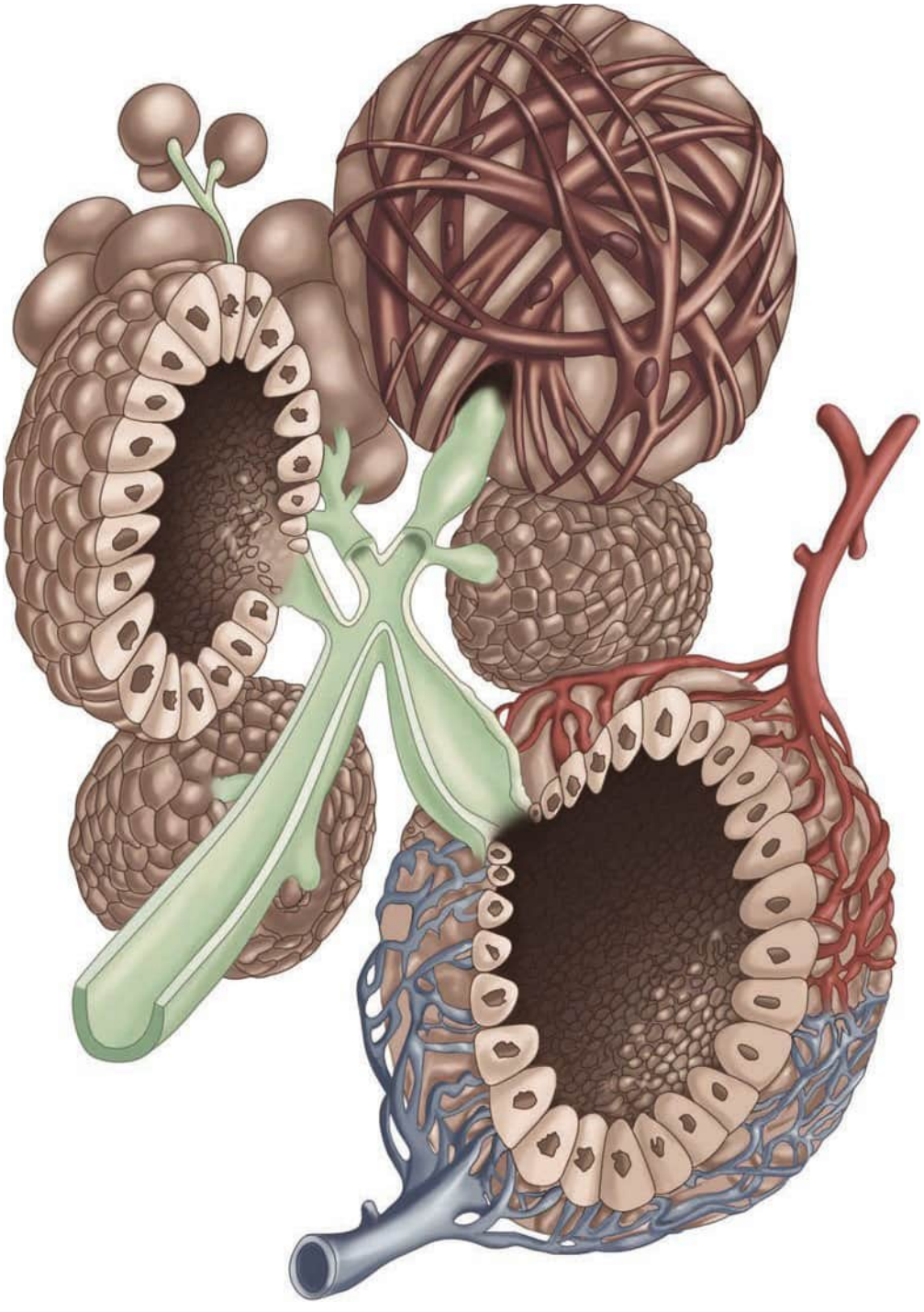
SECTION 10

THE PUERPERIUM



CHAPTER 36

The Puerperium

The word *puerperium* is derived from Latin—*puer*, child + *parus*, bringing forth. It defines the time following delivery during which pregnancy-induced maternal anatomical and physiological changes return to the nonpregnant state. Its duration is inexact but is considered to last between 4 and 6 weeks. Although much less complex compared with pregnancy, the puerperium has appreciable changes, and maternal morbidity is surprisingly common. For example, in a survey of 1246 British mothers, 3 percent required hospital readmission within 8 weeks (Thompson, 2002). Moreover, almost three fourths of women continue to have health problems for up to 18 months (Glazener, 1995). Of self-reported concerns, pain, breastfeeding, and psychosocial topics are prominent. Table 36-1 lists data on these from the Pregnancy Risk Assessment Surveillance System—PRAMS—of the Centers for Disease Control and Prevention (CDC).

THE FOURTH TRIMESTER

Because the weeks following childbirth are a critical period for the woman and her infant, the American College of Obstetricians and Gynecologists (2018a) promulgated the concept of a "fourth trimester." This concept reinforces the importance of the 12 weeks following birth, and components of this model are outlined in Table 36-2. Thus, the comprehensive postpartum visit includes a full assessment of physical, social, and psychological well-being.

An initial visit is recommended at 3 weeks postdelivery and a final summary visit at 12 weeks. Between this time, visits can be added as needed. For example, women with chronic hypertension, overt diabetes, cardiovascular disease, and depression may require additional multidisciplinary care during this period. For all puerpera, a discussion of positive lifestyle changes can be initiated. This time also affords the opportunity to update immunizations (American College of Obstetricians and Gynecologists, 2019). At the end of the 12-week fourth

TABLE 36-1. Concerns Raised by Women in the Puerperium

Concerns	Percent
Pain after cesarean delivery	58
Feeling stressed	54
Breastfeeding issues	48
Perineal pain after vaginal delivery	41
Need for social support	32
Inadequate education about newborn care	21
Help with postpartum depression	10
Perceived need for extended hospital stay	8
Need for maternal insurance coverage postpartum	6

From Childbirth Connection, 2013a,b; Kanotra, 2007.

TABLE 36-2. Components of Postpartum Care for the Fourth Trimester

Care team
Postpartum visits
Lactation support
Infant feeding plan
Reproductive life plan
Contraception
Pregnancy complications
Cardiovascular risk assessment
Mental health
Postpartum problems
Chronic conditions

trimester, follow-up then transitions into well-woman care, ongoing primary or specialty care, and when necessary, preconceptional counseling (Chap. 9, p. 165).

REPRODUCTIVE TRACT INVOLUTION

Birth Canal

Return of the tissues in the birth canal to the nonpregnant state begins soon after delivery. The vagina and its outlet gradually diminish in size but rarely regain their nulliparous dimensions. Rugae begin to reappear by the third week but are less prominent than before. The hymen is represented by several small tags of tissue, which scar to form the myrtiform caruncles. The vaginal epithelium reflects the hypoestrogenic state, and it does not begin to proliferate until 4 to 6 weeks. This timing is usually coincidental with resumed ovarian estrogen production. Lacerations or stretching of the perineum during delivery can lead to vaginal outlet relaxation. Some damage to the pelvic floor may be inevitable, and parturition predisposes to pelvic organ prolapse (Chap. 30, p. 548).

Uterus

The massively augmented uterine blood flow necessary to maintain pregnancy derives from significant hypertrophy and remodeling of pelvic vessels. After delivery, their caliber gradually diminishes to approximately that of the prepregnant state. Within the puerperal uterus, larger blood vessels become obliterated by hyaline changes. They are gradually resorbed and replaced by smaller ones. Minor vestiges of the larger vessels, however, may persist for years.

During labor and vaginal delivery, the margin of the dilated cervix, which corresponds to the external os, may be lacerated. The cervical opening contracts slowly, and for a few days immediately after labor, it readily admits two fingers. By the end of the first week, this opening narrows, the cervix thickens, and the endocervical canal reforms. The external os does not completely resume its pregravid appearance. It remains somewhat wider, and typically, ectocervical depressions at the site of lacerations become permanent. These changes are characteristic of a parous cervix (Fig. 36-1). Cervical epithelium also undergoes

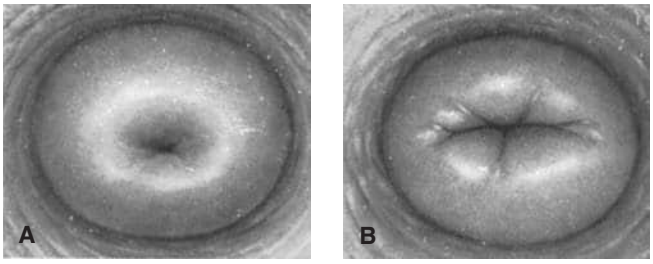


FIGURE 36-1 Common appearance of nulliparous **(A)** and parous **(B)** cervices.

considerable remodeling. This actually may be salutary because almost half of women have regression of high-grade dysplasia following delivery (Ahdoot, 1998; Kaneshiro, 2005).

After delivery, the fundus of the contracted uterus lies slightly below the umbilicus. It consists mostly of myometrium covered by serosa and internally lined by decidua. The markedly attenuated lower uterine segment contracts and retracts, but not as forcefully as the uterine corpus. During the next few weeks, the lower segment is converted from a clearly distinct substructure large enough to accommodate the fetal head to a barely discernible uterine isthmus located between the corpus and internal cervical os. Immediately postpartum, the anterior and posterior walls, which lie in close apposition, are each 4 to 5 cm thick (Buhimschi, 2003). At this time, the uterus weighs approximately 1000 g.

Myometrial involution is a truly remarkable feat of destruction or deconstruction that begins as soon as 2 days after delivery (Williams, 1931). The total number of myocytes does not decline appreciably—rather, their size decreases markedly. Weights from removed uteri approximate 500 g by 1 week postpartum, 300 g by 2 weeks, and at 4 weeks, involution is complete and the uterus weighs approximately 100 g (Williams, 1931). After each successive delivery, the uterus is usually slightly larger than before the most recent pregnancy.

Sonographic Findings

Uterine involution and declining uterine volume is best measured by sonography (Fig. 36-2) (Wataganara, 2015). With

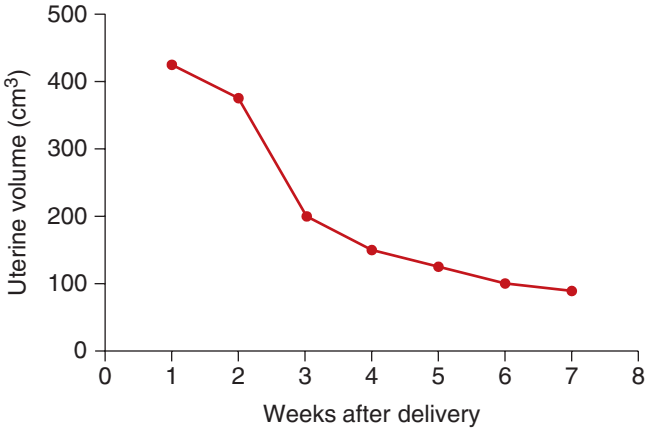


FIGURE 36-2 Pattern of uterine involution through 7 weeks postpartum as estimated by sonography.

this, estimates again show uterine size declines of more than half, from 450 to 200 g, in the first 2 weeks. Sonographically, the uterus and endometrium return to the pregravid size by 8 weeks postpartum. Complete involution in the multiparous uterus is longer than for the nulliparous organ (Paliulyte, 2017). In the event of a cesarean delivery, the residual myometrial thickness over the uterine incision is thicker if a two-layer closure was used (Roberge, 2016).

In a study of 42 normal puerperas, fluid in the endometrial cavity was noted in 78 percent of women at 2 weeks, 52 percent at 3 weeks, 30 percent at 4 weeks, and 10 percent at 5 weeks (Tekay, 1993). Belachew and coworkers (2012) used three-dimensional sonography and visualized intracavitary tissue matter in a third on day 1, 95 percent on day 7, 87 percent on day 14, and 28 percent on day 28. By day 56, the small cavity was empty.

Doppler ultrasound of the uterine artery shows continuously increasing vascular resistance throughout the first 7 weeks postpartum (Sohn, 1988; Wataganara, 2015). Uterine artery flow impedance does not differ between women undergoing vaginal versus cesarean delivery (Baron, 2016).

Decidual and Endometrial Regeneration

Because separation of the placenta and membranes involves the spongy layer, the decidua basalis is not sloughed. The in situ decidua varies markedly in thickness, it has an irregular jagged border, and it is infiltrated with blood, especially at the placental site. Within 2 or 3 days after delivery, the remaining decidua becomes differentiated into two layers. The superficial layer becomes necrotic and is sloughed in the lochia. The basal layer adjacent to the myometrium remains intact and is the source of new endometrium. Decidual vessels are near normal by delivery and endovascular trophoblasts are diminished. These vessels and the spiral arteries also undergo involution (Zhang, 2018).

Endometrial regeneration is rapid, except at the placental site. Within a week or so, the free surface becomes covered by epithelium. Sharman (1953) identified a fully restored endometrium in all biopsy specimens obtained from the 16th day onward. Histological endometritis is part of the normal reparative process. Also, microscopic inflammatory changes characteristic of noninfectious acute salpingitis are seen in almost half of women between 5 and 15 days (Andrews, 1951).

Clinical Aspects

Afterpains. Several clinical findings coincide with uterine involution. In primiparas, the uterus tends to remain tonically contracted following delivery. In multiparas, however, it often contracts vigorously at intervals and gives rise to *afterpains*, which are similar to but milder than labor contractions. These are more pronounced as parity increases and worsen when the newborn suckles, likely because of oxytocin release (Holdcroft, 2003). Usually, afterpains decrease in intensity and become mild by the third day. We have encountered unusually severe and persistent afterpains in women with postpartum uterine infections (Chap. 37, p. 651).

Lochia. Early in the puerperium, sloughing of decidual tissue results in a vaginal discharge of variable quantity. The discharge is termed *lochia* and contains erythrocytes, shredded decidua, epithelial cells, and bacteria. For the first few days after delivery, there is blood sufficient to color it red—*lochia rubra.* After 3 or 4 days, lochia becomes progressively pale in color—*lochia serosa.* After approximately the 10th day, because of an admixture of leukocytes and reduced fluid content, lochia assumes a white or yellow-white color—*lochia alba.* The average duration of lochial discharge ranges from 24 to 36 days (Fletcher, 2012). Because of this expected leukocyte component, saline preparations of lochia for microscopic evaluation in cases of suspected puerperal metritis are typically uninformative.

PLACENTAL SITE INVOLUTION

Complete extrusion of the placental site takes up to 6 weeks (Williams, 1931). Immediately after delivery, the placental site is approximately palm-sized. Within hours of delivery, it normally contains many thrombosed vessels that ultimately undergo organization. By the end of the second week, it measures 3 to 4 cm in diameter.

Placental site involution is an exfoliation process, which is prompted in great part by undermining of the implantation site by new endometrial proliferation (Williams, 1931). Thus, involution is not simply absorption in situ. Exfoliation consists of both extension and "downgrowth" of endometrium from the margins of the placental site, as well as "upward" development of endometrial tissue from the glands and stroma left deep in the decidua basalis after placental separation. Anderson and Davis (1968) concluded that placental site exfoliation results from sloughing of infarcted and necrotic superficial tissues followed by a remodeling process.

Subinvolution

In some cases, uterine involution is hindered because of incompletely remodeled spiral arteries, retained placental fragments, or infection. Such *subinvolution* is accompanied by varied intervals of prolonged lochia and by irregular or excessive uterine bleeding. During bimanual examination, the uterus is larger and softer than would be expected.

Inadequate conversion of spiral arteries into remodeled uteroplacental arteries can cause subinvolution (Kavalar, 2012). These noninvoluted vessels are filled with thromboses and lack an endothelial lining. Perivascular trophoblasts are also identified in the vessel walls, which suggests an aberrant interaction between uterine and trophoblast cells.

With bleeding, pelvic sonography may help differentiate subinvolution from retained placenta. Characteristic findings of retained products include a thickened endometrium or endometrial mass (Fig. 36-3). Vascularity within this area increases the likelihood of retained products (Sellmyer, 2013). Comparatively, subinvolution is characterized by an enlarged uterus with tubular hypoechoic areas in the myometrium. These tubular structures reflect neovascularization and dilated uterine vessels.

For treatment, uterotonics are recommended by many but their efficacy is questionable (Hoyveda, 2001; American College of Obstetricians and Gynecologists, 2017d). At Parkland hospital, conservative management is undertaken with methylergonovine

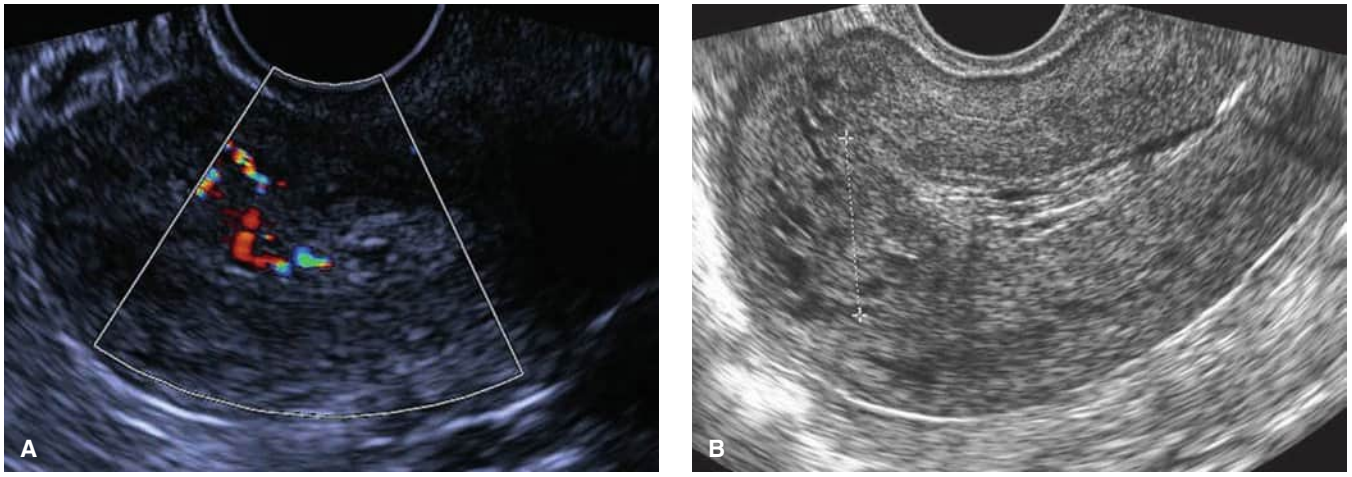


FIGURE 36-3 Sonographic appearance of puerperal uterine complications. **A.** Retained products of conception. Tissue vascularity is highlighted here by color Doppler. **B.** Retained clot marked by calipers shows mixed echogenicity in a woman with subinvolutional hemorrhage. Anechoic cystic areas within the fundal myometrium reflect dilated vessels.

(Methergine) 0.2 mg orally every 3 to 4 hours for 24 to 48 hours. For initially brisk bleeding, an intramuscular dose of methylergonovine may be coupled with an infusion of synthetic oxytocin (Pitocin) (20 units in 1 L crystalloid).

For cases with suspected comorbid infection, antimicrobial therapy usually leads to a good response. Wager and associates (1980) reported that a third of late cases of postpartum metritis are caused by *Chlamydia trachomatis.* Empirical therapy with azithromycin or doxycycline usually prompts resolution regardless of bacterial etiology. At our institution, common oral options taken twice daily for 7 to 10 days include azithromycin, 500 mg; amoxicillin-clavulanate (Augmentin), 875 mg; or doxycycline, 100 mg.

Late Postpartum Hemorrhage

The American College of Obstetricians and Gynecologists (2017d) defines *secondary postpartum hemorrhage* as bleeding 24 hours to 12 weeks after delivery. Clinically worrisome uterine hemorrhage develops within 1 to 2 weeks in perhaps 1 percent of women. Such bleeding most often stems from abnormal involution of the placental site. It occasionally is caused by retention of a placental fragment or by a uterine artery pseudoaneurysm. Rarely, retained products may undergo necrosis with fibrin deposition and neovascularization, thus forming a *placental polypoid mass.* Severe hemorrhage occurs in only 6 percent of these cases due to rupture of blood vessels (Marques, 2011). Sonographically, a discrete hypervascular endometrial mass that may extend into the myometrium is visualized (Fig. 36-4). As discussed in Chapter 59 (p. 1062), delayed postpartum hemorrhage may also be caused by von Willebrand disease or other inherited coagulopathies (Lipe, 2011).

In our experiences, few women with delayed hemorrhage are found to have retained placental fragments. Thus, we and others do not routinely perform curettage (Lee, 1981). Another concern is that curettage may worsen bleeding by avulsing part of the implantation site. Thus, in a stable patient, if sonographic examination shows an empty cavity, then oxytocin, methylergonovine, or a prostaglandin analogue is given. Suitable dosing is found in Table 13-3 (p. 240). Antimicrobials are added if uterine infection is suspected. If large clots are seen in the uterine cavity with sonography, then *gentle* suction curettage is considered. Otherwise, curettage is carried out only if appreciable bleeding persists or recurs after medical management.

URINARY TRACT

Normal pregnancy-induced glomerular hyperfiltration persists during the puerperium but returns to prepregnancy baseline by 2 weeks (Hladunewich, 2004). Parturition induces a transient rise in excretion of glomerular podocytes (Furuta, 2017). Dilated ureters and renal pelves return to their prepregnant state by 2 to 8 weeks postpartum. Because of this dilated collecting system, coupled with residual urine and bacteriuria in a traumatized bladder, symptomatic urinary tract infection remains a concern in the puerperium.

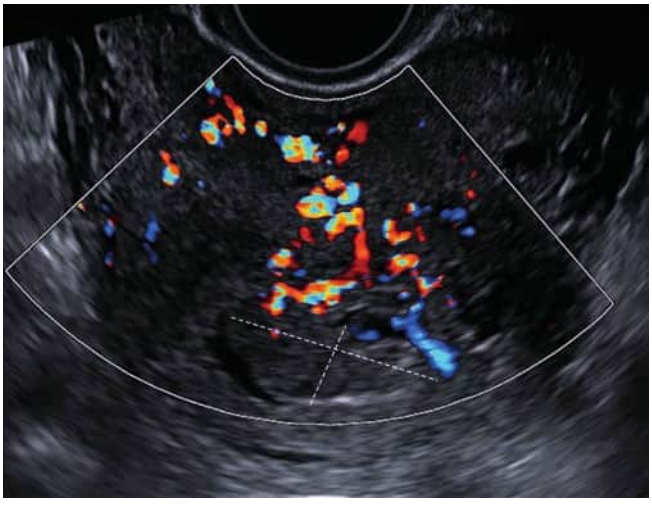


FIGURE 36-4 Sonogram of a polypoid placental mass with color Doppler applied. The mass is demarcated by the dashed white lines. Hypervascularity is seen extending from the mass into the myometrium.

Funnell and colleagues (1954) used cystoscopy immediately postpartum and described varying degrees of submucosal hemorrhage and edema. Bladder trauma is associated most closely with labor length and thus to some degree accompanies normal vaginal delivery. Postpartum, the bladder has a greater capacity and a relative insensitivity to intravesical pressure. Consequently, overdistention, incomplete emptying, and excessive residual urine are frequent (Buchanan, 2014; Mulder, 2014). Acute urinary retention is more common with epidural or narcotic analgesia (Kandadai, 2014). The management of urinary retention is discussed later (p. 643).

Stress urinary incontinence during the puerperium may occur in 5 percent of women (Wang, 2017). Much attention has been given to the potential for subsequent development of urinary incontinence and other pelvic floor disorders in the years following delivery (Colla, 2018). A more detailed discussion is found in Chapter 30 (p. 548).

PERITONEUM AND ABDOMINAL WALL

The broad and round ligaments require considerable time to recover from stretching and loosening during pregnancy. The abdominal wall remains soft and flaccid as a result of ruptured elastic fibers in the skin and prolonged distention by the gravid uterus. If the abdomen is unusually lax or pendulous, an ordinary girdle is often satisfactory. An abdominal binder is another temporary measure. Several weeks are required for these structures to return to normal, and exercise aids recovery. These may be started anytime following vaginal delivery. After cesarean delivery, a 6-week interval to allow anterior abdominal wall fascia to heal and abdominal soreness to diminish is reasonable. Silvery abdominal striae commonly develop as *striae gravidarum* (Chap. 4, p. 55). Except for these, the abdominal wall usually resumes its prepregnancy appearance. When muscles remain atonic, however, the abdominal wall also remains lax.

Marked separation of the rectus abdominis muscles—*diastasis recti*—may result. This separation develops from a gradual thinning and widening of the linea alba and is coupled with a general laxity of the ventral abdominal wall muscles. Importantly, musculofascial continuity and lack of a true hernia sac differentiates this from a ventral hernia (Mommers, 2017).

BLOOD AND BLOOD VOLUME

Hematological and Coagulation Changes

Marked leukocytosis and thrombocytosis may occur during and after labor. The white blood cell count seldom exceeds 25,000/μL, and the rise is predominantly due to granulocytes (Arbib, 2016; Sanci, 2017). A relative lymphopenia and an absolute eosinopenia is typical. Normally, during the first few postpartum days, hemoglobin concentration and hematocrit decrease moderately. If they fall much below prelabor levels, a considerable amount of blood has been lost.

By the end of pregnancy, laboratory values that assess coagulation are altered (Kenny, 2015). These changes are discussed in Chapter 4 (p. 61) and listed in the Appendix (p. 1228). Many extend variably in the puerperium. For example, a markedly higher plasma fibrinogen level is maintained at least through the first week. This contributes to hypercoagulability (Chap. 55, p. 975). As one result, the pregnancy-associated risks for deep-vein thrombosis and pulmonary embolism persist in the 12 weeks following childbirth (Kamel, 2014).

Pregnancy-Induced Hypervolemia

When the amount of blood attained by normal pregnancy hypervolemia is lost as postpartum hemorrhage, the woman almost immediately regains her nonpregnant blood volume (Chap. 42, p. 732). If less has been lost at delivery, blood volume generally nearly returns to its nonpregnant level by 1 week after delivery. Cardiac output usually remains elevated for 24 to 48 hours postpartum and declines to nonpregnant values by 10 days (Robson, 1987). Heart rate changes follow this pattern, and blood pressure similarly returns to nonpregnant values (Fig. 36-5). Correspondingly, systemic vascular resistance remains in the lower range characteristic of pregnancy for 2 days postpartum and then begins to steadily rise to normal nonpregnant values (Hibbard, 2015). Despite this, Morris and coworkers (2015) found that reduced arterial stiffness persists following pregnancy. They suggest a significant favorable effect of pregnancy on maternal cardiovascular remodeling. This may represent a mechanism by which preeclampsia risk is reduced in subsequent pregnancies.

Postpartum Diuresis

Normal pregnancy is associated with appreciable extracellular sodium and water retention, and postpartum diuresis is a physiological reversal of this process. Chesley and associates (1959) demonstrated an approximate 2 liter decline in sodium space during the first week postpartum. This corresponds with loss of residual pregnancy hypervolemia. In preeclampsia, pathological retention of fluid antepartum and then its normal diuresis postpartum may be prodigious (Chap. 41, p. 724).

Postpartum diuresis results in a relatively rapid weight loss of 2 to 3 kg, which is additive to the 5 to 6 kg incurred by delivery and normal blood loss. Weight loss from pregnancy itself likely peaks by the end of the second week postpartum.

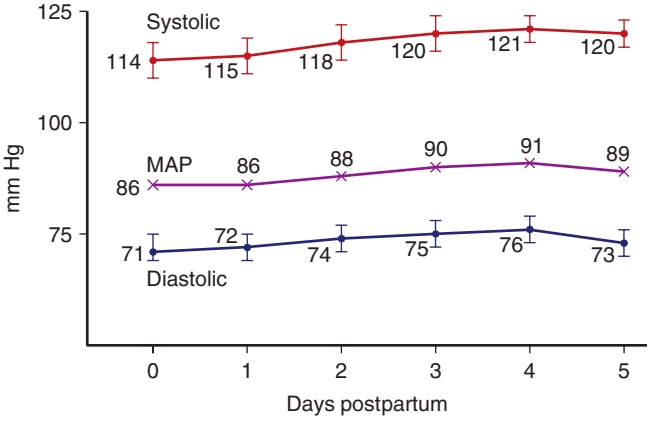


FIGURE 36-5 During the early puerperium, blood pressure normally rises toward nonpregnant values. MAP = mean arterial pressure.

Any residual weight compared with prepregnancy values probably represents fat stores that will persist.

LACTATION AND BREASTFEEDING

Breast Anatomy and Secretory Products

Each mature mammary gland or breast is composed of 15 to 25 lobes. They are arranged radially and are separated from one another by varying amounts of fat. Each lobe consists of several lobules, which in turn are composed of numerous alveoli. Each alveolus is provided with a small duct that joins others to form a single larger duct for each lobe (Fig. 36-6). These *lactiferous ducts* open separately on the nipple, where they may be distinguished as small but distinct orifices. The alveolar secretory epithelium synthesizes the various milk constituents.

After delivery, the breasts begin to secrete *colostrum*, which is a deep-yellow liquid. It usually can be expressed from the nipples by the second postpartum day. Compared with mature milk, colostrum is rich in immunological components and contains more minerals and amino acids (Y de Vries, 2018). It also has more protein, much of which is globulin, but less sugar and fat. Secretion persists for 5 to 14 days, with gradual conversion to mature milk by 4 to 6 weeks. The colostrum content of immunoglobulin A (IgA) offers the newborn protection against enteric pathogens. Other host resistance factors found in colostrum and milk include complement, macrophages, lymphocytes, lactoferrin, lactoperoxidase, and lysozymes.

TABLE 36-3. Average Composition of Human Breast Milk

Fat	g/100 mL
Total	4.2
Fatty acids	Trace
PUFA	0.6
Cholesterol	0.016
Protein	g/100 mL
Total	1.1
Casein	0.3
α-Lactalbumin	0.3
Lactoferrin	0.2
Carbohydrate	g/100 mL
Lactose	7
Oligosaccharides	0.5

PUFA = Polyunsaturated fatty acids.

A lactating mother produces upwards of 600 mL of milk daily, and maternal gestational weight gain has little impact on its quantity or quality. Mature milk is a complex and dynamic biological fluid that includes fat, proteins, carbohydrates, bioactive factors, minerals, vitamins, hormones, and many cellular products (Table 36-3). The contents and concentrations of human milk change even during a single feed and are influenced by maternal diet and by newborn age, health, and needs. Milk is isotonic with plasma, and lactose accounts for half of the osmotic pressure. Essential amino acids are derived from blood, and nonessential amino acids are derived in part from blood or synthesized in the mammary gland. Most milk proteins are unique and include alpha-lactalbumin, beta-lactoglobulin, and casein. Fatty acids are synthesized in the alveoli from glucose and are secreted by an apocrine-like process. Variable amounts of most vitamins are found in human milk. Vitamin K is virtually absent, and thus, an intramuscular dose is given to the newborn (Chap. 33, p. 606). Vitamin D content is low, and newborn supplementation is recommended by the American Academy of Pediatrics and the American College of Obstetricians and Gynecologists (2017).

Whey is milk serum and contains large amounts of interleukin-6 and other chemokines (Polat, 2016). Human milk has a whey-to-casein ratio of 60:40, which is considered ideal for absorption. *Prolactin* appears to be actively secreted into breast milk. *Epidermal growth factor* has been identified, and because it is not destroyed by gastric proteolytic enzymes, it may be absorbed to promote growth and maturation of newborn intestinal mucosa. Other critical components in human milk include melatonin and oligosaccharides.

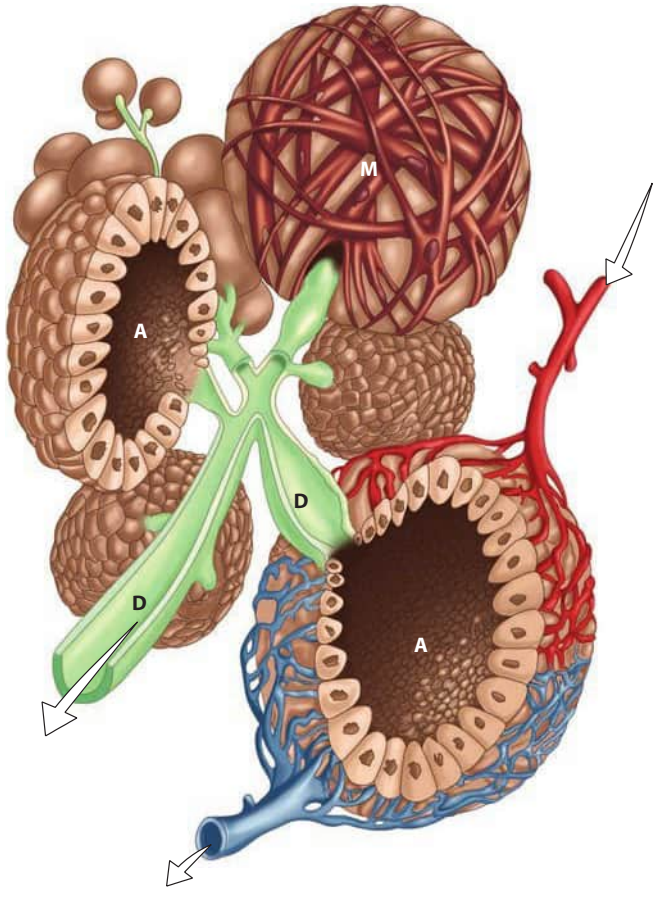


FIGURE 36-6 Schematic of the alveolar and ductal system during lactation. Note the myoepithelial fibers (*M*) that surround the outside of the uppermost alveolus. The secretions from the glandular elements are extruded into the lumen of the alveoli (*A*) and ejected by the myoepithelial cells into the ductal system (*D*), which empties through the nipple. Arterial blood supply to the alveolus is identified by the upper right arrow and venous drainage by the arrow beneath.

Lactation Endocrinology

The precise humoral and neural mechanisms involved in lactation are complex. Progesterone, estrogen, and placental lactogen, as well as prolactin, cortisol, and insulin, appear to act in concert to stimulate the growth and development of the milk-secreting apparatus (Stuebe, 2014). With delivery, the maternal serum levels of progesterone and estrogen decline abruptly and profoundly. This drop removes the inhibitory influence of progesterone on alpha-lactalbumin production and stimulates lactose synthase to raise milk lactose levels. Progesterone withdrawal also allows prolactin to act unopposed in its stimulation of alpha-lactalbumin production. Activation of calcium-sensing receptors in mammary epithelial cells downregulates parathyroid hormone–related protein (PTHrP) and increases calcium transport into milk (Vanhouten, 2013). Serotonin also is produced in mammary epithelial cells and has a role in maintaining milk production (Collier, 2012).

The intensity and duration of subsequent lactation are controlled, in large part, by the repetitive stimulus of suckling and emptying of milk from the breast. Prolactin is essential for lactation, and women with extensive pituitary necrosis—*Sheehan syndrome*—do not lactate (Chap. 61, p. 1104). Although plasma prolactin levels fall after delivery to levels lower than during pregnancy, each act of suckling triggers a rise in levels. Presumably a stimulus from the breast curtails the release of dopamine—also known as *prolactin-inhibiting factor*—from the hypothalamus. In turn, this transiently induces increased prolactin secretion.

The posterior pituitary secretes oxytocin in pulsatile fashion. This stimulates milk expression from a lactating breast by causing contraction of myoepithelial cells in the alveoli and small milk ducts (see Fig. 36-6). Milk ejection, or *letting down*, is a reflex initiated especially by suckling, which stimulates the posterior pituitary to liberate oxytocin. The reflex may even be provoked by an infant cry and can be inhibited by maternal fright or stress (Stuebe, 2014).

Immunological Consequences of Breastfeeding

Human milk contains several protective immunological substances, including secretory IgA and growth factors. The antibodies in human milk are specifically directed against maternal environmental antigens such as *Escherichia coli* (Macpherson, 2017). According to the CDC, breastfeeding decreases the incidence of ear, respiratory, and gastrointestinal infections; necrotizing enterocolitis; and sudden infant death syndrome (SIDS) (Perrine, 2015). Breastfeeding is especially important for immunity in preterm infants (Lewis, 2017).

Much attention has been directed to the role of maternal breast milk lymphocytes in neonatal immunological processes. Milk contains both T and B lymphocytes, but the T lymphocytes appear to differ from those found in blood. Specifically, milk T lymphocytes are almost exclusively composed of cells that exhibit specific membrane antigens. These memory T cells appear to be an avenue for the neonate to benefit from the maternal immunological experience.

TABLE 36-4. Advantages of Breastfeeding

Nutritional
Immunological
Developmental
Psychological
Social
Economic
Environmental
Optimal growth and development
Decrease risks for acute and chronic diseases

Lactation

The ideal time to begin breastfeeding is within an hour of birth. Human milk is ideal food for newborns in that it provides age-specific nutrients, immunological factors, and antibacterial substances. Milk also contains factors that act as biological signals for promoting cellular growth and differentiation. A list of the advantages of breastfeeding is shown in Table 36-4. Lactation has long-term benefits for both the mother and the infant. For example, women who breastfeed have a lower risk of breast and reproductive cancer. Children who were breastfed have higher adult intelligence scores independent of a wide range of possible confounding factors (Jong, 2012; Kramer, 2008). In the short term, lactation is associated with less postpartum weight retention (Baker, 2008). In addition, rates of SIDS are significantly lower among breast-fed infants. Bartek and colleagues (2013) estimate that a 90-percent breastfeeding rate for 12 months would save more than $3 billion annually in excess infant and maternal morbidity costs. For all these reasons, the American Academy of Pediatrics and American College of Obstetricians and Gynecologists (2017) support the World Health Organization (2011) recommendations of exclusive breastfeeding for up to 6 months.

Currently, 55 percent of women breastfeed at 6 months compared with a Healthy People 2020 goal of 61 percent. (American College of Obstetricians and Gynecologists 2018b). The Baby-Friendly Hospital Initiative is an international program to raise rates of exclusive breastfeeding and to extend its duration. It is based on the World Health Organization (2018) *Ten Steps to Successful Breastfeeding* (Table 36-5). Worldwide, almost 20,000 hospitals are deemed "baby-friendly," however, only 15 to 20 percent of hospitals in the United States are so designated (Baby-Friendly USA, 2018; Perrine, 2015). In a large population-based study done in the United States, fewer than two thirds of term neonates were exclusively breastfed at the time of discharge (McDonald, 2012). By 3 months, according to the CDC, less than half of these infants are exclusively breastfed (Olaiya, 2016).

Various individual resources are available online for lactating mothers from the American Academy of Pediatrics (www.aap.org) and La Leche League International (www.llli.org).

Breast Care

The nipples require little attention other than cleanliness and attention to skin fissures. Fissured nipples render lactation

TABLE 36-5. Ten Steps to Successful Breastfeeding

1. Have a written breastfeeding policy that is regularly communicated to all health-care staff
2. Train all staff in skills necessary to implement this policy
3. Inform all pregnant women about the benefits and management of breastfeeding
4. Help mothers initiate breastfeeding within an hour of birth
5. Show mothers how to breastfeed and how to sustain lactation, even if they should be separated from their infants
6. Feed newborns nothing but breast milk, unless medically indicated, and prioritize donor breast milk when supplementation is needed
7. Practice rooming-in, which allows mothers and newborns to remain together 24 hours a day
8. Encourage breastfeeding on demand
9. Give no artificial pacifiers to breastfeeding newborns
10. Help start breastfeeding support groups and refer mothers to them

Adapted from the World Health Organization, 2018.

painful, and they may have a deleterious influence on milk production. These cracks also provide a portal of entry for pyogenic bacteria. Because dried milk is likely to accumulate and irritate the nipples, washing the areola with water and mild soap is helpful before and after nursing. When the nipples are irritated or fissured, some recommend topical lanolin and a nipple shield for 24 hours or longer (Dennis, 2014). If fissuring is severe, the newborn should not be permitted to nurse on the affected side. Instead, the breast is emptied regularly with a pump until the lesions are healed.

Poor latching of the neonate to the breast can create such fissures. For example, the newborn may take into its mouth only the nipple, which is then is forced against the hard palate during suckling. Ideally, the nipple and areola are both taken in to evenly distribute suckling forces. Moreover, the force of the hard palate against the lactiferous sinuses aids their efficient emptying, while the nipple is thereby positioned closer to the soft palate.

Breastfeeding Contraindications

Lactation is contraindicated in women who take street drugs or do not control their alcohol use; have an infant with galactosemia; have human immunodeficiency virus (HIV) infection; have active, untreated tuberculosis; take certain medications; or are undergoing breast cancer treatment (American Academy of Pediatrics, 2017). Breastfeeding has been recognized for some time as a mode of HIV transmission and is proscribed in developed countries in which adequate nutrition is otherwise available (Chap. 68, p. 1222). Other viral infections do not contraindicate lactation. For example, with maternal cytomegalovirus infection, both virus and antibodies are present in breast milk. And, although hepatitis B virus is excreted in milk, breastfeeding is not contraindicated if hepatitis B immune globulin is given to the newborns of affected mothers. Maternal hepatitis C infection is not a contraindication because breastfeeding has not been shown to transmit infection. Women with active herpes simplex virus may suckle their infants if there are no breast lesions and if particular care is directed to hand washing before nursing. From the CDC (2021a), those with COVID-19 should wear a mask and practice hand-hygiene.

Drugs Secreted in Milk

Most drugs given to the mother are secreted in breast milk, although the amount ingested by the infant typically is small. Factors influencing drug excretion include plasma concentration, degree of protein binding, plasma and milk pH, degree of ionization, lipid solubility, and molecular weight (Rowe, 2013). The ratio of drug concentration in breast milk to that in maternal plasma is the *milk-to-plasma drug-concentration ratio.* Ideally, to minimize infant exposure, medication selection favors drugs with a shorter half-life, poorer oral absorption, and lower lipid solubility. If multiple daily drug doses are required, each is taken by the mother *after* the closest feed. Single daily-dosed drugs may be taken just before the longest infant sleep interval—usually at bedtime.

Only a few drugs are absolutely contraindicated while breastfeeding (American Academy of Pediatrics and American College of Obstetricians and Gynecologists, 2017). Cytotoxic drugs may interfere with cellular metabolism and potentially cause immune suppression or neutropenia, affect growth, and at least theoretically, increase the childhood cancer risk. Examples include cyclophosphamide, cyclosporine, doxorubicin, methotrexate, and mycophenolate (Briggs, 2017). If a medication presents a concern, its importance should be ascertained. A provider can also seek a safer alternative or determine if neonatal exposure can be minimized if the medication dose is taken immediately after each breastfeeding session. Last, recreational drugs such as marijuana and alcohol should be avoided (American College of Obstetricians and Gynecologists, 2017c; Metz, 2018). Data on individual drugs are available through the National Institutes of Health website, LactMed, which can be found at www.ncbi.nlm.nih.gov/books/NBK501922/.

Radioactive isotopes of copper, gallium, indium, iodine, sodium, and technetium rapidly appear in breast milk. Consultation with a nuclear medicine specialist is recommended before performing a diagnostic study with these isotopes (Chap. 49, p. 875). Ideally, a radionuclide with the shortest excretion time in breast milk is selected. The mother should pump her breasts before the study and store enough milk in a freezer to feed the infant. After the study, she should pump her breasts to maintain milk production but discard all milk produced during

the time that radioactivity is present. This ranges from 15 hours to 2 weeks, depending on the isotope used. Importantly, radioactive iodine concentrates and persists in the thyroid. Its special considerations are discussed in Chapter 66 (p. 1174). For magnetic resonance (MR) imaging, breastfeeding should not be interrupted after gadolinium administration (American College of Obstetricians and Gynecologists, 2017a).

Breast Engorgement

This is common in women who do not breastfeed. It is typified by milk leakage and breast pain, which peak 3 to 5 days after delivery. Up to half of affected women require analgesia for breast pain relief, and as many as 10 percent report severe pain for up to 14 days.

Evidence is insufficient to firmly support any specific treatment (Mangesi, 2016). That said, breasts can be supported with a well-fitting brassiere, breast binder, or sports bra. Cool packs and oral analgesics for 12 to 24 hours aid discomfort. Pharmacological or hormonal agents in general are not recommended to suppress lactation.

Fever caused by breast engorgement was common before the renaissance of breastfeeding. In one study, 13 percent of puerperas with engorgement had fever ranging from 37.8 to 39°C (Almeida, 1986). Fever seldom persists for longer than 4 to 16 hours. The incidence and severity of engorgement and of the fever associated with it are much lower if women breastfeed. Other causes of fever, especially those due to infection, must be excluded. *Mastitis* is infection of the mammary parenchyma and is relatively common in lactating women (Chap. 37, p. 659).

Other Lactation Issues

With *inverted nipples*, lactiferous ducts open directly into a depression at the center of the areola. With these depressed nipples, nursing is difficult. If the depression is not deep, milk sometimes can be drawn out by a breast pump. If instead the nipple is greatly inverted, daily attempts are made during the last few months of pregnancy to draw or "tease" the nipple out with the fingers.

Extra breasts—*polymastia*, or extra nipples—*polythelia*, may develop along the former embryonic mammary ridge. Also termed the *milk line*, this line extends from the axilla to the groin bilaterally. In some women, rests of accessory breast tissue can be found in the mons pubis or vulva (Wagner, 2013). In the general population, the incidence of accessory breast tissue ranges from 0.22 to 6 percent (Loukas, 2007). These breasts may be so small as to be mistaken for pigmented moles, or if without a nipple, for lymphadenopathy or lipoma. Polymastia has no obstetrical significance, although occasionally enlargement of these accessory breasts during pregnancy or engorgement postpartum may result in patient discomfort and anxiety.

Galactocele is a milk duct that becomes obstructed by inspissated secretions. The amount is ordinarily limited, but an excess may form a fluctuant mass—a galactocele—that can cause pressure symptoms and have the appearance of an abscess. It may resolve spontaneously or require aspiration.

Among individuals, the volume of milk secreted varies markedly. This depends not on general maternal health but on breast glandular development. Rarely, there is complete lack of mammary secretion—*agalactia*. Occasionally, mammary secretion is excessive—*polygalactia*.

Lactation-Associated Osteoporosis

This is a rare disorder of unknown etiology that may be associated with severe back pain or vertebral fractures (Li, 2018; Zhang, 2017). Preliminary studies indicate that bisphosphonates are effective in its management. However, for almost all women, lactation is not associated with later-onset osteoporosis (Crandall, 2017). Pregnancy-associated osteoporosis is discussed in Chapter 61 (p. 1100).

HOSPITAL CARE

For 2 hours after delivery, blood pressure and pulse are taken every 15 minutes, at minimum. Temperature is assessed every 4 hours for the first 8 hours and then at least every 8 hours subsequently (American Academy of Pediatrics and American College of Obstetricians and Gynecologists, 2017). If regional analgesia or general anesthesia was used for labor or delivery, the mother should be observed in an appropriately equipped and staffed recovery area. Expected anesthesia recovery and complications are described in Chapter 25 (p. 473).

Because the likelihood of significant hemorrhage is greatest immediately postpartum, vaginal bleeding is closely monitored. The uterine fundus is palpated to ensure that it is well contracted. If relaxation is detected, the uterus should be massaged through the abdominal wall until it remains contracted. Uterotonics also are sometimes required. Blood may accumulate within the uterus without external bleeding. This may be detected early by uterine enlargement during fundal palpation in the first postdelivery hours. Postpartum hemorrhage is discussed in Chapter 41.

Early ambulation within a few hours after delivery is encouraged. An attendant should be present for at least the first time, in case the woman becomes syncopal. The many confirmed advantages of early ambulation include fewer bladder complications, less frequent constipation, and reduced rates of puerperal venous thromboembolism. As discussed, deep-vein thrombosis and pulmonary embolism are common in the puerperium. In our audits of puerperal women at Parkland Hospital, the frequency of venous thromboembolism is extremely low. We attribute this to early ambulation. Risk factors and other measures to diminish the frequency of thromboembolism are discussed in Chapter 55 (p. 984).

Diets need not be restricted for women who give birth vaginally. Generally, two hours after uncomplicated vaginal delivery, a woman is allowed to eat. With lactation, the level of calories and protein consumed during pregnancy is increased slightly as recommended by the Food and Nutrition Board of the National Research Council (Chap. 10, p. 184). If the mother does not breastfeed, dietary requirements are the same as for a nonpregnant woman. We recommend oral iron supplementation for at least 3 months after delivery and hematocrit evaluation at the first postpartum visit.

As noted earlier, profound drops in estrogen levels follow removal of the placenta. Reminiscent of the menopause,

postpartum women may experience hot flushes, especially at night. Importantly, the patient's temperature is assessed to differentiate these physiological vasomotor events from infection.

In women with migraines, dramatic hypoestrogenism may trigger headaches. Importantly, severe headaches should be differentiated from postdural puncture headache or hypertensive complications. Care varies depending on headache severity. Mild headaches may respond to analgesics such as ibuprofen or acetaminophen. For more severe headaches, oral or systemic narcotics can be used. Alternatively, a triptan, such as sumatriptan (Imitrex), can relieve headaches by causing intracranial vasoconstriction, and it is breastfeeding compatible.

Perineal Care

The woman is instructed to clean the vulva from anterior to posterior—the vulva toward the anus. A cool pack applied to the perineum may help reduce edema and discomfort during the first 24 hours if there is a perineal laceration or an episiotomy. Most women also appear to obtain a measure of relief from the periodic application of a local anesthetic spray. *Severe perineal, vaginal, or rectal pain always warrants careful inspection and palpation.* Severe discomfort usually indicates a problem, such as a hematoma within the first day or so and infection after the third or fourth day (Chap. 37, p. 657 and Chap. 42, p. 740). Beginning approximately 24 hours after delivery, moist heat as provided by warm sitz baths can reduce local discomfort. Tub bathing after uncomplicated delivery is allowed. The episiotomy incision normally is firmly healed and nearly asymptomatic by the third week.

Rarely, the cervix, and occasionally a portion of the uterine body, may protrude from the vulva following delivery. This is accompanied by variable degrees of anterior and posterior vaginal wall prolapse. Symptoms include a palpable mass at or past the introitus, voiding difficulties, or pressure. Puerperal procidentia typically improves with time as the weight of the uterus lessens with involution. As a temporizing measure for pronounced prolapse, the uterus can be replaced and held in position with a space-filling pessary, such as a donut type.

Rectal veins are often congested at term. Thrombosis of these hemorrhoids is common and may be promoted by second-stage pushing. Treatment includes topically applied anesthetics, warm soaks, and stool-softening agents. Nonprescription topical preparations containing corticosteroids, astringents, or phenylephrine are often used. However, no randomized studies support their efficacy compared with symptomatic care.

Bladder Function

In most delivery units, intravenous fluids are infused during labor and for an hour or so after vaginal delivery. Oxytocin, in doses that have an antidiuretic effect, is typically infused postpartum, and rapid bladder filling is common. Moreover, both bladder sensation and capability to empty spontaneously may be diminished by components of the labor and delivery process. Thus, urinary retention and bladder overdistention is common in the early puerperium. The incidence in more than 5500 women studied with a bladder scanner was 5 percent (Buchanan, 2014). It is much less clinically. Risk factors that increased the likelihood of retention include primiparity, epidural analgesia, cesarean delivery, perineal lacerations, operative vaginal delivery, catheterization during labor, and prolonged second-stage labor (Stephansson, 2016; Wang, 2017).

Prevention of bladder overdistention demands observation after delivery to ensure that the bladder does not overfill and that it empties adequately with each voiding. The enlarged bladder can be palpated suprapubically, or it is evident abdominally indirectly as it elevates the fundus above the umbilicus. Most currently use an automated sonography system to detect high bladder volumes and thus postpartum urinary retention (Buchanan, 2014).

If a woman has not voided within 4 hours after delivery, it is likely that she cannot. If she has trouble voiding initially, she also is likely to have further trouble. First, an examination for perineal and genital-tract hematomas is completed, as these may be contributory. With an overdistended bladder, an indwelling catheter should be placed and left until the factors causing retention have abated. Even without a demonstrable cause, it usually is best to leave the catheter in place for at least 24 hours. This prevents recurrence and allows recovery of normal bladder tone and sensation.

When the catheter is removed, a voiding trial is completed to demonstrate an ability to void appropriately. If a woman cannot void after 4 hours, urine volumes are measured sonographically. If more than 200 mL, the bladder is not functioning appropriately, and the catheter is replaced and remains for another 24 hours. Although rare, if retention persists after a second voiding trial, an indwelling catheter and leg bag can be elected, and the patient returns in 1 week for an outpatient voiding trial. In a study of 27 women with a protracted course, all resumed normal voiding by 3 weeks postpartum (Mevorach Zussman, 2020).

During a voiding trial, if less than 200 mL of urine is obtained, the catheter can be removed and the bladder subsequently monitored clinically and sonographically as described earlier. Harris and coworkers (1977) reported that 40 percent of such women develop bacteriuria, and thus a single dose or short course of antimicrobial therapy against uropathogens is reasonable after the catheter is removed.

Pain, Mood, and Cognition

Discomfort and its causes following cesarean delivery are considered in Chapter 30 (p. 565). During the first few days after vaginal delivery, the mother may be uncomfortable because of afterpains, episiotomy and lacerations, breast engorgement, and at times, postdural puncture headache. Mild analgesics containing codeine, ibuprofen, or acetaminophen, preferably in combinations, are given as frequently as every 4 hours during the first few days.

It is important to screen the postpartum woman for depression (Mangla, 2019). Commonly, mothers exhibit some degree of depressed mood a few days after delivery. Termed *postpartum blues,* this likely is the consequence of several factors. These include the emotional letdown that follows the excitement and fears experienced during pregnancy and delivery, discomforts of the early puerperium, fatigue from sleep deprivation, anxiety over the ability to provide appropriate newborn care, and

body image concerns. In most women, effective treatment includes anticipation, recognition, and reassurance. This disorder is usually mild and self-limited to 2 to 3 days, although it sometimes lasts for up to 10 days. Should these moods persist or worsen, an evaluation for symptoms of major depression is done (Chap. 64, p. 1145).

Last, postpartum hormonal changes in some women may affect brain function. Bannbers and colleagues (2013) observed a functional decline in executive function in postpartum women.

Neuromusculoskeletal Problems

Obstetrical Neuropathies

Pressure on branches of the lumbosacral nerve plexus during labor may manifest as complaints of intense neuralgia or cramplike pains extending down one or both legs as soon as the head descends into the pelvis. If the nerve is injured, pain may continue after delivery, and variable degrees of sensory loss or muscle paralysis can result. In some cases, there is footdrop, which can be secondary to injury at the level of the lumbosacral plexus, sciatic nerve, or common fibular (peroneal) nerve (Bunch, 2014). Components of the lumbosacral plexus cross the pelvic brim and can be compressed by the fetal head or by forceps. The common fibular nerves may be externally compressed when the legs are positioned in stirrups, especially during prolonged second-stage labor.

Obstetrical neuropathy is relatively infrequent. Evaluation of more than 6000 puerperas found that approximately 1 percent had a confirmed nerve injury (Wong, 2003). Lateral femoral cutaneous neuropathies were the most common (24 percent), followed by femoral neuropathies (14 percent). A motor deficit accompanied a third of injuries. Nulliparity, prolonged second-stage labor, and pushing for a long duration in the semi-Fowler position were risk factors. The median duration of symptoms was 2 months, and the range was 2 weeks to 18 months.

Injury of the iliohypogastric and ilioinguinal nerves may occur with cesarean delivery (Rahn, 2010; Yazici Yilmaz, 2018). We have rarely encountered lumbar arachnoiditis following epidural analgesia causing severe bilateral neuropathic pain.

Musculoskeletal Injuries

Pain in the pelvic girdle, hips, or lower extremities may follow stretching or tearing injuries sustained at normal or difficult delivery. MR imaging is often informative when clinical examination is normal (Miller, 2015). Most injuries resolve with antiinflammatory agents and physical therapy. Rarely, there may be septic pyomyositis such as with iliopsoas muscle abscess (Nelson, 2010; Young, 2010).

Separation of the symphysis pubis or one of the sacroiliac synchondroses during labor leads to pain and marked interference with locomotion (Fig. 36-7). Estimates of the frequency of this event vary widely from 1 in 600 to 1 in 30,000 deliveries (Reis, 1932; Taylor, 1986). In our experiences, symptomatic separations are uncommon. Their onset of pain is often acute during delivery, but symptoms may manifest either antepartum or up to 48 hours postpartum (Snow, 1997). Radiography is typically used for evaluation. The normal distance of the symphyseal joint is 0.4 to 0.5 cm, and symphyseal separation >1 cm is diagnostic for diastasis. Treatment is generally conservative, with rest in a lateral decubitus position and an appropriately fitted pelvic binder (Lasbleiz, 2017). Surgery is occasionally necessary in some symphyseal separations >4 cm (Kharrazi, 1997). The recurrence risk is high in subsequent pregnancies, and Culligan and associates (2002) recommend consideration for cesarean delivery.

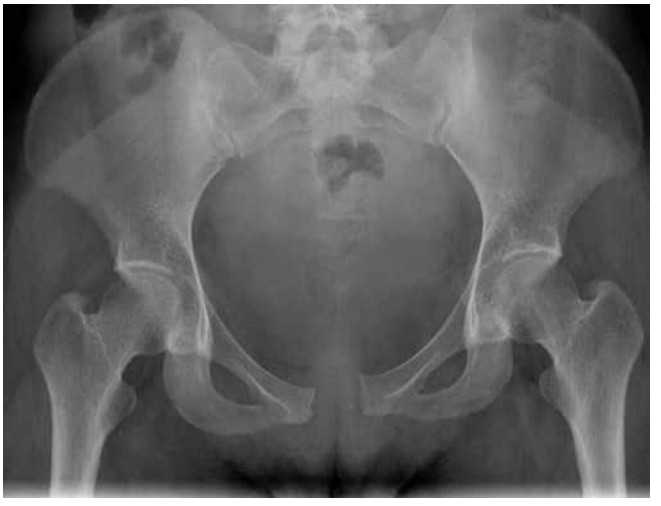


FIGURE 36-7 Pubic symphyseal separation found on the first postpartum day following vaginal delivery of a 2840-g newborn. The patient had pain over the pubic bone and pain with ambulation. A shuffling gait was noted, and she had difficulty with leg elevation when supine. The patient was treated with physical therapy and analgesics. A pelvic binder was applied, and a rolling walker was provided. She improved quickly and was discharged home on postpartum day 5.

In rare cases, fractures of the sacrum or pubic ramus are caused by even uncomplicated deliveries (Alonso-Burgos, 2007; Speziali, 2015). Discussed in Chapter 61 (p. 1100), the latter is more likely with osteoporosis associated with heparin or corticosteroid therapy. In rare but serious cases, bacterial osteomyelitis—*osteitis pubis*—can be devastating. Lawford and coworkers (2010) reported such a case that caused massive vulvar edema.

Immunizations

The D-negative woman who is not isoimmunized and whose newborn is D-positive is given 300 μg of anti-D immune globulin shortly after delivery (Chap. 18, p. 357). Women who are not already immune to rubella or varicella are excellent candidates for vaccination before discharge (Swamy, 2015). Those who have not received a tetanus/diphtheria (Tdap/Td) or influenza vaccine should be given these (American College of Obstetricians and Gynecologists, 2017e) (Table 10-7, p. 189). The CDC (2021b) recommends the COVID-19 vaccine, and includes breastfeeding women. Morgan and colleagues (2015) reported that implementation of a best-practices alert in the electronic medical record was associated with a Tdap immunization rate of 97 percent at Parkland Hospital. When permissible by law, the American College of Obstetricians and Gynecologists (2019) recommends standing orders for indicated immunizations.

Contraception

During the hospital stay, a concerted effort is made to provide family planning education. Various forms of contraception are discussed throughout Chapter 38 and sterilization procedures in Chapter 39. The immediate puerperium is an ideal time for consideration of long-acting reversible contraception—LARC (American College of Obstetricians and Gynecologists, 2017b).

Women not breastfeeding have return of menses usually within 6 to 8 weeks. At times, however, it is difficult clinically to assign a specific date to the first menstrual period after delivery. A minority of women bleed small to moderate amounts intermittently starting soon after delivery. Ovulation occurs at a mean of 7 weeks but ranges from 5 to 11 weeks (Perez, 1972). That said, ovulation before 28 days has been described (Hytten, 1995). Thus, conception is possible during the early puerperium. *Women who become sexually active during the puerperium and who do not desire to conceive should initiate contraception.* Kelly and associates (2005) reported that by the third month postpartum, 58 percent of adolescents had resumed sexual intercourse, but only 80 percent of these were using contraception. Because of this, many recommend LARC during the puerperium.

Women who breastfeed ovulate much less frequently compared with those who do not, but variation is great. Timing of ovulation depends on individual biological variation and the intensity of breastfeeding. Lactating women may first menstruate as early as the second or as late as the 18th month after delivery. Campbell and Gray (1993) analyzed daily urine specimens in 92 lactating women. Breastfeeding in general delays resumption of ovulation, although it does not invariably forestall it. Other findings in their study included the following:

1. Resumption of ovulation was frequently marked by return of normal menstrual bleeding.
2. Breastfeeding episodes lasting 15 minutes seven times daily delayed ovulation resumption.
3. Ovulation can occur without bleeding.
4. Bleeding can be anovulatory.
5. The risk of pregnancy in breastfeeding women was approximately 4 percent per year.

For the breastfeeding woman, progestin-only contraceptives, such as progestin pills, depot medroxyprogesterone, or progestin implants or IUDs, do not affect the quality or quantity of milk. Not available in the United States, success with the progesterone-releasing vaginal ring also has been described (Carr, 2016). These may be initiated any time during the puerperium. Estrogen-progestin contraceptives likely reduce the quantity of breast milk, but under the proper circumstances, they too can be used by lactating women. These hormonal methods are discussed in Chapter 38 (p. 671).

Hospital Discharge

Following uncomplicated vaginal delivery, hospitalization is seldom warranted for more than 48 hours. Hospital stay length following labor and delivery is now regulated by federal law (Chap. 32, p. 596). Currently, the norms are hospital stays up to 48 hours following uncomplicated vaginal delivery and up to 96 hours following uncomplicated cesarean delivery (American Academy of Pediatrics and American College of Obstetricians and Gynecologists, 2017; Blumenfield, 2015). Earlier hospital discharge is acceptable for appropriately selected women if they desire it. A woman should receive instructions concerning anticipated normal physiological puerperal changes, including lochia patterns, weight loss from diuresis, and milk let-down. She also should receive instructions concerning fever, excessive vaginal bleeding, or leg pain, swelling, or tenderness. Persistent headaches, shortness of breath, or chest pain warrant immediate concern.

HOME CARE

Coitus

No evidence-based data guide resumption of coitus after delivery, and practices are individualized (Minig, 2009). After 2 weeks, coitus may be resumed *based on desire and comfort.* Wallwiener and colleagues (2017) reported that 60 percent of women resumed sexual activity by 1 week and 80 percent by 4 months. They also reported that a third of these women had sexual dysfunction.

Intercourse too soon may be unpleasant, if not painful, and this may be related to episiotomy incisions or perineal lacerations. In a study of women without an episiotomy, only 0.4 percent of those with a first- or second-degree tear had dyspareunia (Ventolini, 2014). Conversely, in primiparas with an episiotomy, 67 percent had sexual dysfunction at 3 months, 31 percent at 6 months, and 15 percent at 12 months (Chayachinda, 2015). Only 40 percent of women with an anal sphincter injury had resumed intercourse by 12 weeks (Leader-Cramer, 2016). Last, dyspareunia was also common following cesarean delivery (McDonald, 2015).

Postpartum, the vulvovaginal epithelium is thin, and very little lubrication follows sexual stimulation. This stems from the hypoestrogenic state following delivery, which lasts until ovulation resumes. It may be particularly problematic in breastfeeding women who are hypoestrogenic for many months postpartum (Palmer, 2003). For treatment, small amounts of topical estrogen cream can be applied daily for several weeks to vulvar tissues. Additionally, vaginal lubricants may be used with coitus.

This same thinning of the vulvovaginal epithelium can lead to dysuria. Topical estrogen can again be offered once cystitis is excluded.

Follow-Up Care

By discharge, women who had an uncomplicated vaginal delivery can resume most activities, including bathing, driving, and household functions. Despite this, Tulman and Fawcett (1988) reported that only half of mothers regained their usual level of energy by 6 weeks. Women who delivered vaginally were twice as likely to have normal energy levels at this time compared with those with a cesarean delivery. Ideally, the care and nurturing of the infant should be provided by the mother with ample help from the father. Jimenez and Newton (1979) tabulated cross-cultural information on 202 societies from various international geographical regions. Following childbirth, most

societies did not restrict work activity, and approximately half expected a return to full duties within 2 weeks. Wallace and coworkers (2013) reported that 80 percent of women who worked during pregnancy resume work by 1 year after delivery.

Discussed on page 634, during this fourth trimester, the American College of Obstetricians and Gynecologists (2018a) recommends a comprehensive visit within 12 weeks after delivery. This has proved quite satisfactory to identify abnormalities beyond the immediate puerperium and to initiate contraceptive practices.

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CHAPTER 37

Puerperal Infection

Women are susceptible to several potentially serious complications during the fourth trimester. Many of these conditions are encountered during pregnancy, and others are unique to the puerperium. Historically, infection was the most important source of postpartum maternal morbidity and mortality, since emphasized by the studies of Semmelweis and Lister (Kadar, 2021). Puerperal infections include pelvic infections, mastitis, and breast abscesses. Discussed in their respective chapters, cardiovascular disease (Chap. 52, p. 915), venous thromboembolism (Chap. 55, p. 980), and hemorrhage (Chap. 42, p. 731) currently are leading noninfectious puerperal complications (Callaghan, 2012; Creanga, 2017). However, the incidence of postpartum hospitalization due to sepsis is rising. Other puerperal issues and their management are discussed in Chapter 36.

PUERPERAL PELVIC INFECTIONS

Traditionally, the term *puerperal infection* describes any bacterial infection of the genital tract after delivery. Infection, preeclampsia, and obstetrical hemorrhage formed the lethal triad of maternal death causes before and during the 20th century. Fortunately, maternal mortality from puerperal infection is uncommon because of effective antibiotics. Creanga and associates (2017) reported results from the Pregnancy Mortality Surveillance System, which contained 4693 pregnancy-related maternal deaths in the United States from 2006 through 2010. Infection caused 13.6 percent of the deaths and was the second leading etiology. In an analysis of the North Carolina population, Berg and colleagues (2005) reported that 40 percent of infection-related maternal deaths were preventable.

Puerperal Fever

Several infective and noninfective factors cause *puerperal fever* defined by a temperature of 38.0°C (100.4°F) or higher. Using this conservative definition, Filker and Monif (1979) reported that only approximately 20 percent of women febrile within the first 24 hours after vaginal delivery were subsequently diagnosed with pelvic infection. This value was 70 percent in those undergoing cesarean delivery. *Most persistent fevers after childbirth are caused by genital tract infection.* Of note, spiking fevers ≥39°C within the first 24 hours postpartum may be associated with virulent pelvic infection caused by group A streptococcus (p. 651).

Other sources of puerperal fever include breast engorgement, urinary infections, episiotomy and abdominal incisions, perineal lacerations, and postcesarean respiratory complications. Approximately 15 percent of women who do not breastfeed develop fever from *breast engorgement*. "Breast fever" rarely exceeds 39°C in the first few postpartum days and usually lasts <24 hours. The incidence of fever is lower in breastfeeding women (Chap. 36, p. 642). Postpartum *urinary infections* are

uncommon because of the normal diuresis. *Acute pyelonephritis* has a variable clinical picture. The first sign of renal infection may be fever, followed later by costovertebral angle tenderness, nausea, and vomiting. *Atelectasis* following general anesthesia for cesarean delivery is caused by hypoventilation and is best prevented by coughing and deep breathing on a fixed schedule following surgery. Fever with atelectasis is due to infection triggered by proliferation of normal flora distal to obstructing mucus plugs.

Uterine Infection

Postpartum uterine infection has been called *endometritis*, *endomyometritis*, and *endoparametritis.* Following vaginal delivery, infection involves not only the decidua but also the myometrium and parametrial tissues. Infection after cesarean delivery is essentially a surgical site infection involving the incised myometrium. In either case, we prefer the inclusive term *metritis with pelvic cellulitis*.

Predisposing Factors

Route of delivery is the single most significant risk factor for the development of uterine infection (Boggess, 2017; Moulton, 2018). In women undergoing cesarean delivery, rehospitalization rates for wound complications and metritis are higher than those with a vaginal birth (Axelsson, 2018; Fein, 2019). In the French Confidential Enquiry on Maternal Deaths, Deneux-Tharaux and coworkers (2006) cited a nearly 25-fold greater infection-related mortality rate with cesarean delivery.

With vaginal delivery, women delivered at Parkland Hospital have a 1- to 2-percent incidence of metritis. This rate rises to 5 to 6 percent in those with ruptured membranes, prolonged labor, and multiple cervical examinations. If intrapartum chorioamnionitis is present, the risk of persistent uterine infection has exceeded 13 percent (DeNoble, 2019; Maberry, 1991). These figures are similar to those reported by the Maternal Fetal Medicine Units Network from a cohort of more than 115,000 women in whom the overall pelvic infection rate approximated 5 percent (Grobman, 2015).

With operative vaginal delivery, women carry higher risks for metritis and perineal infections than spontaneous birth (Mohamed-Ahmed, 2019). Notably, these deliveries are often implemented in the context of prolonged labor, which is a known metritis risk. One study of 3500 such women showed that those receiving a single dose of prophylactic antibiotics had a lower maternal infection rate (Knight, 2019). Infections include those of the urinary tract, uterus, or perineal wound. Labor lengths were not presented, but in approximately 50 percent of participants, "failure to progress" was the operative vaginal delivery indication. Moreover, 10 percent of women had rupture of membranes lengths between 24 and 48 hours. The contribution of these, rather than the delivery mode, will require further investigation before this prophylaxis is widely adopted solely for the indication of operative vaginal delivery.

With cesarean delivery, hysterotomy is associated with significant infectious morbidity. In the 1970s, pelvic infection complicated 50 percent of cesarean deliveries at Parkland Hospital. Fortunately, antimicrobial prophylaxis has done more to decrease the incidence and severity of postcesarean infections than any other intervention in the past 30 years. Thus, a single dose of perioperative antibiotics is recommended for all women undergoing cesarean delivery (American College of Obstetricians and Gynecologists, 2018b). Such practices lower the puerperal pelvic infection risk by 65 to 75 percent (Smaill, 2014). β-lactam antimicrobials are superior to other agents, and elements of this prophylaxis are outlined in Chapter 30 (p. 551) (Harris, 2019). Important risk factors for infection following surgery include prolonged labor, membrane rupture, multiple cervical examinations, and internal fetal monitoring.

Regardless of delivery route, pelvic infection generally is more frequent in women of lower socioeconomic status (Maharaj, 2007). Except in extreme cases usually not seen in developed countries, it is uncommon that anemia or poor nutrition predispose to infection. *Bacterial colonization* of the lower genital tract with certain microorganisms—for example, group B streptococcus, *Chlamydia trachomatis*, *Mycoplasma hominis*, *Ureaplasma urealyticum*, and *Gardnerella vaginalis*—has been associated with an increased postpartum infection risk (Andrews, 1995; Jacobsson, 2002; Watts, 1990). Other factors associated with a greater risk include general anesthesia, significant hysterotomy extension, young maternal age, nulliparity, prolonged labor induction, chorioamnionitis, obesity, and meconium-stained amnionic fluid (Acosta, 2012; Leth, 2011; Patel, 2019; Siriwachirachai, 2014).

Microbiology

Common Pathogens. Most pelvic infections are caused by bacteria indigenous to the genital tract and listed in Table 37-1. Most of these infections are polymicrobial, which enhances bacterial synergy. Other factors that promote virulence are hematomas and devitalized tissue. Although the cervix and vagina routinely harbor bacteria, the uterine cavity is usually sterile before rupture of the amnionic sac. As the consequence of labor and delivery and associated manipulations, anaerobic and aerobic bacteria contaminate the amnionic fluid and uterus.

TABLE 37-1. Bacteria Commonly Responsible for Female Genital Infections

Aerobes

Gram-positive cocci: group A, B, and D streptococci, enterococcus, *Staphylococcus aureus*, *Staphylococcus epidermidis*

Gram-negative bacteria: *Escherichia coli*, *Klebsiella*, *Proteus* spp.

Gram-variable—*Gardnerella vaginalis*

Others

Mycoplasma spp., *Chlamydia trachomatis*, *Neisseria gonorrhoeae*

Anaerobes

Cocci: *Peptostreptococcus*, *Peptococcus* spp.

Others: *Clostridium*, *Bacteroides*, *Fusobacterium*, *Mobiluncus* spp.

Prior to the routine use of antimicrobial prophylaxis, Gilstrap and Cunningham (1979) cultured amnionic fluid obtained at cesarean delivery from women in labor with membranes ruptured more than 6 hours. All had bacterial growth, and an average of 2.5 organisms was identified from each specimen. Anaerobic and aerobic organisms were found in 63 percent, anaerobes alone in 30 percent, and aerobes alone in only 7 percent. Anaerobes included *Peptostreptococcus* and *Peptococcus* species in 45 percent, *Bacteroides* species in 9 percent, and *Clostridium* species in 3 percent. Clostridial species rarely cause puerperal infections, but infections can be severe in those cases (Herrera, 2016). Aerobes included *Enterococcus* in 14 percent, group B *Streptococcus* in 8 percent, and *Escherichia coli* in 9 percent of isolates. Sherman and associates (1999) later showed that bacterial isolates at cesarean delivery correlated with those taken from women with metritis at 3 days postpartum. Group B streptococci, *E coli*, and enterococci are some of the more common blood culture isolates with metritis (Cape, 2013; O'Higgins, 2014). In the past 15 years, skin and soft-tissue infections due to methicillin-resistant *Staphylococcus aureus* (*MRSA*) have become prevalent (Chap. 67, p. 1196). However, *MRSA* is more commonly implicated in abdominal and perineal incisional infections and less often in puerperal metritis (Anderson, 2007; Patel, 2007).

Group A β-hemolytic streptococcal infections have a reported incidence of 1 in 1220 births (Rottenstreich, 2019). During the past 25 years, group A streptococcus has been reported to cause a toxic shock–like syndrome and life-threatening infection (Donders, 2021; Gustafson, 2017; Shinar, 2016). In reviews by Crum (2002) and Udagawa (1999), group A streptococcal infections manifested before, during, or within 12 hours of delivery. Affected women had a maternal mortality rate of almost 90 percent, and the fetal mortality rate exceeded 50 percent.

The role of other organisms in the etiology of these infections is unclear. Observations of Chaim and coworkers (2003) suggest that heavy cervical colonization of *U urealyticum* may contribute to metritis development. To counter this potential pathogen, azithromycin-based extended-spectrum antibiotic prophylaxis reduces postoperative cesarean delivery infections from 12 to 6 percent compared with β-lactam agents alone (Harper, 2017; Tita, 2016). Chlamydial infections have been implicated in late-onset, indolent metritis (Ismail, 1985). Last, Jacobsson and colleagues (2002) reported a threefold higher risk of puerperal infection in a group of Swedish women in whom bacterial vaginosis was identified in early pregnancy (Chap. 68, p. 1216).

Bacterial Cultures. Routine genital tract cultures obtained before treatment serve little clinical use and add significant costs. Women with a temperature >102°F are more likely to have bacteremia (Easter, 2017). Even so, routine blood cultures seldom modify care. In two studies done before perioperative prophylaxis was used, blood cultures were positive in 13 percent of women with postcesarean metritis at Parkland Hospital and in 24 percent of those at Los Angeles County Hospital (Cunningham, 1978; DiZerega, 1979). In a later Finnish study, bacteremia was identified in only 5 percent of women with puerperal sepsis (Kankuri, 2003). Exceptions might be women with exceedingly high temperature spikes that may signify virulent infection with group A streptococci (Chap. 50, p. 890).

Pathogenesis and Clinical Course

Puerperal infection following vaginal delivery primarily involves the placental implantation site, decidua and adjacent myometrium, or cervicovaginal lacerations. The pathogenesis of uterine infection following cesarean delivery is that of an infected surgical incision. Bacteria that colonize the cervix and vagina gain access to the uterus during labor. Postpartum, they invade devitalized uterine tissue. Parametrial cellulitis follows with infection of the pelvic retroperitoneal fibroareolar connective tissue. With early treatment, infection is contained within the parametrial and paravaginal tissue, but it may extend deep into the pelvis.

Fever is the most important criterion for the diagnosis of postpartum metritis. Intuitively, the degree of fever is believed proportional to the extent of infection and sepsis. Temperatures usually are 38 to 39°C, and temperatures >39°C suggest bacteremia or endotoxemia (Easter, 2017; Suffredini, 1989). Women usually complain of abdominal pain, and parametrial tenderness is elicited on abdominal and bimanual examination. Leukocytosis may range from 15,000 to 30,000 cells/μL, but recall that cesarean delivery itself raises the leukocyte count. Although an offensive odor can develop, many women have foul-smelling lochia without evidence for infection, and vice versa. Some other infections, notably those caused by group A β-hemolytic streptococci, may be associated with scant, odorless lochia (Anderson, 2014).

Treatment

If metritis develops following vaginal delivery, treatment with an oral or intramuscular antimicrobial agent may be sufficient (Meaney-Delman, 2015). For moderate to severe infections, however, intravenous therapy with a broad-spectrum antibiotic regimen is indicated. Improvement occurs in 48 to 72 hours in nearly 90 percent of women treated with one of several regimens discussed below. Persistent fever after this interval mandates a careful search for causes of refractory pelvic infection. These include a parametrial phlegmon—an area of intense cellulitis; an abdominal incisional or pelvic abscess or infected hematoma; and septic pelvic thrombophlebitis. In our experience, persistent fever is seldom due to antimicrobial-resistant bacteria or due to drug side effects. The woman may be discharged home after she has been afebrile for at least 24 hours, and further oral antimicrobial therapy is not needed (Mackeen, 2015).

Choice of Antimicrobials. Therapy is empirical and initial treatment is directed against the mixed flora shown in Table 37-1. For infections following vaginal delivery, as many as 90 percent of women respond to regimens such as ampicillin plus gentamicin. In contrast, anaerobic coverage is included for infections following cesarean delivery (Table 37-2).

In 1979, DiZerega and coworkers compared the effectiveness of clindamycin plus gentamicin with that of penicillin G plus gentamicin for treatment of pelvic infections following cesarean delivery. Women given the clindamycin-gentamicin regimen had a 95-percent response rate, and this regimen is still considered by most to be the standard by which others are measured (Mackeen, 2015). Despite this standard therapy, enterococcal cultures may be persistently positive. The addition

TABLE 37-2. Antimicrobial Regimens for Pelvic Infections Following Cesarean Delivery

Regimen	Comments
Clindamycin + gentamicin	"Gold standard," 90–97% efficacy, once-daily gentamicin dosing acceptable ***Plus*** Ampicillin added to regimen with sepsis or suspected enterococcal infection
Clindamycin + aztreonam	Gentamicin substitute for renal insufficiency
Extended-spectrum penicillins	Piperacillin, piperacillin/tazobactam, ampicillin/sulbactam, ticarcillin/clavulanate
Cephalosporins	Cefotetan, cefoxitin, cefotaxime, ceftriaxone
Vancomycin	Added to other regimens for suspected *Staphylococcus aureus* infections
Metronidazole + ampicillin + gentamicin	Metronidazole has excellent anaerobic coverage
Carbapenems	Imipenem/cilastatin, meropenem, ertapenem; all reserved for special indications

of ampicillin, either initially or following no response after 48 to 72 hours, targets enterococci (Brumfield, 2000).

Many authorities recommend periodical monitoring of serum gentamicin levels. At Parkland Hospital, we do not routinely do so if a woman has adequate renal function, which is evidenced by a normal serum creatinine level. Once-daily dosing versus multiple dosing with gentamicin provides adequate serum levels, and either method has similar cure rates (Livingston, 2003). In the event of diminished glomerular filtration, some recommend a combination of clindamycin and a second-generation cephalosporin, because of potential nephrotoxicity and ototoxicity with gentamicin. Instead, others recommend a combination of clindamycin and aztreonam—the latter is a monobactam compound with activity similar to the aminoglycosides.

The spectra of *β-lactam antimicrobials* include activity against many anaerobic pathogens. Some examples include cephalosporins such as cefoxitin, cefotetan, cefotaxime, and ceftriaxone. Extended-spectrum penicillins are piperacillin, ticarcillin, and mezlocillin. β-lactam antimicrobials are inherently safe and, except for allergic reactions, are free of major toxicity. The *β-lactamase inhibitors* clavulanic acid, sulbactam, and tazobactam have been combined with ampicillin, amoxicillin, ticarcillin, and piperacillin to extend their spectra. *Metronidazole* has superior in vitro activity against most anaerobes. This agent given with ampicillin and an aminoglycoside provides coverage against most organisms encountered in serious pelvic infections. It is also used second line to treat some cases of *Clostridioides difficile* colitis.

Imipenem and similar antimicrobials are in the carbapenem family. These offer broad-spectrum coverage against most organisms associated with metritis. Imipenem coupled with *cilastatin* inhibits the antibiotic's renal metabolism. Because of imipenem's higher cost, it is reasonable from both a medical and an economic standpoint to reserve this drug for serious nonobstetrical infections.

Vancomycin is a glycopeptide antimicrobial active against gram-positive bacteria. It is used in lieu of β-lactam therapy for a patient with a type 1 allergic reaction and given for suspected infections due to *S aureus* and to treat *C difficile* colitis (Chap. 57, p. 1019).

Perioperative Prophylaxis

The use of periprocedural techniques for infection prevention is common in obstetrics (Table 37-3). Numerous studies show that prophylactic antibiotics at the time of cesarean delivery reduce wound and postpartum pelvic infection rates (Carter, 2017; Smaill, 2014). The observed benefit applies to both elective and nonelective cesarean delivery. As noted from preliminary data, antimicrobials may decrease pelvic infection rates after operative vaginal delivery (p. 650). However, data are insufficient to suggest prophylactic antimicrobials lower infection rates after spontaneous vaginal delivery, repair of all episiotomies, or manual extraction of the placenta (Bonet 2017a,b; Chongsomchai, 2014). The American College of Obstetricians and Gynecologists (2018a) concluded that a single antibiotic dose with third- and fourth-degree perineal laceration is reasonable and has evidenced-based support.

Single-dose prophylaxis with a 2-g dose of a first-generation cephalosporin is ideal. This regimen has similar efficacy of broad-spectrum agents or multiple-dose regimens (American College of Obstetricians and Gynecologists, 2018b). For obese women, evidence supports a 3-g dose of cefazolin to reach optimal tissue concentrations (Swank, 2015). Some evidence supports addition of azithromycin to lower postcesarean uterine infection rates (Markwei, 2021; Pierce, 2021; Tita, 2016). Women colonized with *MRSA* are given vancomycin

TABLE 37-3. Various Prophylactic Methods for Decreasing Pelvic and Wound Infection Rates Following Delivery

Route	Method	Study Results
Routine delivery	Peripartum antimicrobials	Limited evidence, may reduce risk (Bonet, 2017a)
Episiotomy	Perioperative prophylaxis	Insufficient evidence (Bonet, 2017b)
Operative vaginal delivery	Peripartum antimicrobials	Limited evidence, may reduce risk (Knight, 2019)
Cesarean delivery	Perioperative antimicrobial prophylaxis	Decreased 70–80% (Carter, 2017; Smaill, 2014)
Cesarean delivery	Skin preparation	Decreased incidence (Hadiati, 2018)

in addition to a cephalosporin (Chap. 67, p. 1196). It is controversial whether the infection rate is reduced further if the antimicrobial is given before the skin incision compared with after umbilical cord clamping (Baaqeel, 2013; Macones, 2012; Sun, 2013; Ward, 2016). The American College of Obstetricians and Gynecologists (2018b) has concluded that the evidence favors predelivery administration.

Most women with a stated allergy to penicillin are not prone to developing anaphylaxis. Without a history of anaphylaxis, most of these women can safely be given a cephalosporin (Chap. 30, p. 551). If not, then vancomycin is given along with clindamycin and gentamicin (American College of Obstetricians and Gynecologists, 2018b).

Preoperative abdominal skin preparation decreases the risk for pelvic and wound infections (Hadiati, 2018). Skin preparation with chlorhexidine-alcohol is superior to iodine-alcohol for preventing surgical-site infections (Tuuli, 2016). Additive beneficial effects may be gained by preoperative vaginal cleansing with povidone-iodine rinse or application of metronidazole gel (Caissutti, 2017; Felder, 2019; Haas, 2018).

Other Methods of Prophylaxis. Several studies have addressed the value of prenatal cervicovaginal cultures. These are obtained in the hope of identifying pathogens that might be eradicated to lower incidences of preterm labor, chorioamnionitis, and puerperal infections. Unfortunately, treatment of asymptomatic vaginal infections does not prevent these complications. For asymptomatic bacterial vaginosis, Carey and associates (2000) reported no beneficial effects for women treated. For asymptomatic *Trichomonas vaginalis* infection, a similar postpartum infection rate was found in women treated in the second trimester compared with placebo-treated women (Klebanoff, 2001).

Technical maneuvers done to alter the postcesarean infection rate have been studied (Chap. 30, p. 551). Allowing the placenta to separate spontaneously and exteriorizing the uterus to close the hysterotomy may reduce the infection risk (Jacobs-Jokhan, 2004; Lasley, 1997). However, changing gloves after placental delivery, cleaning the intrauterine cavity, and dilating the lower segment and cervix do not alter the infection rate (Atkinson, 1996; Eke, 2019; Liabsuetrakul, 2018). No differences were found in postoperative infection rates when single- and two-layer uterine closures were compared (Hauth, 1992). Similarly, infection rates are not affected by closure versus nonclosure of the peritoneum (Bamigboye, 2014; Tulandi, 2003). Importantly, closure of subcutaneous tissue in obese women does not lower the wound infection rate, but it does decrease the wound separation incidence (Chelmow, 2004). Similarly, skin closure with staples versus suture has a greater incidence of noninfectious skin separation (Mackeen, 2012; Tuuli, 2011).

Complications of Uterine and Pelvic Infections

Metritis responds to antimicrobial treatment within 48 to 72 hours in more than 90 percent of women. In some of the remainder, any of several complications may arise. These include wound infection, complex pelvic infection such as a phlegmon or an abscess, and septic pelvic thrombophlebitis (Brown, 1999; Jaiyeoba, 2012). As with other aspects of puerperal infections, the incidence and severity of these complications are reduced by perioperative antimicrobial prophylaxis.

Abdominal Incisional Infections

Wound infection is a common cause of persistent fever in women treated for metritis. Incisional infection risk factors include obesity, diabetes, corticosteroid therapy, immunosuppression, anemia, hypertension, and hematoma formation from inadequate hemostasis. If prophylactic antimicrobials are given, the incidence of wound infection following cesarean delivery ranges from 2 to 10 percent depending on risk factors (Andrews, 2003; Chaim, 2000). From our experiences at Parkland Hospital, the incidence is closer to 2 percent, but this risk rises with increasing body mass (Hussamy, 2018).

Incisional abscesses that develop following cesarean delivery usually cause persistent fever or fever that begins on approximately the fourth day. The wound is erythematous and drains pus. Organisms that cause wound infections are generally the same as those isolated from amnionic fluid at cesarean delivery, however, hospital-acquired pathogens also may be causative.

Treatment includes antimicrobials and surgical drainage and debridement of devitalized tissue. This typically requires spinal analgesia or general anesthesia. The fascia is carefully inspected to document integrity. Local wound care thereafter is completed twice daily. Before each dressing change, procedural analgesia is tailored to wound size and location, and oral, intramuscular, or intravenous dosage routes are suitable. Topical lidocaine also may be added. Necrotic tissue is removed, and the wound is repacked with moist gauze. At 4 to 6 days, healthy granulation tissue is typically present, and secondary en bloc closure of the open layers can usually be accomplished (Wechter, 2005). As shown in Figure 37-1, a polypropylene or

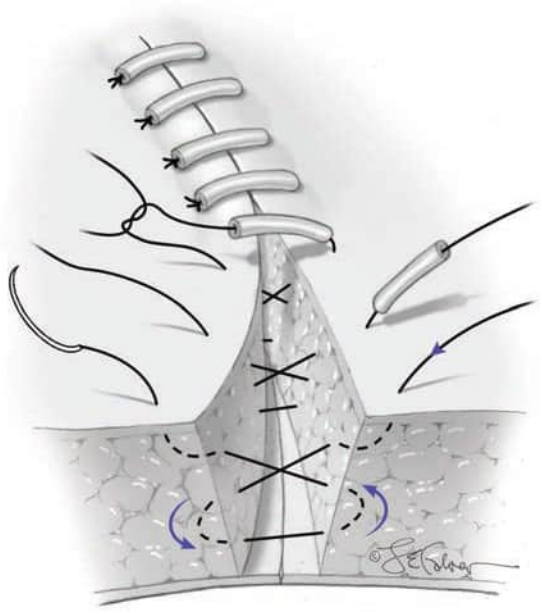

FIGURE 37-1 Secondary abdominal wound closure technique. (Reproduced with permission from Worley KC: Postoperative complications. In Yeomans ER, Hoffman BL, Gilstrap LC III, et al [eds]: Cunningham and Gilstrap's Operative Obstetrics, 3rd ed. New York, NY: McGraw Hill; 2017).

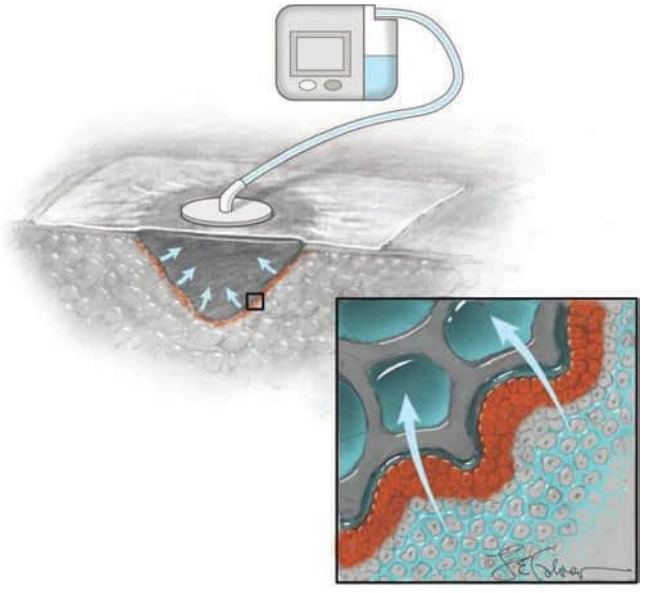

FIGURE 37-2 Theoretical effects of negative-pressure wound therapy include macro- and microdeformation, removal of tissue fluid, and creation of a warm and moist environment. As shown in the inset, tissue fluid is drawn out by suction tubing. It travels through the porous sponge dressing that fills the wound and into an adjacent collection canister. As healing progresses, a layer of granulation tissue (*red*) forms at the wound-sponge interface. (Reproduced with permission from Cunningham FG: Surgical instruments. In Yeomans ER, Hoffman BL, Gilstrap LC III, et al [eds]: Cunningham and Gilstrap's Operative Obstetrics, 3rd ed. New York, NY: McGraw Hill; 2017.)

nylon suture of appropriate gauge enters 2 to 3 cm from one wound edge. It crosses the wound to incorporate the full wound thickness and emerges 3 cm from the other wound edge. These are placed in series to close the opening. In most cases, sutures may be removed on postprocedural day 10.

Vacuum-Assisted Wound Closure

This system promotes healing by applying negative pressure to the wound (Fig. 37-2). The technique is variably referred to as *vacuum-assisted closure (VAC), topical negative pressure (TNP)*, and *negative-pressure wound therapy (NPWT)*. Negative-pressure systems are used for open wounds after infection or for prophylaxis against wound disruption. Mouës and colleagues (2011) confirmed that NPWT enhances blood flow to the wound, promotes angiogenesis, induces cellular proliferation, and shrinks wound size. Several systems are available and widely accepted, despite meager formal evidence for clinical efficacy.

Open abdominal wounds once infection has cleared or an "open surgical abdomen" is a major indication for NPWT. Vacuum therapy is the most efficient method of temporary abdominal closure for patients with open abdominal wounds (Bruhin, 2014; Quyn, 2012). However, no trials have compared vacuum-assisted wound closure with conventional wound care after cesarean delivery. Also, these devices are used for closure of perineal wounds resulting from infected episiotomies, hematomas, or abscesses (Aviki, 2015). Very few randomized trials have compared vacuum-assisted wound closure with conventional wound care (Kawakita, 2021; Yu, 2018).

Prophylaxis. Negative-pressure devices are also marketed to prevent wound infections in incisions closed to heal by primary intention. Such prophylactic use in 441 obese women undergoing cesarean delivery has been evaluated in two large randomized trials. Hussamy and associates (2019) found in obese women that the incidence of wound morbidity was similar in the standard dressing group compared with the NPWT group (Table 37-4). The second trial was a multicenter study from Denmark of 876 obese women (Hyldig, 2019). In the NPWT group, the surgical site infection rate was 4.6 percent compared with 9.2 percent in the group of women treated with standard dressing. Similarly, a systematic review found use of prophylactic NPWT reduced wound complications (Yu, 2018). The cost effectiveness of these systems is inconclusive in multiple studies (Echebiri, 2015; Lewis, 2014). Smid and coworkers (2017) questioned the effectiveness of such therapy. Because of these uncertainties, we agree with Tuuli (2019) that routine use of prophylactic NPWT needs more evaluation before its widespread acceptance.

Fascial Dehiscence

This separation of the fascial layer is a serious complication, and bowel evisceration can be comorbid. Wound infection and obesity are prominent risk factors (Poole, 1985; Subramaniam, 2014). For example, McNeeley and associates (1998) reported a fascial dehiscence rate of approximately 1 per 300 operations in almost 9000 women undergoing cesarean delivery. Two thirds of the 27 fascial dehiscences in this study were associated with concurrent fascial infection and tissue necrosis.

Fascial dehiscence generally presents within the first 7 to 10 postoperative days. Superficial disruption of the subcutaneous layer and extensive leakage of peritoneal fluid or purulent drainage are indicative. In unclear cases, CT scanning may be elected preoperatively, if obtained expeditiously.

Dehiscence is a surgical emergency. If abdominal contents have eviscerated, sterile towels or gauze soaked in saline can be used early to cover and gently replace bowel or omentum. Broad-spectrum antibiotics are generally recommended to minimize ensuing peritonitis.

Given the high mortality risk associated with fascial dehiscence and bowel evisceration, examination under anesthesia to estimate the extent of separation is often warranted. Surgery aims to assess bowel health, debride necrotic wound tissue, and close the fascia, if possible. For closure, an interrupted mass closure using a no. 2 permanent suture is recommended typically (Fig. 37-3). In cases with infection, the subcutaneous layers are left to close secondarily. General surgery consultation is considered if bowel ischemia or difficult fascial closure is anticipated.

■ Necrotizing Fasciitis

This uncommon severe wound infection is associated with high mortality rates. In obstetrics, necrotizing fasciitis may involve abdominal incisions, or it may complicate episiotomy or other perineal lacerations. As the name implies, tissue necrosis is significant. Of the risk factors for fasciitis summarized by Owen and Andrews (1994), diabetes, obesity, and hypertension are increasingly common in gravidas. Like pelvic infections, this wound complication usually is polymicrobial and caused by

TABLE 37-4. Randomized Trial of Prophylactic Incisional Negative-Pressure Wound Therapy (iNPWT) Versus Standard Surgical Dressing for Morbidly Obese Women Undergoing Cesarean Delivery

Factor	iNPWT (N = 222)	Standard (N = 219)	Significance
BMI at delivery	46.6 ± 6.0	45.8 ± 5.8	NS
Cesarean delivery			
Primary	43%	37%	$p = 0.18$
Secondary	57%	63%	$p = 0.18$
Scheduled	32%	33%	$p = 0.99$
Unscheduled	68%	67%	$p = 0.99$
Pfannenstiel	23%	28%	$p = 0.29$
Vertical midline	77%	72%	$p = 0.29$
Incision			
Depth	5.5 ± 1.7	5.3 ± 1.8	$p = 0.19$
Length	14.5 ± 2.5	14.6 ± 2.9	$p = 0.74$
Wound morbidity			
Cellulitis	32%	38%	RR = 0.7 (95% CI, 0.3 – 1.7)
Superficial SSI	54%	61%	RR = 0.8 (95% CI, 0.4 – 1.5)
Dehiscence	11%	2%	RR = 3.9 (95% CI, 0.4 – 194)
Composite outcome	17%	19%	RR = 0.9 (95% CI, 0.5 – 1.4)
Readmission	5%	4%	RR = 1.3 (95% CI, 0.5 – 3.5)
Reoperation	6%	5%	RR = 1.4 (95% CI, 0.6 – 3.5)

BMI = body mass index; CI, confidence interval; NS = not significant; RR = relative risk; SSI = surgical site infection.
Data from Hussamy, 2018, 2019.

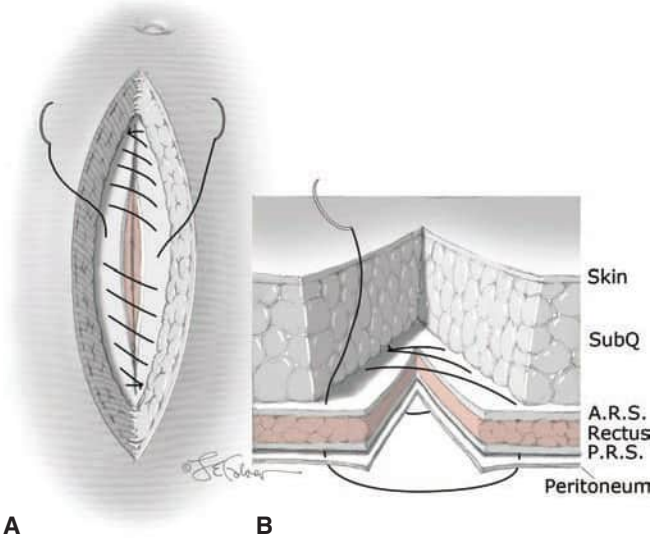

FIGURE 37-3 Mass closure: each stitch is placed 1.5 to 2 cm from the wound edge **(A)** and incorporates the peritoneum, rectus muscle, and rectus sheath **(B)**. Stitches are spaced 1 cm apart along the length of the incision. A.R.S. = anterior rectus sheath; P.R.S. = posterior rectus sheath; SubQ = subcutaneous layer. (Reproduced with permission from Cundiff GW: Incisions and closures. In Yeomans ER, Hoffman BL, Gilstrap LC III, et al [eds]: Cunningham and Gilstrap's Operative Obstetrics, 3rd ed. New York, NY: McGraw Hill; 2017.)

organisms that make up the normal vaginal flora. In some cases, however, infection is caused by a single virulent bacterial species such as group A β-hemolytic streptococcus (Anderson, 2014; Rimawi, 2012). Occasionally, rarely encountered pathogens cause necrotizing infections (Chong, 2016; Swartz, 2004).

Goepfert and coworkers (1997) described nine cases of necrotizing fasciitis in more than 5000 cesarean deliveries. The infection was fatal in two women—one with metastatic breast cancer and the other with sepsis. In another report, Schorge and colleagues (1998) described five women with fasciitis following cesarean delivery. None of these women had predisposing risk factors, and none died.

Infection may involve skin, superficial and deep subcutaneous tissues, and any of the abdominopelvic fascial layers. In some cases, muscle also is involved—*myofasciitis*. Most of these necrotizing infections do not cause symptoms until 3 to 5 days after delivery. Some virulent infections develop earlier. Clinical findings vary, and it is frequently difficult to differentiate more innocuous superficial wound infections from a deep fascial one. If myofasciitis progresses, the woman may become ill from septicemia. A high index of suspicion, with surgical exploration if the diagnosis is uncertain, may be lifesaving (Goh, 2014). We aggressively pursue early exploration (Chap. 50, p. 890).

Successful treatment of necrotizing soft-tissue infections involves early diagnosis, source control by surgical

debridement, antimicrobials, and intensive care (Gallup, 2002; Goh, 2014; Society for Maternal-Fetal Medicine, 2019). Surgery includes thorough debridement of all infected tissue, leaving wide margins of healthy bleeding tissue. This may include extensive abdominal or vulvar debridement and excision of abdominal, thigh, or buttock fascia. Death is virtually universal without surgical treatment, and rates approach 50 percent even if exhaustive debridement is performed (Johnson, 2020). With substantial resection, synthetic mesh may ultimately be required later to close the fascial incision once infection is cleared (Gallup, 2002; McNeeley, 1998).

■ Peritonitis and Adnexal Abscesses

Following cesarean delivery, peritonitis is infrequent. It almost always is preceded by metritis, especially cases with uterine incisional necrosis and dehiscence. However, it may stem from a ruptured adnexal abscess or an inadvertent intraoperative bowel injury. Perforative appendicitis also can cause peritonitis (Chap. 57, p. 1024). In these cases, prompt surgical treatment is usually indicated.

After vaginal delivery, peritonitis is rarely encountered, and many such cases are due to virulent strains of group A β-hemolytic streptococci or similar organisms. Importantly, abdominal rigidity may not be prominent with puerperal peritonitis because of physiological abdominal wall laxity from pregnancy. Pain may be severe, but frequently, the first symptoms of peritonitis are those of *adynamic ileus.* Marked bowel distention may develop, which is unusual after vaginal birth. Normally, if the infection begins in an intact uterus and extends into the peritoneum, antimicrobial treatment alone suffices.

An *ovarian abscess* rarely develops in the puerperium. These are presumably caused by bacterial invasion through an opening in the ovarian capsule (Wetchler, 1985). The abscess is usually unilateral, and women typically present 1 to 2 weeks after delivery. Rupture is common, and peritonitis may be severe.

■ Parametrial Phlegmon

For some women in whom metritis develops following cesarean delivery, parametrial cellulitis is intense and forms an area of induration—a *phlegmon*—within the leaves of the broad ligament (Fig. 37-4). These infections are considered when fever persists longer than 72 hours despite intravenous antimicrobial therapy (Brown, 1999; DePalma, 1982).

Phlegmons are usually unilateral, and they frequently are limited to the parametrium at the base of the broad ligament. If the inflammatory reaction is more intense, cellulitis extends along natural lines of cleavage. The most common form of extension is laterally along the broad ligament, with a tendency to extend to the pelvic sidewall. Occasionally, posterior extension may involve the rectovaginal septum, producing a firm mass posterior to the cervix. In most women, clinical improvement follows continued treatment with a broad-spectrum antimicrobial regimen. Typically, fever resolves in 5 to 7 days.

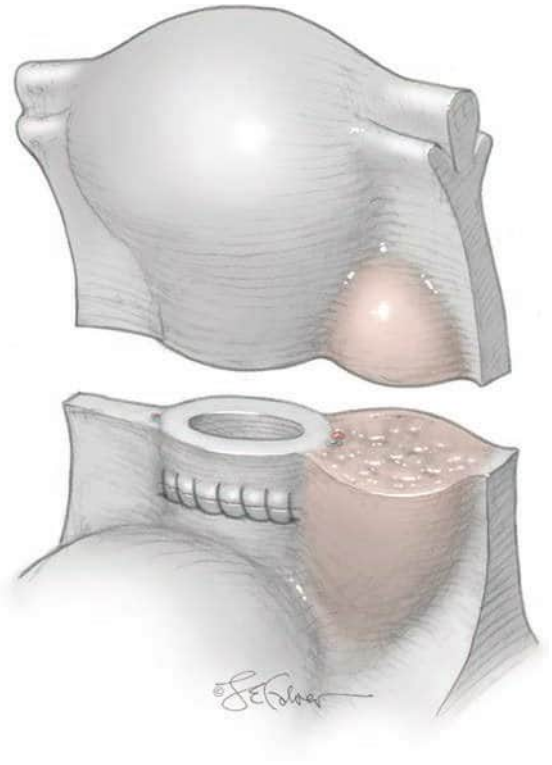

FIGURE 37-4 Left-sided parametrial phlegmon: cellulitis causes induration in the parametrium adjacent to the hysterotomy incision. (Reproduced with permission from Worley KC: Postoperative complications. In Yeomans ER, Hoffman BL, Gilstrap LC III, et al [eds]: Cunningham and Gilstrap's Operative Obstetrics, 3rd ed. New York, NY: McGraw Hill; 2017).

Severe cellulitis of the uterine incision may ultimately lead to necrosis and separation (Treszezamsky, 2011). Extrusion of purulent material causes intraabdominal abscess formation and peritonitis as described above. Surgery is reserved for women in whom uterine incisional necrosis is suspected. For most, hysterectomy and surgical debridement are needed. These cases are difficult because the cervix and lower uterine segment are involved with an intense inflammatory process that extends to the pelvic sidewall. The adnexa are seldom involved, and one or both ovaries can usually be conserved. Blood loss is often appreciable, and transfusion is common.

Imaging Studies

Persistent puerperal infections can be evaluated using computed tomography (CT) or magnetic resonance (MR) imaging (Wang, 2020). Brown and associates (1991) used CT imaging in women in whom pelvic infection was refractory to antimicrobial therapy given for 5 days. They found at least one abnormal radiological finding in 75 percent of these women, and most were nonsurgical lesions. Fishel Bartal and colleagues (2018) reported abnormal CT findings in almost 60 percent of women with refractory fever persisting >3 days. Pelvic fluid collections were seen in 22 percent, and surgical intervention was prompted in 8 percent. Thus, imaging can be used to dissuade surgical exploration in most cases.

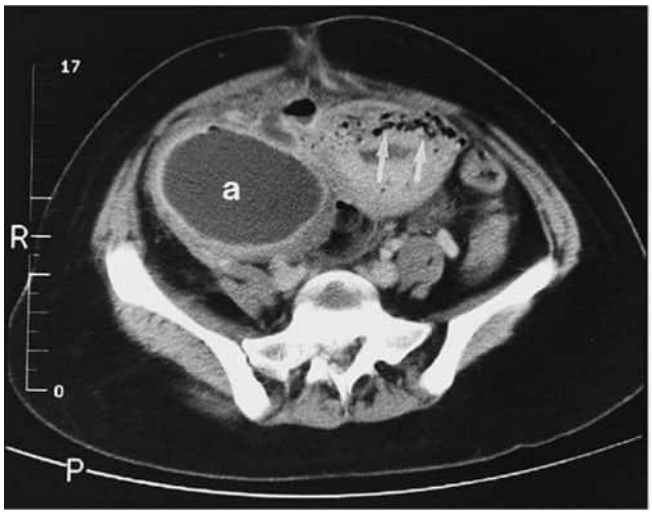

FIGURE 37-5 Pelvic computed tomography scan showing necrosis of the uterine incision with gas in the myometrium (*arrows*). A large abscess (*a*) fills the right parametrium.

Uterine incisional dehiscence such as shown in Figure 37-5 can sometimes be confirmed based on CT images. These findings must be interpreted within the clinical context because apparent uterine incisional defects thought to represent edema can be seen even after uncomplicated cesarean delivery. Shown in Figure 37-6 is a necrotic hysterotomy incision, which had leaked into the peritoneal cavity.

Occasionally, a parametrial phlegmon may suppurate, forming a fluctuant broad ligament abscess that may point above the inguinal ligament. These abscesses can dissect anteriorly and be amenable to CT-directed needle drainage. A *psoas abscess* is rare, and despite antimicrobial therapy, percutaneous drainage may be required to effectively treat it (Shahabi, 2002; Swanson, 2008). If a phlegmon involving the rectovaginal septum suppurates, surgical drainage is easily effected by colpotomy. Absorption of the induration may require several days to weeks.

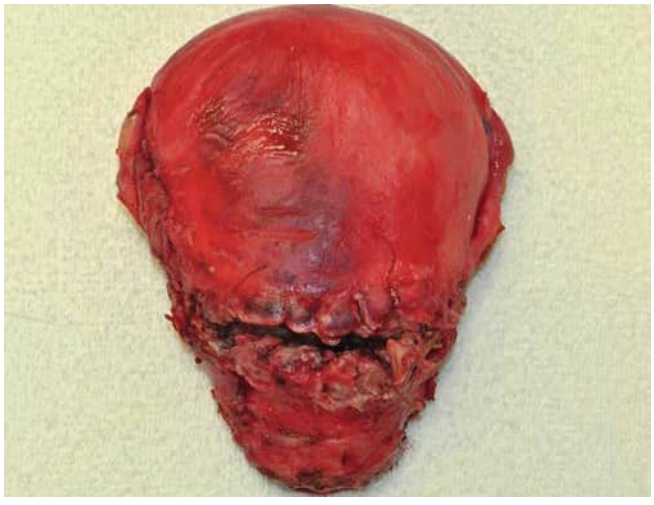

FIGURE 37-6 Necrotic hysterotomy infection. Severe cellulitis of the uterine incision resulted in dehiscence with subsequent leakage into the peritoneal cavity. Hysterectomy was required for sufficient debridement of necrotic tissue. (Reproduced with permission from Dr. Denisse Holcomb.)

Septic Pelvic Thrombophlebitis

Suppurative thrombophlebitis was a frequent complication in the preantibiotic era, and septic embolization was common. However, with the advent of antimicrobial therapy, the mortality rate and need for surgical therapy for these infections diminished. Septic phlebitis arises as an extension along venous routes and may cause thrombosis. Lymphangitis often coexists. The ovarian veins may then become involved because they drain the upper uterus and therefore the placental implantation site. The experiences of Witlin and Sibai (1995) and Brown and coworkers (1999) suggest that puerperal septic thrombophlebitis is likely to involve one or both ovarian venous plexuses. In a fourth of women, the clot extends into the inferior vena cava and occasionally to the renal vein.

The incidence of septic phlebitis varies in several reports. In a 5-year survey of 45,000 women who were delivered at Parkland Hospital, Brown and workers (1999) found an incidence of 1 case per 9000 vaginal births and 1 per 800 cesarean deliveries. In a cohort of 16,650 women undergoing primary cesarean delivery, Rouse and coworkers (2004) reported an incidence of 1 case per 400 surgeries. Incidences approximated 1 per 175 cesarean deliveries if chorioamnionitis was antecedent, but only 1 per 500 if there was no intrapartum infection.

Except for chills and occasional lower quadrant pain, women with septic thrombophlebitis usually lack symptoms (Wouterlood, 2021). The diagnosis can be confirmed by pelvic CT or MR imaging (Fig. 37-7). Using either, Brown and coworkers (1999) found that 20 percent of 69 women with persistent fever following >5 days of antimicrobial therapy for metritis had septic pelvic thrombophlebitis. In a later study, Fischel Bartal and associates (2018) reported that 6 percent of women with refractory fever ≥3 days had septic phlebitis. These women normally have symptomatic improvement with antimicrobial treatment, however, they continue to have fever.

Treatment with heparin is controversial. In a randomized study of 14 women, the addition of heparin to antimicrobial therapy for septic pelvic thrombophlebitis did not hasten recovery or improve outcome (Brown, 1999). We and others are of the opinion that heparin is unnecessary (Witlin, 1995). Others, however, continue to recommend anticoagulation (Klima, 2008; Lenz, 2017). Certainly, no evidence supports long-term anticoagulation (Brown, 2018).

Perineal Infections

Episiotomy infections are uncommon, because the operation is now performed less frequently (American College of Obstetricians and Gynecologists, 2018a; Dillon, 2019). Reasons for this are discussed in Chapter 27 (p. 510). In an older study, Owen and Hauth (1990) described only 10 episiotomy infections in 20,000 women delivered vaginally. With infection, however, dehiscence is a concern. Ramin and colleagues (1992) reported an episiotomy dehiscence rate of 0.5 percent at Parkland Hospital, and 80 percent of these were infected. Uygur and associates (2004) reported a 1-percent dehiscence rate and attributed two thirds to infection.

When the anal sphincter is disrupted at delivery, the subsequent infection rate is higher and is likely influenced by intrapartum antimicrobial treatment (Buppasiri, 2014; Stock, 2013).

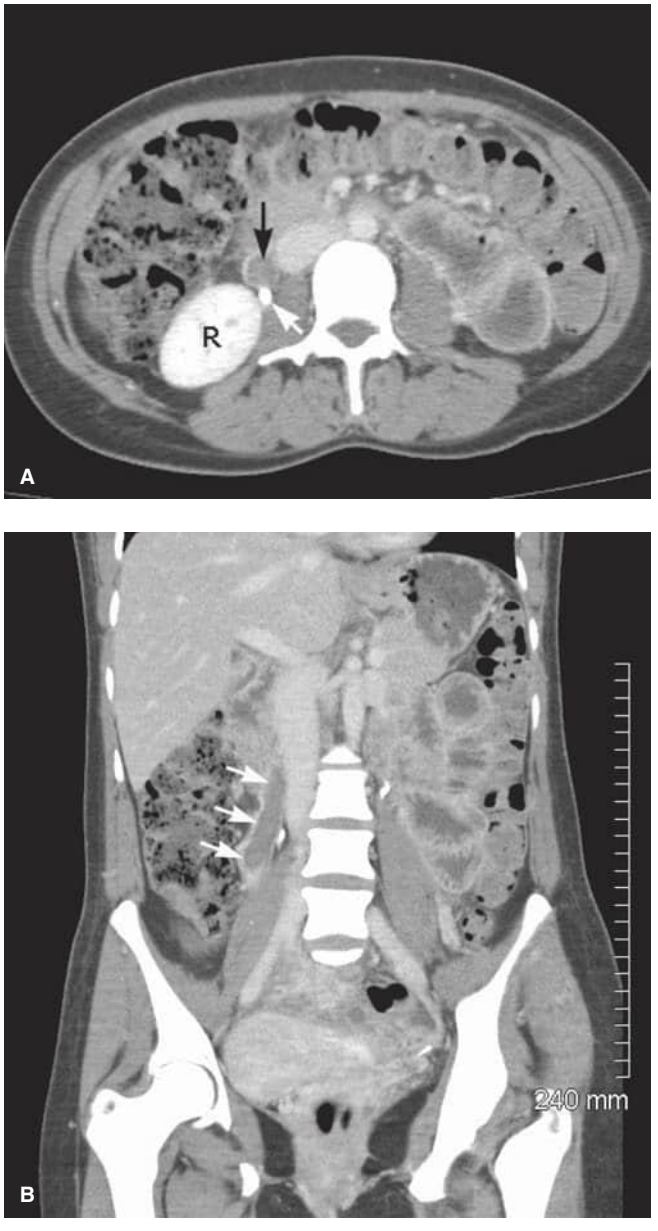

FIGURE 37-7 Septic ovarian vein thrombosis—contrast-enhanced computed tomography scan: **A.** Enlarged right ovarian vein filled with low-density thrombus (*black arrow*). Contrast is seen in ureter (*white arrow*). *R* = lower pole, right kidney. **B.** Coronal image demonstrates enlarged right ovarian vein filled with low-density thrombus (*arrows*). (B: Reproduced with permission from Dr. April Bailey in Worley KC: Postoperative complications. In Yeomans ER, Hoffman BL, Gilstrap LC III, et al [eds]: Cunningham and Gilstrap's Operative Obstetrics, 3rd ed. New York, NY: McGraw Hill; 2017.)

Lewicky-Gaupp and colleagues (2015) reported a 20-percent infection rate when the sphincter was torn. Goldaber and coworkers (1993) described fourth-degree lacerations in 390 parturients, of whom 5.4 percent had morbidity. In these women, 2.8 percent had infection and dehiscence, 1.8 percent had only dehiscence, and 0.8 percent only infection.

Pathogenesis and Clinical Course

As noted, perineal laceration infection may be complicated by dehiscence. Other factors for separation include coagulation disorders, smoking, and human papillomavirus infection (Ramin, 1994). No data suggest that dehiscence is related to faulty repair.

With infection, local pain and dysuria, with or without urinary retention, are frequent symptoms. Ramin and colleagues (1992) reported that the most common findings were pain in 65 percent, purulent discharge in 65 percent, and fever in 44 percent. In extreme cases, the entire vulva may become edematous, ulcerated, and covered with exudate. Although life-threatening, septic shock or necrotizing fasciitis is rare (p. 654).

Vaginal lacerations may also become infected directly or by extension from the perineum. The epithelium becomes red and swollen and may then become necrotic and slough. Parametrial extension can lead to lymphangitis. Cervical lacerations are seldom noticeably infected, but instead may manifest as metritis. Deep lacerations that extend directly into the base of the broad ligament may become infected and cause lymphangitis, parametritis, and bacteremia.

Treatment

Infected episiotomies are managed similar to other infected surgical wounds. In women with obvious cellulitis but no purulence, close observation and broad-spectrum antimicrobial therapy alone may be appropriate. With purulence, drainage is established, and in most cases, sutures are removed and the infected wound debrided. With dehiscence, local wound care is coupled with intravenous antimicrobials. Hauth and associates (1986) were the first to advocate for early episiotomy repair after infection subsided. Hankins and colleagues (1990) described successful early repair in 94 percent of women, and the average duration from dehiscence to repair was 6 days. The two women with failures developed a pinpoint rectovaginal fistula that was treated with a small rectal flap. Other studies have shown similar high rates with early repair (Ramin, 1992; Uygur, 2004).

Before performing early repair, diligent preparation is essential (Table 37-5). The surgical wound must be properly cleaned and cleared of infection. Once the surface of the wound is free

TABLE 37-5. Preoperative Protocol for Early Repair of Episiotomy Dehiscence

Open wound, remove sutures, begin intravenous antimicrobials
Initiate wound care:
Institute sitz bath several times daily or hydrotherapy
Provide adequate analgesia or anesthesia—regional analgesia or general anesthesia may be necessary for initial debridements
Scrub wound twice daily with a povidone-iodine solution
Debride necrotic tissue
Close wound when afebrile and pink, healthy granulation tissue present
Provide enemas prior to fourth-degree repair
Institute postoperative stool softeners; normal diet, nothing per vagina or rectum

of exudate and covered by pink granulation tissue, secondary repair can be accomplished. The tissue must be adequately mobilized, with special attention to identify and mobilize the anal sphincter muscle. A tension-free suture line is essential to avoid repeated dehiscence. Secondary closure of the wound is accomplished in layers, as described for primary episiotomy closure (Chap. 27, p. 510). Postoperative care includes local wound care, stool softeners, and nothing per vagina or rectum until healed. Hard stools risk wound disruption, but liquid stool can seep between sutures to reincite infection. Thus, soft formed stools are the goal.

■ Toxic Shock Syndrome

This acute febrile illness with severe multisystem derangement has a case-fatality rate of 10 to 15 percent. Usual findings are fever, headache, mental confusion, diffuse macular erythematous rash, nausea, vomiting, watery diarrhea, and marked hemoconcentration. Renal failure followed by hepatic failure, disseminated intravascular coagulation, and circulatory collapse may progress in rapid sequence. During recovery, the rash-covered areas desquamate. In early investigations of toxic shock syndrome (TSS), *Staphylococcus aureus* was recovered from almost all afflicted persons. Specifically, a staphylococcal exotoxin, termed *toxic shock syndrome toxin 1 (TSST-1)*, was found to cause the clinical manifestations by provoking profound endothelial injury. A very small amount of TSST-1 can activate T cells to create a "cytokine storm" (Heying, 2007; Que, 2005). Toxic shock syndrome has also been reported with *MRSA* (Deguchi, 2018).

Subsequent investigations have also implicated virulent group A β-hemolytic streptococcal infection (Anderson, 2014; Rottenstreich, 2019; Shinar, 2016). Heavy colonization or infection is complicated in some cases by *streptococcal toxic shock syndrome,* which is produced when pyrogenic exotoxin is elaborated. Serotypes M1 and M3 are particularly virulent (Beres, 2004; Okumura, 2004). Last, almost identical findings of toxic shock have been reported in pregnant women with *Clostridium sordellii* and *novyi* colonization (Herrera, 2016; Robbie, 2000).

Thus, in some cases of toxic shock syndrome, infection is not apparent, and colonization of a mucosal surface is the presumed source (Olp, 2020). At least 10 to 20 percent of pregnant women have vaginal colonization with *S aureus.* And *Clostridium perfringens* and *sordellii* are cultured from 3 to 10 percent of asymptomatic women (Chong, 2016). Thus, it is not surprising that the disease develops in postpartum women when growth of vaginal bacteria is abundant (Chen, 2006; Guerinot, 1982).

Delayed diagnosis and treatment are associated with maternal mortality (Schummer, 2002). Crum and colleagues (2002) described a neonatal death following antenatal toxic shock syndrome. Principal therapy is supportive, while allowing reversal of capillary endothelial injury. Antimicrobial therapy includes coverage against staphylococcal and streptococcal species. With evidence of pelvic infection, antimicrobial therapy must also include agents used for polymicrobial infections. Women with these infections may require wound debridement and possibly hysterectomy. Because the toxin is so potent, the mortality rate is correspondingly high (Hotchkiss, 2003).

BREAST INFECTIONS

Parenchymal infection of the mammary glands is a rare antepartum complication, but the postpartum incidence of mastitis approximates 3 percent (Lee, 2010). No evidence supports use of prophylactic measures to prevent breast infection (Crepinsek, 2012). Risk factors include nursing difficulties, cracked nipples, and oral antibiotic therapy (Branch-Elliman, 2012; Mediano, 2014).

Symptoms of suppurative mastitis seldom appear before the end of the first week postpartum and usually are not seen until the third or fourth week. Infection almost invariably is unilateral, and marked engorgement usually precedes inflammation. Symptoms include chills or actual rigors, which are soon followed by fever and tachycardia. Pain is severe, and the breast(s) becomes hard and red. Approximately 10 percent of women with mastitis develop an abscess. Detection of fluctuation may be difficult, and sonography is usually diagnostic (Fig. 37-8). Although rare, toxic shock syndrome from mastitis caused by *S aureus* has been reported (Demey, 1989; Fujiwara, 2001).

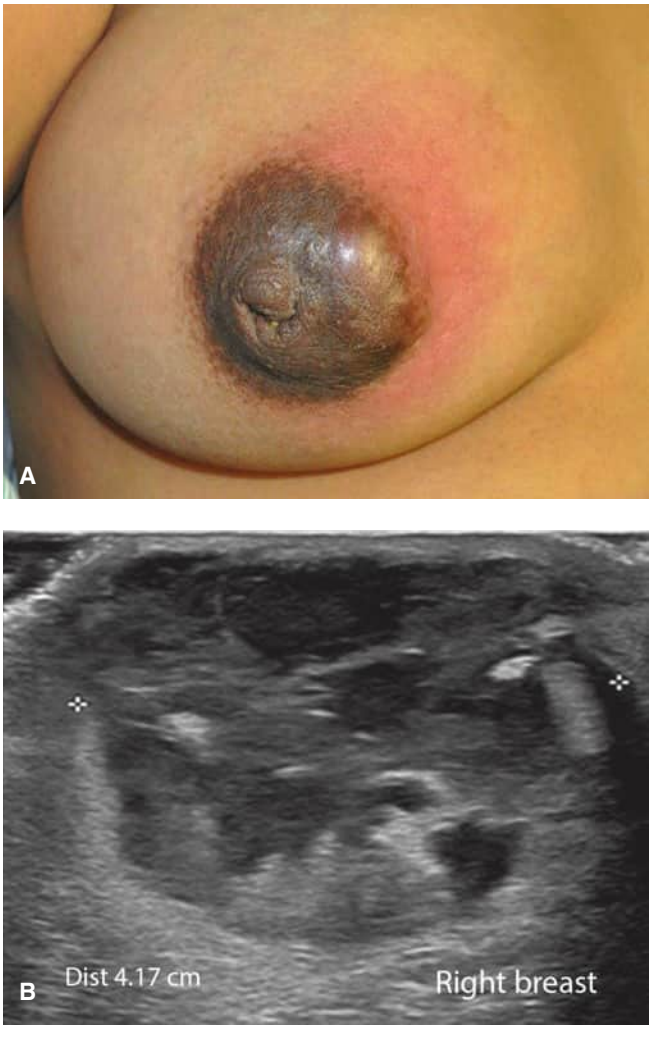

FIGURE 37-8 Puerperal mastitis with breast abscess. **A.** Indurated, erythematous skin overlies the area of right-sided breast infection. **B.** Sonographic picture of this 5-cm abscess.

Etiology

S aureus, especially *MRSA*, is the most commonly isolated organism in breast infections. Matheson and coworkers (1988) found it in 40 percent of women with mastitis. Other commonly isolated organisms are coagulase-negative staphylococci and viridans streptococci. The immediate source of mastitis-causing organisms is almost always the newborn's nose and throat. Bacteria enter the breast through the nipple at fissures or small abrasions. The infecting organism can usually be cultured from milk.

At times, suppurative mastitis reaches epidemic levels among nursing mothers. Such outbreaks most often coincide with the appearance of a new strain of antibiotic-resistant staphylococcus. A contemporaneous example is *MRSA*, which has rapidly become the most commonly isolated staphylococcal species in some areas (Berens, 2010; Klevens, 2007). At Parkland Hospital from 2000 to 2004, Laibl and associates (2005) reported that a fourth of community-acquired *MRSA* isolates were from pregnant or postpartum women with mastitis. Hospital-acquired *MRSA* may cause mastitis when the newborn becomes colonized after contact with nursery personnel who are colonized (Centers for Disease Control and Prevention, 2006). Stafford and colleagues (2008) found a higher incidence of recurrent abscess in those with *MRSA*-associated mastitis.

Management

Provided that appropriate therapy for mastitis is started before suppuration begins, the infection usually resolves within 48 hours. Many recommend that milk be expressed from the affected breast onto a swab and cultured before beginning therapy. Bacterial identification and antimicrobial sensitivities can provide information for a successful program of nosocomial infection surveillance (Lee, 2010).

The most effective treatment has not been clarified (Jahanfar, 2013). Thus, the initial antimicrobial choice is influenced by current experience with staphylococcal infections at a given institution. Dicloxacillin, 500 mg orally four times daily, may be started empirically. Erythromycin is given to women who are penicillin sensitive. If the infection is caused by resistant, penicillinase-producing staphylococcus species or if resistant organisms are suspected while awaiting the culture results, then vancomycin, clindamycin, or trimethoprim-sulfamethoxazole is given (Sheffield, 2013). Although clinical response may be prompt, treatment is recommended for 10 days.

Marshall and coworkers (1975) demonstrated the importance of continued breastfeeding. They reported that of 65 women with mastitis, the only three who developed abscesses were among the 15 women who quit breastfeeding. Vigorous milk expression may be sufficient treatment alone (Thomsen, 1984). Sometimes the infant will not nurse on the inflamed breast. This probably is not related to any changes in the milk taste but is secondary to engorgement and edema, which can make the areola harder to grip. Pumping can alleviate this. When nursing bilaterally, it is best to begin suckling on the uninvolved breast. This allows let-down to commence before moving to the tender breast.

In resource-poor countries, breastfeeding in women infected with the human immunodeficiency virus (HIV) is not contraindicated. However, in the setting of mastitis or breast abscess, it is recommended to stop feeding from the infected breast. This is because HIV RNA levels rise in affected breast milk. These levels return to baseline after symptoms resolve (Semrau, 2013).

Breast Abscess

In a population-based study of nearly 1.5 million Swedish women, the incidence of breast abscess was 0.1 percent (Kvist, 2005). An abscess should be suspected when defervescence does not follow within 48 to 72 hours of treatment or when a mass is palpable. Again, sonographic imaging is valuable. Breast abscesses can be large, and in one case report, 2 L of pus were released (Martic, 2012). Traditional therapy has been surgical drainage, which usually requires general anesthesia. The incision ideally is placed along Langer skin lines for a cosmetic result (Stehman, 1990). In early cases, a single incision over the most dependent portion of fluctuation is usually sufficient. Multiple abscesses require several incisions and disruption of loculations. The resulting cavity is loosely packed with gauze, which should be replaced at the end of 24 hours by a smaller pack.

More recently, sonographically guided needle aspiration using local analgesia has become favored (Patani, 2018). This has an 80- to 90-percent success rate (Geiss, 2014). In a randomized trial, Naeem and colleagues (2012) compared surgical drainage with aspiration. At 8 weeks, they found 93 percent undergoing aspiration were healed compared with 77 percent undergoing surgical drainage. Sonographic findings, initial choice of antimicrobials, and infecting organism do not predict aspiration failure (David, 2018).

Other etiologies should be considered in the setting of a nonhealing abscess. Rarely, *granulomatous mastitis* presents as puerperal mastitis (Ding, 2021 Freeman, 2017). Cancer or tuberculosis are other considerations (Wu, 2020).

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CHAPTER 38

Contraception

The puerperium offers an excellent opportunity to provide effective contraception. For mothers who are nursing exclusively, ovulation during the first 10 weeks after delivery is unlikely. Nursing, however, is not a reliable method of family planning for women whose infants breastfeed only during the day. Moreover, waiting for first menses involves a risk of pregnancy, because ovulation usually antedates menstruation. Certainly, after the first menses, contraception is essential unless the woman desires pregnancy.

Nearly half of all pregnancies each year in the United States are unintended (Finer, 2016). These may follow contraceptive method failure or stem from lack of contraceptive use. For those seeking contraception, effective options are available (Table 38-1). Among these, estimated failure rates of perfect and typical use during the first year differ widely (Trussell, 2018). Efficacy tiers reflect these failure rates, and implants and intrauterine devices (IUDs) are found in the top tier (Steiner, 2006). They effectively drop unintended pregnancy rates and are considered long-acting reversible contraception (LARC). Clinicians provide counseling on *all* options and encourage LARC for appropriate candidates (American College of Obstetricians and Gynecologists, 2019d).

No contraceptive method is completely without side effects, but contraception usually poses less risk than pregnancy. However, some disorders or medications can raise the risks of certain contraceptives. The World Health Organization (2015) has provided guidelines for the use of effective reversible contraceptive methods by women with various health conditions. Individual countries have subsequently modified these guidelines. The *United States Medical Eligibility Criteria (US MEC)* was updated in 2016 by the Centers for Disease Control and Prevention and is available at their website (Curtis, 2016b).

In the US MEC, reversible contraceptive methods are organized into six groups: levonorgestrel-releasing intrauterine system (LNG-IUS), copper intrauterine devices (Cu-IUDs), implants, depot medroxyprogesterone acetate (DMPA), progestin-only pills (POPs), and combination hormonal contraceptives (CHCs). This last group includes combination oral contraceptives (COCs), rings, and patches. For a given health condition, each method is categorized 1 through 4. The score describes the safety profile for a typical woman with that condition: (1) no restriction of method use, (2) method advantages outweigh risks, (3) method risks outweigh advantages, and (4) method poses an unacceptable health risk.

Alternatively, depending on the underlying disorder or patient desire, male or female sterilization may be a preferred or recommended permanent contraceptive method. These options are discussed in Chapter 39.

INTRAUTERINE DEVICES

The five IUDs currently approved for use in the United States are *chemically active* and continually elute either copper or a progestin. All have a flexible, T-shaped, polyethylene frame

TABLE 38-1. Contraceptive Failure Rates of Reversible Methods During the First Year and Use Rates[a]

Method	Perfect Use	Typical Use	Percent Use[b]
Top tier (most effective)			
Intrauterine devices:			11.8
52-mg LNG-IUS	0.1	0.1	–
T380A Cu-IUD	0.6	0.8	–
Etonogestrel implant	0.1	0.1	2.6
Female sterilization	0.5	0.5	21.8
Male sterilization	0.1	0.15	6.5
Second tier (very effective)			
Combination pill	0.3	7	24.9
Vaginal ring	0.3	7	2.4
Patch	0.3	7	0.2
DMPA	0.2	4	3.9
Progestin-only pill	0.3	7	0.4
Third tier (effective)			
Condom			14.6
Male	2	13	–
Female	5	21	–
Diaphragm + spermicides[c]	16	24	–
Fourth tier (least effective)			
Spermicides[c]	18	28	–
Sponge[c]			–
Multiparas	20	27	–
Nulliparas	9	14	–

[a]Among women in the United States using contraception.
[b]This sum totals less than 100% as withdrawal (8.1%) and natural family planning (2.2%) values are not presented in the table.
[c]Combined into "other method" category, which has a use rate of 0.6%.
Cu-IUD = copper-containing intrauterine device; DMPA = depot medroxyprogesterone acetate; LNG-IUS = levonorgestrel-releasing intrauterine system.
From Guttmacher Institute, 2020; Hall, 2012; Kavanaugh, 2018; Steiner, 2006; Trussell, 2018.

compounded with barium to render them radiopaque. The progestin-eluting devices are similarly shaped, but each differs by size, string color, longevity, and presence or absence of a silver band at the junction of the stem and arms (Table 38-2). Among these, smaller-sized devices are thought to better fit a nulliparous uterus (Gemzell-Danielsson, 2012). In contrast, the copper device, the T380A IUD named *ParaGard,* contains a thin copper strand wound around its stem and a copper bracelet on each arm.

■ Contraceptive Action

The contraceptive mechanism of IUDs is not precisely defined, but prevention of fertilization is now favored. Within the uterus, an intense local endometrial inflammatory response is induced, especially by the Cu-IUD. Inflammatory fluid fills the uterine cavity and fallopian tubes to decrease sperm and egg viability (Ortiz, 2007). Also, in the unlikely event that fertilization does occur, the same inflammatory actions are directed against the blastocyst. With the LNG-IUS, progestin release atrophies the endometrium to hinder normal implantation and creates scant viscous cervical mucus to obstruct sperm motility (Apter, 2014; Silverberg, 1986). The above effects are considered primary because ovulation inhibition is inconsistent with the LNG-IUS and lacking with the Cu-IUD (Nilsson, 1984).

■ Method-specific Adverse Effects

Ectopic Pregnancy

In the past, IUDs were perceived to increase the risk of ectopic pregnancy, but this has since been clarified. Specifically, IUDs provide effective contraception and lower the absolute number of ectopic pregnancies by half compared with the rate in noncontracepting women (World Health Organization, 1985). But, the IUD mechanisms of action are more effective in preventing *intrauterine* implantation. Thus, if an IUD fails, a higher proportion of pregnancies are likely to be ectopic (Furlong, 2002; Teal, 2019).

Lost Device

Expulsion of an IUD from the uterus is most common during the first month. Thus, women are examined approximately 4 to 6 weeks following IUD insertion, usually after menses, to identify the tails trailing from the cervix. Following this, a woman is instructed to palpate the strings each month after menses. Regardless of IUD type, the cumulative 3-year expulsion rate

TABLE 38-2. Properties of Intrauterine Devices

Active Agent	Quantity of Active Agent	Width × Height (mm)	Inserter Tube Diameter (mm)	FDA-approved Duration of Use (yr)	String Color	Silver Ring	Brand Name
LNG	52 mg	32 × 32	4.4	5	Tan	No	Mirena
LNG	52 mg	32 × 32	4.8	6	Blue	No	Liletta
LNG	19.5 mg	28 × 30	3.8	5	Blue	Yes	Kyleena
LNG	13.5 mg	28 × 30	3.8	3	Tan	Yes	Skyla, Jaydess
Copper	380 mm^3	32 × 36	4.4	10	White	No	ParaGard

FDA = U.S. Food and Drug Administration; LNG = levonorgestrel.

approximates 10 percent following nonpuerperal insertion (Madden, 2014; Simonatto, 2016).

If the tail of an IUD cannot be visualized, the device may have been expelled, may have perforated the uterus, or may be malpositioned. Alternatively, the device may be normally positioned with its tail folded within the endocervical canal or uterine cavity. To investigate, after excluding pregnancy, a cytological brush can be twirled within the endocervical canal to entangle the strings and bring them gently into the vagina. If unsuccessful, the uterine cavity is probed gently with a Randall stone clamp or with a specialized rod with a terminal hook to retrieve the strings.

One should not assume that a device has been expelled unless it was seen. Thus, if tails are not visible and the device is not felt by gentle probing of the uterine cavity, transvaginal sonography (TVS) can be used to ascertain if the device lies within the uterus. Although traditional TVS will document IUD position adequately in most cases, three-dimensional TVS offers improved views (Moschos, 2011). If sonography is inconclusive or if no device is seen, a plain radiograph of the abdominopelvis is taken. Computed tomography (CT) scanning or magnetic resonance (MR) imaging is an alternative depending on coexisting pregnancy and study access. MR imaging at 1.5 or 3 Tesla with an IUD in place is safe (Ciet, 2015).

Perforation

During sounding or IUD insertion, the uterus may be perforated, which is identified by the tool traveling farther than expected based on initial bimanual uterine examination. Rates approximate 1 case per 1000 insertions, and risks include puerperal insertion and breastfeeding (Barnett, 2017; Kaislasuo, 2012).

With acute perforation, the fundus is the more common site, and bleeding is often minimal due to myometrial contraction around the puncture site. If no brisk bleeding is noted from the os following removal of the wounding tool, patient observation alone is reasonable. Rarely, lateral perforations may lacerate the uterine artery, and subsequent heavy bleeding prompts laparoscopy or laparotomy for control.

With occult perforation, a device can penetrate the myometrium to varying degrees. Abdominal pain, uterine bleeding, or missing strings are clues, and imaging described in the last section is a primary step (Kaislasuo, 2013). A device with an arm partially embedded can sometimes be removed transcervically with steady traction. Otherwise, IUDs with a mainly intrauterine location are usually removed hysteroscopically. Devices that have nearly or completely perforated through the uterine wall are more easily extracted laparoscopically. Devices often embed on posterior cul-de-sac structures and omentum, but bowel and bladder perforations are possible (Şengül, 2014; Zeino, 2011).

Menstrual Changes

Dysmenorrhea and irregular bleeding can complicate IUD use. These can be treated with some degree of success by nonsteroidal antiinflammatory drugs (NSAIDs) or tranexamic acid, which is an antifibrinolytic (Friedlander, 2015). Of IUD types, heavy bleeding more often complicates Cu-IUD use and may cause iron-deficiency anemia, for which oral iron salts are given. With the LNG-IUS, irregular spotting for up to 6 months after placement often gives way to progressive amenorrhea, which is reported by approximately 10 percent of women after year 1 and 35 percent after 3 years (Goldthwaite, 2019). This is frequently associated with improved dysmenorrhea.

Infection

The risk of upper genital tract device-related infection is greatest during the first 3 weeks following IUD insertion (Farley, 1992; Turok, 2016). Pathogens include *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, and vaginal flora. Women at risk for sexually transmitted diseases (STDs) should be screened either before or at the time of IUD insertion (Centers for Disease Control and Prevention, 2015). That said, device insertion need not be delayed while awaiting STD or Pap test results in asymptomatic women (Birgisson, 2015). If these bacteria are subsequently found, the IUD may remain and treatment may be prescribed. Routine antimicrobial prophylaxis before insertion is not recommended (Grimes, 2012). Bacterial endocarditis prophylaxis is not needed with insertion (Nishimura, 2017).

After the first month, infection risk is not elevated in IUD users who would otherwise be at low risk of STDs. Correspondingly, IUDs cause little, if any, increase in infertility rates in these low-risk patients (Hubacher, 2001). The American College of Obstetricians and Gynecologists (2020a) recommends that women at low risk for STDs, including adolescents, be considered good candidates for IUDs. The IUD is also safe and effective in women with immunosuppression, including human immunodeficiency virus (HIV) infection (Tepper, 2016a). Moreover, IUD use does not appear to raise HIV acquisition rates (Curtis, 2020).

If infection does develop, it may take several forms and typically requires broad-spectrum antibiotics. *Pelvic inflammatory disease (PID)* without abscess is treated with antibiotics. There are theoretical concerns that a coexistent IUD may worsen the infection or delay resolution. A provider may choose to remove an IUD in this setting, although growing evidence supports allowing device retention during treatment in those with mild or moderate PID (Curtis, 2016a; Tepper, 2013). If infection fails to improve during 48 to 72 hours of treatment, the device is removed. *Tuboovarian abscess* can complicate PID and is treated aggressively with intravenous broad-spectrum antibiotics and IUD removal. Last, *septic abortion* mandates immediate uterine evacuation and antibiotics.

Actinomyces israelii is a gram-positive, slow-growing, anaerobic, indigenous vaginal bacterium. It is frequently identified in the vaginal flora or on the Pap smears of IUD users (Curtis, 1981; Kim, 2014). If found, an asymptomatic woman may retain her IUD and does not require antibiotics (Lippes, 1999; Westhoff, 2007a). However, with infection in a woman who harbors *Actinomyces* species, the device is removed and antibiotics with gram-positive coverage are given. Early findings with infection include fever, weight loss, abdominal pain, and abnormal uterine bleeding or discharge.

Pregnancy with an IUD

For women who become pregnant despite an IUD, ectopic pregnancy and pelvic infection each must be excluded. Pregnant women with a retained IUD and infection are treated with broad-spectrum antibiotics and prompt uterine evacuation.

For those with intrauterine pregnancy without infection, the IUD tail can be grasped, and the IUD removed by gentle outward traction. This action reduces rates of subsequent abortion, chorioamnionitis, and preterm birth (Brahmi, 2012). Specifically, in one cohort, a 54-percent abortion rate and 17-percent preterm delivery rate was noted if the device remained in situ. More favorably, rates of 25 percent and 4 percent, respectively, resulted from prompt Cu-IUD removal (Tatum, 1976). Few data guide management with the LNG-IUS, and most practice extrapolates from copper devices.

If the tail is not visible, attempts to locate and remove the device may result in abortion. Some case reports and small series describe sonography or hysteroscopy to assist difficult device removals, but this is not our practice (Pérez-Medina, 2014; Schiesser, 2004). In women who give birth with a device in place, appropriate steps should be taken at delivery to identify and remove the IUD.

Intrauterine Device Insertion

Timing

Before insertion, IUD contraindications are sought (Table 38-3). Candidates are counseled, and written consent obtained.

To reduce expulsion rates, IUD insertion traditionally has followed complete uterine involution and is termed *interval* placement. Instead, immediately following miscarriage, surgical abortion, or delivery, an IUD may be inserted in the absence of overt infection (Roe, 2019; Whitaker, 2018). Also, early insertion 1 week after mifepristone and completed medical abortion has been described (Sääv, 2012; Shimoni, 2011). Compared with interval insertion, the IUD expulsion rate is slightly higher with *immediate* placement, defined as the first 10 minutes after placenta delivery. The highest rates are with *early* placement, defined as later than 10 minutes but within the first month postpartum (Jatlaoui, 2018). The higher US MEC scores seen in Table 38-4 reflect these early-placement expulsion risks.

TABLE 38-3. Contraindications to IUD Use

Both IUD Types
Pregnancy or suspicion of pregnancy
Distorted uterine cavity
Acute PID
Postpartum/postabortal endometritis in past 3 months
Uterine bleeding of unknown etiology
Acute untreated LGT infection
Conditions linked to pelvic infection risk[a]
Allergy to device components
Coexisting retained IUD

Specific to Cu-IUD
Known or suspected uterine or cervical cancer
Wilson disease

Specific to LNG-IUS
Prior PID unless a subsequent IUP has occurred
Known or suspected uterine or cervical neoplasia
Acute liver disease or benign/malignant liver tumor
Known or suspected current or prior breast cancer or other progestin-sensitive cancer

[a]These include multiple sexual partners, severe immune compromise, intravenous drug use, and recent PID or endometritis.
Cu-IUD = copper-containing intrauterine device; IUD = intrauterine device; IUP = intrauterine pregnancy; LGT = lower genital tract; LNG-IUS = levonorgestrel-releasing intrauterine system; PID = pelvic inflammatory disease.
Bayer HealthCare Pharmaceuticals, 2017; CooperSurgical, 2020.

TABLE 38-4. U.S. Medical Eligibility Criteria Category of Contraceptive Methods Related to Breastfeeding and Time After Delivery

Method CHCs[a]	Cat.	DMPA, POPs, Implants	Cat.	LNG-IUS	Cat.	Cu-IUD	Cat.
Breastfeeding		Breastfeeding		± Breastfeeding[c]		± Breastfeeding[c]	
<21 d	4	<1 month	2	<10 mins	2	<10 min	1
21 d to <30 d	3	≥1 month	1	10 mins to ≤4 wks	2	10 min to ≤4 wks	2
30–42 d[b]	2			≥4 wks	1	≥4 wks	1
>42 d	2			Puerperal sepsis	4	Puerperal sepsis	4
Nonbreastfeeding		Nonbreastfeeding	1				
<21 d	4						
21–42 d[b]	2						
>42 d	1						

[a]Combined hormonal contraceptive (CHC) group includes pills, vaginal ring, and patch.
[b]Associated risks that increase puerperal category score include: age ≥35, transfusion at delivery, body mass index ≥30, postpartum hemorrhage, cesarean delivery, smoking, preeclampsia.
[c]With or without breastfeeding.
Cat. = category; Cu-IUD = copper-containing intrauterine device; DMPA = depot medroxyprogesterone acetate; LNG-IUS = levonorgestrel-releasing intrauterine system; POPs = progestin-only pills.
From Curtis, 2016b; Kapp, 2009b.

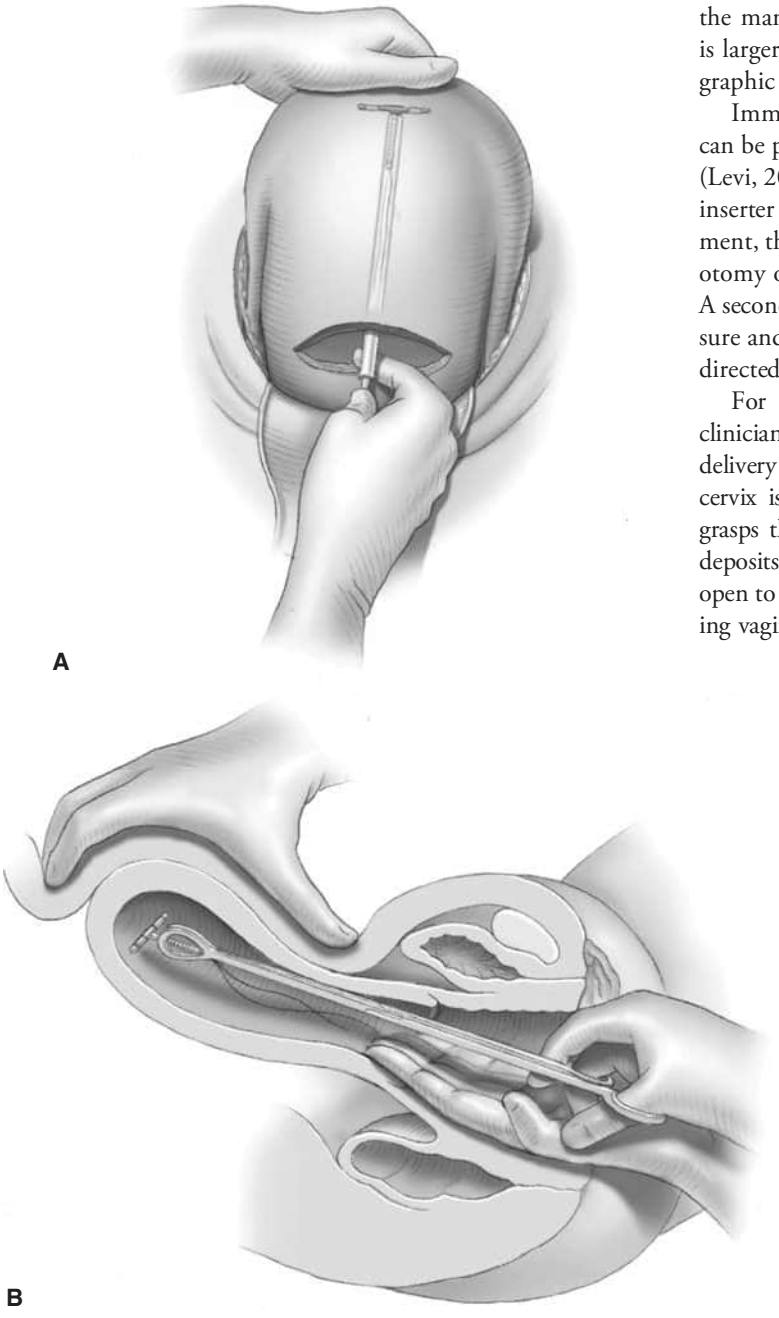

FIGURE 38-1 A. Intrauterine device (IUD) insertion at cesarean delivery. The device inserter guides the device to the uterine fundus. A hand at the fundus can provide back pressure to stabilize the uterus during insertion. **B.** IUD insertion after vaginal delivery. Ring forceps direct the device to the uterine fundus. Back pressure against the fundus by an abdominal hand can help guide positioning. (Reproduced with permission from Stuart GS, Hoffman BL: Puerperal sterilization. In Yeomans ER, Hoffman BL, Gilstrap LC III, et al (eds): Cunningham and Gilstrap's Operative Obstetrics, 3rd ed. New York, McGraw Hill; 2017.)

However, the number of women in immediate-placement groups who ultimately receive and retain an IUD is greater than in groups scheduled for interval placement, because some fail to return for insertion (Bednarek, 2011; Chen, 2010).

Postpregnancy Insertion Techniques

With immediate insertion, techniques depend on uterine size. After first-trimester evacuation, the IUD can be placed using the manufacturer's standard instructions. If the uterine cavity is larger, the IUD can be placed using ring forceps with sonographic guidance (Fox, 2011).

Immediately following vaginal or cesarean delivery, an IUD can be placed by a hand, by its inserter tube, or by ring forceps (Levi, 2015). The arms of the IUD need not be folded into the inserter tube prior to insertion. During cesarean delivery placement, the hand or inserter travels through the unsutured hysterotomy opening to deposit the device at the fundus (Fig. 38-1). A second hand cupping the outer fundus can provide back pressure and stabilize the uterus during insertion. Strings are gently directed but not pulled toward the cervix.

For instrumented insertion following vaginal delivery, the clinician resterilizes the vulva and changes gloves after placental delivery but before perineal repairs. The anterior lip of the floppy cervix is held with ring forceps. A second ring forceps gently grasps the IUD stem, guides it up into the uterine cavity, and deposits it at the fundus. During forceps removal, the jaws remain open to avoid ensnaring the strings. For manual insertion following vaginal delivery, the provider holds the IUD between fingers to deposit the device. In either case, back pressure against the fundus by an abdominal hand can guide fundal positioning (Stuart, 2017).

Interval Insertion Technique

For placement not related to pregnancy, insertion near the end of normal menstruation, when the cervix is usually softer and somewhat more dilated, may be easier and also helps exclude early pregnancy. However, for the woman who is sure she is not pregnant and does not want to be pregnant, insertion is done at any time.

To ease insertional pain, applying lidocaine-prilocaine cream locally or placing paracervical blockade can be helpful (Akers, 2017; Samy, 2019). Bimanual pelvic examination delineates uterine position and size. Abnormalities are evaluated, as they may contraindicate insertion. Mucopurulent cervicitis or significant vaginitis is appropriately treated and resolved before IUD insertion.

The ectocervix is cleansed with an antiseptic solution, and sterile instruments are used. A tenaculum is placed on the cervical lip, and the endocervical canal and uterine cavity are straightened by applying gentle outward traction. A uterine sound is guided into the cavity to identify its direction and depth. Specific steps of Cu-IUD and LNG-IUS insertions are outlined in their respective package inserts.

Following insertion, only the threads should be visible trailing from the cervix. These are trimmed to allow 3 to 4 cm to protrude into the vagina, and their length is recorded. An oral NSAID can be used for cramping after insertion (Ngo, 2015).

If improper device positioning is suspected, placement should be confirmed, using sonography if necessary. If the IUD is not positioned completely within the uterus, it is removed and replaced with a new device. An expelled or partially expelled device should not be reinserted.

PROGESTIN-ONLY CONTRACEPTIVES

Actions and Side Effects

Progestin-only contraceptives include implants, injectables, and pills. These suppress luteinizing hormone (LH) to block ovulation, cervical mucus thickens to retard sperm passage, and atrophy renders the endometrium unfavorable for implantation. Fertility is restored rapidly following cessation except for DMPA, described later (Mansour, 2011).

After placenta delivery, progesterone withdrawal may contribute to lactogenesis, and early progestin use theoretically could hinder breastmilk establishment. Although studies support the safety of early puerperal use of progestins, this theoretical risk is still reflected in their higher US MEC score (see Table 38-4) (Carmo, 2017; Phillips, 2016).

For all progestin-only methods, irregular uterine bleeding is the most frequent adverse event prompting discontinuation. Often, counseling and reassurance is sufficient. In others, troublesome bleeding may be improved by combining the progestin method with a 2-week course of estrogen or with a short course of NSAIDs (Abdel-Aleem, 2013). A few cycles of COCs combined with DMPA or an implant is another option. Fortunately, with prolonged use, progestins induce endometrial atrophy, which can lead to sustained amenorrhea. For the informed patient, this is often an advantage. Iron-deficiency anemia is also less likely.

Most progestin-only contraceptive methods do not significantly affect lipid metabolism, glucose levels, hemostatic factors, liver function, thyroid function, or blood pressure (Dorflinger, 2002). However, the increased low-density lipoprotein (LDL) cholesterol and decreased high-density lipoprotein (HDL) cholesterol levels seen with DMPA are less desirable for women with cardiovascular disease risks (Kongsayreepong, 1993).

Risks for genital tract, liver, or breast neoplasia are not increased with progestin-only methods (Samson, 2016; Wilailak, 2012; World Health Organization, 1991a,b, 1992). Weight gain and bone fracture are not prominent side effects of this contraceptive group, except for DMPA, discussed later (Lopez, 2012, 2013). Functional ovarian cysts are seen more often in women using progestin-only agents, although intervention is not usually required (European Society of Human Reproduction and Embryology, 2001). Last, concern for a higher depression rate is not supported by recent studies (Skovlund, 2016; Worly, 2018).

Progestin Contraindications

Current pregnancy, breast cancer, acute liver disease, liver tumors, and undiagnosed abnormal genital bleeding are absolute contraindications. For Nexplanon and DMPA, their manufacturers also add current or past history of thromboembolic disorders (Merck, 2019; Pfizer, 2017). However, for women with these disorders, the US MEC considers progestin-containing methods category 2 (Curtis, 2016b).

Progestin Implants

These thin, pliable, progestin-containing cylinders can be implanted in the upper arm to release contraceptive hormone over several years. Implants are an effective, top-tier method (Mommers, 2012; Sivin, 1998; Steiner, 2010).

These systems are placed subdermally on the inner arm approximately 8 cm from the elbow. Implants vary in their insertion technique, and manufacturer instructions should be consulted. After their expiration date, implants are removed, and may be replaced at the same site or in the opposite arm.

Nexplanon is a single-rod etonogestrel implant that releases at least 30 µg of hormone daily and may be used for 3 years. The inserter design assists with subdermal positioning and averting deeper placement. Nexplanon replaced *Implanon*, which is still approved by the Food and Drug Administration (FDA) but no longer distributed by the manufacturer.

Levonorgestrel implants are two-rod systems available outside the United States and contain a total LNG dose of 150 mg. *Jadelle* provides contraception for 5 years. It is approved by the FDA but not marketed in the United States. *Sino-implant II* provides 3 years of contraception (Steiner, 2019).

Method-specific Adverse Effects

In addition to the hormonal side effects listed earlier, the implants themselves can cause adverse events. These complicate approximately 1 percent of implant insertions and 5 percent of removals (Creinin, 2017; Reed, 2019). Of serious events, branches of the medial antebrachial cutaneous nerve and median nerve can be injured during an implant insertion that is too deep or during exploration for implant removal (Laumonerie, 2018). Thus, implants found deep in muscle or near neurovascular structures are best removed by surgeons with a clear understanding of upper arm anatomy (American College of Obstetricians and Gynecologists, 2019a).

Nonpalpable devices are not uncommon and require imaging for localization prior to attempted removal. Nexplanon is radiopaque and can be imaged by two-dimensional x-ray views. Implanon is not radiopaque, and sonography using a 10- to 15-MHz linear array transducer or MR imaging is needed (Correia, 2012; Shulman, 2006). Rarely, an implant can migrate to distant sites such as the lung (Kang, 2017). If imaging fails to locate an implant, etonogestrel blood levels can help verify that the implant is indeed in situ. This assay must be coordinated with the manufacturer (877-888-4231).

Implant Insertion

The etonogestrel implant is ideally inserted within 5 days of menses onset. With LNG-releasing implants, contraception is established within 24 hours if inserted within the first 7 days of the menstrual cycle. For transitioning methods, an implant is placed on the day of the first placebo COC pill; on the day that the next DMPA injection would be due; or within 24 hours of the last POP (Merck, 2019). In women certain that they are not pregnant, insertion at other times of the cycle is followed by an additional method that serves as a back-up method for 7 days. Postabortion or postpartum, an implant may be inserted before discharge home (Madden, 2012; Sothornwit, 2017).

For insertion, the supine patient positions her nondominant arm against the bed so that the arm is abducted and the elbow is flexed. With a sterile pen, the insertion site is marked 8 to 10 cm proximal to the humerus' medial condyle and 3 to

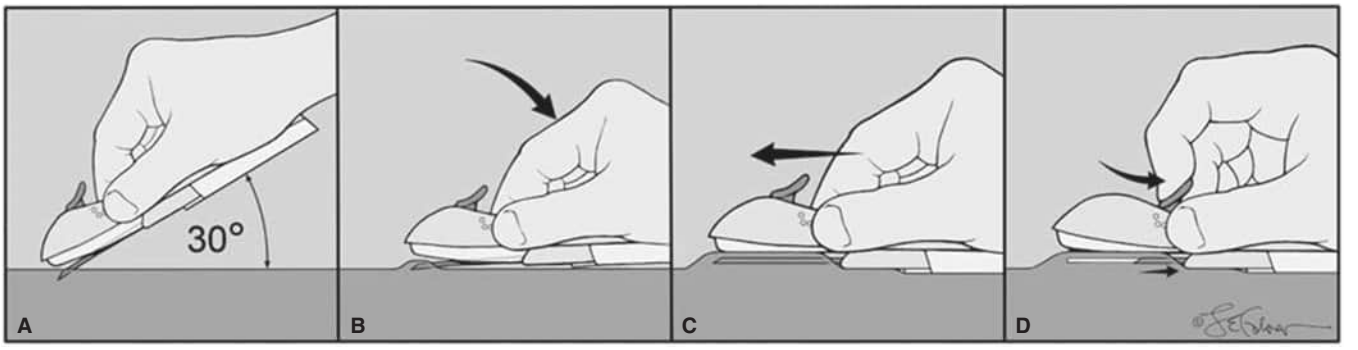

FIGURE 38-2 Nexplanon insertion. A sterile pen marks the insertion site, which is 8 to 10 cm proximal to the medial humeral condyle. A second mark is placed 4 cm proximally along the arm's long axis. The area is cleaned aseptically, and a 1-percent lidocaine anesthetic track is injected along the planned insertion path. **A.** The insertion device is grasped at its gripper bubbles found on either side, and the needle cap is removed outward. The device can be seen within the needle bore. The needle bevel then pierces the skin at a 30-degree angle. **B.** Once the complete bevel is subcutaneous, the needle is quickly angled downward to lie horizontally. **C.** Importantly, the skin is tented upward by the needle as the needle is slowly advanced horizontally and subdermally. **D.** Once the needle is completely inserted, the lever on the top of the device is pulled backward toward the operator. This retracts the needle and thereby deposits the implant. The device is then lifted away from the skin. After placement, both patient and operator should palpate the 4-cm implant.

5 cm posterior to the groove between biceps and triceps muscles (Iwanaga, 2019). A second mark is placed 4 cm proximal to the first and serves as a guide for the insertion path along the arm's long axis. The Nexplanon is inserted using sterile technique. The area is cleansed aseptically, and a 1-percent lidocaine anesthetic track is injected beneath the skin along the planned insertion path. The implant is then placed as shown in Figure 38-2. After placement, both patient and provider should palpate and identify both ends of the 4-cm implant. To minimize bruising at the site, a pressure bandage is created around the arm and is removed the following day.

With implant extraction, the removal site is first cleansed with antiseptic. The proximal end of the implant is depressed with a finger to allow the distal end to lift up toward the skin. After anesthetizing the skin over this bulge, the skin is incised 2 mm toward the elbow along the arm's long axis. The implant's proximal butt is then pushed toward this incision. Once visible, the implant's distal end is grasped with a hemostat and removed. Superficial adhesions surrounding an implant are common and are dissected away with hemostat tips.

■ Injectable Progestin Contraceptives

DMPA, 150 mg every 3 months, and norethisterone enanthate, 200 mg every 2 months, are two intramuscular injectable progestin-only contraceptives used worldwide. Of the two, DMPA is available in the United States and marketed as *Depo-Provera*. DMPA is injected into the deltoid or gluteus muscle, but massage is avoided to ensure that the drug is released slowly. A subcutaneous version, *depo-subQ provera 104*, is injected into the subcutaneous tissue of the anterior thigh or abdomen every 3 months. This form may be self-administered (Curtis, 2021).

Initial injection is given within the first 5 days following menses onset. Serum levels sufficient for contraception are present by 24 hours. Thus, no additional contraceptive method is required for initiation within this window. Limited data support a *quick start*, or initiation of DMPA regardless of cycle day. If so implemented, investigators recommend an initial negative pregnancy test result before injection, a supplemental contraceptive method during the 7 days following injection, and a second pregnancy test after 3 to 6 weeks to identify an early pregnancy (Sneed, 2005). Conceptions during DMPA use do not have higher fetal anomaly rates (Katz, 1985).

Method-specific Adverse Effects

Unique to DMPA, prolonged anovulation can follow discontinuation and results in delayed fertility resumption (Paulen, 2009). After injections are stopped, a fourth of patients do not resume regular menses for up to 1 year (Gardner, 1970). Thus, DMPA may be less ideal for women who plan to use birth control only briefly before attempting conception.

As with other progestins, DMPA is not associated with cardiovascular events or stroke in otherwise healthy women. However, in those with severe hypertension, a higher risk of stroke has been found in DMPA users (World Health Organization, 1998). The US MEC authors express concerns regarding DMPA's hypoestrogenic effects and reduced HDL levels for women with vascular disease or multiple cardiovascular disease risks (Curtis, 2016b).

Weight gain is generally attributed to DMPA, and ranges from 1 to 3 kg in the first year (Dianat, 2019). In long-term users, bone density loss is also greater than in nonusers (Petitti, 2000; Scholes, 1999). It is somewhat reassuring that bone loss appears to slowly reverse after cessation (Clark, 2006; Scholes, 2002). In 2004, the FDA added a black box warning to DMPA labeling, which notes that this concern is probably most relevant for adolescents, who are building bone mass, and perimenopausal women, who will soon have increased bone loss during menopause. Despite this, DMPA should not be restricted in those high-risk groups (American College of Obstetricians and Gynecologists, 2019b).

■ Progestin-only Pills

Also called *mini-pills*, this group contains norethindrone-only, desogestrel-only, and drospirenone-only pills. Of these, each

norethindrone-only pill provides 0.35 mg of hormone and is taken daily and continuously. This specific drug does not reliably inhibit ovulation. Efficacy stems from cervical mucus thickening and endometrial atrophy. Because mucus changes are not sustained, these pills are best taken at the same time each day. If the pill is taken even 3 hours late (missed-pill window), a backup form of contraception is used for the next 48 hours.

In contrast, the drospirenone-only pill marketed as *Slynd* delivers 4 mg of hormone and is taken for 24 consecutive days out of a 28-day cycle. Progestin withdrawal during the last 4 days aims to minimize irregular bleeding (Archer, 2015). Both drospirenone and desogestrel pills alter mucus and endometrium *plus* reliably inhibit ovulation. *Slynd* offers a 24-hour missed-pill window, which mirrors that of COC pills (Duijkers, 2016).

Drospirenone is structurally similar to spironolactone. It displays antiandrogenic activity, provides an antialdosterone action to minimize water retention, and has antimineralocorticoid properties that may, in theory, cause potassium retention and hyperkalemia (Krattenmacher, 2000). Thus, contraindications are renal or adrenal insufficiency in addition to traditional progestin contraindications, listed earlier (p. 669). Serum potassium level monitoring is recommended in the first month for patients chronically treated with any drug associated with potassium retention. These include NSAIDs, angiotensin-converting enzyme (ACE) inhibitors, angiotensin II antagonists, heparin, aldosterone antagonists, and potassium-sparing diuretics.

Last, desogestrel-only pills contain 0.075 mg of hormone and are used daily and continuously. Its missed-pill window is 12 hours. These are not available in the United States.

TABLE 38-5. Estrogen and Progestins Used in FDA-Approved Combination Oral Contraceptive Pills

Estrogen Type (Pill Dose)	Paired Progestin[a]
Ethinyl estradiol 10 μg	Norethindrone acetate
Ethinyl estradiol 20 μg	Desogestrel Drospirenone Levonorgestrel Norethindrone acetate
Ethinyl estradiol 25 μg	Desogestrel Norgestimate
Ethinyl estradiol 30–35 μg	Desogestrel Drospirenone Ethynodiol diacetate Levonorgestrel Norethindrone Norethindrone acetate Norgestimate Norgestrel
Ethinyl estradiol 50 μg	Ethynodiol diacetate Norgestrel
Estradiol valerate 2 mg Estetrol 14.2 mg Mestranol 50 μg	Dienogest Drospirenone Norethindrone

[a]Progestins are listed alphabetically.
FDA = U.S. Food and Drug Administration.

COMBINATION HORMONAL CONTRACEPTIVES

Mechanism of Action

The most important contraceptive effect of both the estrogen and progestin components of CHCs is suppression of hypothalamic gonadotropin-releasing factors to inhibit ovulation. The progestin also thickens cervical mucus to retard sperm passage and renders the endometrium unfavorable for implantation. Estrogen stabilizes the endometrium, which prevents intermenstrual bleeding—also known as *breakthrough bleeding*. This benefit is termed *cycle control*. The net effect is an extremely effective yet highly reversible contraceptive method.

Combination Oral Contraceptive Pills

Composition

COCs are marketed in various estrogen and progestin combinations (Table 38-5). Ethinyl estradiol is the most common estrogen present in formulations in the United States. Less frequently, mestranol, estetrol, or estradiol valerate is used. Unwanted effects most often attributed to the estrogen component are breast tenderness, weight gain, nausea, and headache.

COCs contain one of several progestins that are structurally related to progesterone, testosterone, or spironolactone. Thus, these progestins bind variably to progesterone, androgen, glucocorticoid, and mineralocorticoid receptors. These affinities explain many pill-related side effects and are often used to compare one progestin with another. However, the advantage of one progestin over another is less apparent clinically (Lawrie, 2011; Moreau, 2007).

To minimize adverse effects, estrogen and progestin content in COCs has dropped remarkably. Currently, the lowest acceptable dose is limited by the ability to prevent pregnancy yet maintain cycle control. Thus, the daily estrogen content varies from 10 to 50 μg of ethinyl estradiol, and most contain ≤35 μg.

In a few COCs, inert placebo pills have been replaced by tablets containing iron. These have the suffix Fe added to their name. Instead, *Beyaz* and *Sayfral* have a form of folate—*levomefolate calcium*—within both its active and placebo pills.

With COCs termed *monophasic*, the progestin dose remains constant. In others, the dose frequently is varied, and term *biphasic, triphasic,* or *quadriphasic* is used depending on the number of dose changes within one cycle. In some formulations, the estrogen dose also varies. In general, phasic pills aim to reduce the total progestin content and associated side effects per cycle without sacrificing contraceptive efficacy or cycle control. The theoretical advantage of this approach, however, has not been borne out clinically (Moreau, 2007). Cycle control also appears similar among mono-, bi-, and triphasic pills (van Vliet, 2011a,b,c).

Administration

Hormones are taken daily for a specified time (21 to 81 days) and then replaced by placebo for a specified time (4 to 7 days), which is called the *pill-free interval*. During these pill-free days, bleeding prompted by hormonal withdrawal is expected.

With the trend toward lower estrogen doses, follicular growth and ovulation may occur. To counter this, the active-pill duration in some formulations is extended to 24 days. In comparison, these 24/4 regimens perform similarly to 21/7 regimens (Anttila, 2011; Marr, 2012).

Longer durations of active hormone are designed to minimize the number of withdrawal bleeding episodes. This practice has similar efficacy and safety profiles compared with traditional administration (Edelman, 2014). These *extended-cycle* products produce a 13-week cycle, that is, 12 weeks of hormone use, followed by a week for withdrawal menses. Instead, the product *Amethyst* provides continuous active hormone pills for 365 days each year. These extended-cycle and continuous regimens may be especially suited for women with significant menstrual symptoms (Mendoza, 2014).

Women ideally begin COCs on the first day of a menstrual cycle. In such cases, a back-up method is unnecessary. With the more traditional "Sunday start," women begin pills on the first Sunday that follows menses onset, and a back-up method is added for 1 week. If menses begin on a Sunday, pills are begun that day and no back-up method is required. Alternatively, with a quick start, COCs are started on any day, commonly the day prescribed. A back-up method is added for 1 week (Westhoff, 2007b). If the woman is unknowingly already pregnant, COCs are not teratogenic (Rothman, 1978; Savolainen, 1981). A missed menses after COC initiation should prompt pregnancy testing. Similar initiation methods are used for contraceptive vaginal rings or patches.

For maximum efficiency, pills are best taken at the same time each day. If one dose is missed, the missed pill is taken immediately; the scheduled dose for that day is taken on time; and then daily pills are continued. If two or more doses are missed, the most recent missed pill is taken immediately; the scheduled dose for that day is taken on time; and a back-up method is used for 7 days while daily pills are then continued (Curtis, 2016a). If withdrawal bleeding fails to occur during the pill-free interval, a woman should continue her pills but exclude pregnancy.

With COC initiation, spotting or bleeding is common. It does not reflect contraceptive failure and typically resolves within one to three cycles. If unscheduled bleeding persists, those with bleeding during the first part of a pill pack may benefit from an increase in the estrogen dose, whereas those with bleeding during the second part may improve with a higher progestin dose (Nelson, 2011).

Method-specific Effects

Altered Drug Efficacy

Some drugs decrease COC effectiveness, and choosing another contraceptive method is preferable. Most notable are rifampin/rifabutin, but other antibiotics are not implicated (Simmons, 2018). Cytochrome P450–inducing anticonvulsants are another group and include phenytoin, phenobarbital, primidone, carbamazepine, oxcarbazepine, topiramate, rufinamide, and felbamate (American College of Obstetricians and Gynecologists, 2020b). Some antiretroviral drugs, mainly among the protease inhibitor group, can interact with COCs. A rapidly evolving list is provided by the U.S. Department of Health and Human Services (2019).

In obese women, COCs are effective (Simmons, 2016). With the *Ortho Evra* transdermal patch, however, obesity may alter pharmacokinetics and lower efficacy (p. 674).

On the other hand, some COCs lower the actions of certain drugs. Notably, lamotrigine efficacy is lowered by COCs (Gaffield, 2011).

Metabolic Changes, Risks, and Benefits

The hormones in COCs can induce metabolic changes that may aggravate underlying medical conditions. Most of the contraindications to COCs reflect these metabolic alterations (Table 38-6).

Hepatic angiotensinogen synthesis is augmented by COCs. Its conversion by renin to angiotensin I may be associated with pill-induced hypertension. Thus, patients return 8 to 12 weeks after COC initiation for evaluation of blood pressure and other symptoms. However, women using low-dose COC formulations rarely develop clinically significant hypertension (Chasan-Taber, 1996).

In women with well-controlled hypertension, COC use is linked to greater risks than in nonusers for stroke, acute myocardial infarction, and peripheral arterial disease, and in these women, COCs are considered US MEC category 3 (Curtis, 2016b). Severe forms of hypertension, especially those with end-organ involvement, preclude COC use.

The estrogen component of COCs boosts hepatic production of fibrinogen and many of the clotting factors. Deep-vein thrombosis and pulmonary embolism rates are increased in women who use COCs (Stadel, 1981). These events are estrogen-dose related, and rates have substantively declined with lower-dose formulations containing 10 to 35 μg of ethinyl estradiol. The general-population risk of venous thromboembolism (VTE) is 4 to 5 events per 100,000 woman-years. The incidence of VTE with COC use increases three- to fivefold compared with nonusers (Shaw, 2013; van Hylckama Vlieg,

TABLE 38-6. Contraindications to the Use of Combination Oral Contraceptive Pills

Pregnancy
Uncontrolled hypertension
Smokers older than 35 years
Diabetes with vascular involvement
Cerebrovascular or coronary artery disease
Migraines with associated focal neurologic deficits
Thrombophlebitis or thromboembolic disorders
History of deep-vein thrombophlebitis or thrombotic disorders
Thrombogenic heart arrhythmias
Thrombogenic cardiac valvulopathies
Undiagnosed abnormal genital bleeding
Known or suspected breast carcinoma
Cholestatic jaundice of pregnancy or jaundice with pill use
Hepatic adenomas and carcinomas
Cirrhosis or active liver disease with abnormal liver function
Known or suspected estrogen-dependent neoplasia

2009). Obesity raises the general VTE risk, which is compounded by COCs (Horton, 2016; Suchon, 2016). Accordingly, in an obese woman, COCs are considered a US MEC category 2. VTE rates are also significantly increased in women smokers older than 35 years, and COCs are not recommended. Those most at risk for VTE include women with thrombophilias (ESHRE Capri Workshop Group, 2013). Moreover, COC use during the month before a major operative procedure appears to double the risk for postoperative VTE (Robinson, 1991). Thus, the American College of Obstetricians and Gynecologists (2021) recommends balancing the risks of VTE and the degree of postoperative immobility with the risk of unintended pregnancy during the 4 to 6 weeks required to reverse the thrombogenic effects of COCs before surgery. In the early puerperium, VTE risks are also increased, and COCs are not recommended early (see Table 38-4).

Certain progestins within COC are also linked with greater VTE rates. A slightly higher VTE risk with drospirenone-containing COCs has been shown in two studies. In response, an assessment of benefits and VTE risks in users of these pills has been emphasized (Food and Drug Administration, 2012; Jick, 2011; Parkin, 2011). Desogestrel and gestodene are also implicated and carry similarly elevated risks (Stegeman, 2013; Vinogradova, 2015).

For women with prior myocardial infarction, COCs should not be considered. Also, for women with multiple cardiovascular risk factors, which include smoking, hypertension, older age, dyslipidemias, and diabetes, the risk for myocardial infarction outweighs the benefits of this method. For women with no cardiovascular risks, low-dose oral contraceptives are not associated with an increased risk of myocardial infarction (Margolis, 2007; World Health Organization, 1997).

For nonsmoking women younger than 35, stroke is rare (World Health Organization, 1996). COCs are associated with a small increased risk for ischemic stroke (Chan, 2004; Lidegaard, 2012). Rates rise significantly for women who have hypertension, who smoke, or who have migraine headaches with visual aura or other focal neurological changes *and* use COCs (MacClellan, 2007; Tepper, 2016b). The evidence for stroke risk in migraineurs without aura is less clear (Etminan, 2005; Schürks, 2009). COC initiation may be considered for women with preexisting migraines without aura if they are otherwise healthy, younger, normotensive nonsmokers. For women with prior stroke, COCs should not be considered to avoid repeat events.

Regarding carbohydrate metabolism, the risk of developing diabetes is not increased with COC use (Kim, 2002). For diabetic women, COCs may be used in nonsmokers with disease duration <20 years and without associated vascular disease, nephropathy, retinopathy, or neuropathy (Curtis, 2016b). In general, COCs raise serum triglycerides and total and HDL cholesterol levels but lower LDL cholesterol concentrations. Last, studies do not support a connection between COCs and weight gain (Gallo, 2014).

Regarding neoplasia, COCs offer a protective effect against ovarian and endometrial cancers (Collaborative Group on Epidemiological Studies of Ovarian Cancer, 2008; Tsilidis, 2011). As an exception, the relative risk of cervical dysplasia and cervical cancer is higher in current COC users, but this declines after use is discontinued. Following 10 or more years, risk returns to that of never users (International Collaboration of Epidemiological Studies of Cervical Cancer, 2007). It is unclear whether COCs contribute to breast cancer development. Major studies show no risk or a small risk among current users, which drops with time following cessation (Collaborative Group on Hormonal Factors in Breast Cancer, 1996; Hannaford, 2007; Marchbanks, 2002).

COCs are not a risk for liver tumors (Heinemann, 1998; Maheshwari, 2007). For women with known tumors, COCs may be used in those with focal nodular hyperplasia, but avoided in those with benign hepatic adenoma and hepatocellular carcinoma (Kapp, 2009c). Rates of colorectal cancer appear to be reduced in ever users (Bosetti, 2009; Luan, 2015).

Of other potential effects, cholestasis and cholestatic jaundice are uncommon and resolve when COCs are discontinued. In women who have active hepatitis, COCs should not be initiated, but these may be continued in women who experience a flare of their liver disease while already taking COCs. Use of progestin-only contraception in these women is not restricted. Moreover, COCs are suitable for women who have recovered. Mild compensated cirrhosis does not limit the use of COCs or progestin-only methods. With severe decompensated disease, all hormonal methods are avoided (Kapp, 2009a).

Chloasma, which is hyperpigmentation of the face and forehead, is more likely in women who demonstrated such a change during pregnancy. This is less common with low-dose estrogen formulations.

Previously, COCs were used to treat functional ovarian cysts. However, data do not support use of current low-dose COC formulations to resolve or prevent these (European Society of Human Reproduction and Embryology, 2001; Grimes, 2014).

Last, many noncontraceptive benefits are associated with COC use (American College of Obstetricians and Gynecologists, 2018). COCs are often selected for these effects, even in those without contraceptive needs. First, dysmenorrhea and heavy menstrual bleeding declines. COCs also elevate hepatic production of sex hormone–binding globulin. This binds bioavailable testosterone to diminish the action of androgens. Thus, conditions such as acne and hirsutism can improve. For women with premenstrual dysphoric disorder, drospirenone-containing COCs can lessen symptoms (Pearlstein, 2005; Yonkers, 2005).

Intravaginal Rings

NuvaRing is a flexible clear intravaginal ring that measures 54 mm in diameter and 4 mm in cross section. Its core releases ethinyl estradiol and etonogestrel, which are absorbed across the vaginal epithelium. *Annovera* is a new ring that releases ethinyl estradiol and segesterone acetate. Colored white, it measures 56 mm in diameter and 8.4 mm in cross section.

For both, the ring is inserted within 5 days of menses onset and, after 3 weeks of use, is removed for 1 week to allow withdrawal bleeding. *Nuvaring* is single use, and after menses, a new ring is placed. In contrast, after removal and washing, the same *Annovera* ring is reinserted for another 3 weeks. One ring can function for 13 such cycles (Nelson, 2019).

With insertion, the ring is compressed and advanced into the vagina, but no specific final orientation within the vagina is

required. Patient satisfaction is high with this method, although vaginitis, ring-related events, and leukorrhea are more common than with COCs (Gemzell-Danielsson, 2019; Oddsson, 2005). A ring may be used concurrently with vaginal medications or with a tampon (Verhoeven, 2004a,b). However, with *Annovera*, miconazole suppositories raised hormone levels. These were not altered with miconazole cream, and thus cream or oral antifungals are preferable (Simmons, 2018). Partners may feel the ring during intercourse (Dieben, 2002). If this is bothersome, the ring may be removed for intercourse but should be replaced within 3 hours for *Nuvaring* and within 2 hours for *Annovera* to maintain efficacy.

Transdermal Patches

The *Ortho Evra* patch and its generic *Xulane* each contain ethinyl estradiol and norelgestromin. A newer patch, *Twirla*, releases ethinyl estradiol and levonorgestrel. Either patch may be applied to the buttocks, upper outer arm, lower abdomen, or upper torso, but the breasts are avoided. Rates of application-site skin reaction are low (Kaunitz, 2015; Smallwood, 2001). If a patch is so poorly adhered that it requires reinforcement with tape, it should be replaced. Women can wear the patch in saunas and whirlpools without decreased efficacy (Abrams, 2001; Archer, 2013). However, with *Twirla*, swimming is limited to 30 minutes.

Initiation of the patch is the same as for COCs, and a new patch is applied weekly for 3 weeks, followed by a patch-free week to allow withdrawal bleeding. In general, the transdermal patches and vaginal rings produce metabolic changes, side effects, and efficacy rates comparable to those with COC pills.

However, the *Ortho Evra* patch has been associated with a higher VTE risk in some but not all studies (Cole, 2007; Jick, 2010; Lidegaard, 2011). Labeling for the patch states that the risk for VTE may be increased compared with COCs, and relative risk estimates range from 1.2 to 2.2. In addition, obesity—90 kg or greater—may be associated with a higher risk for patch contraceptive failure (Zieman, 2002).

In contrast, the LNG-containing patch showed comparable VTE rates compared with COCs in one randomized trial (Kaunitz, 2015). Moreover, efficacy was similar between obese and normal-weight users.

BARRIER METHODS

Male Condom

For many years, male and female condoms, vaginal diaphragms, and periodic abstinence have been used for contraception with variable success. When used properly, condoms provide considerable but not absolute protection against a broad range of STDs, including HIV (Eaton, 2014). Contraceptive efficacy of the male condom is enhanced by a reservoir tip and by the addition of a spermicide. Adjunct lubricant and spermicides should be water-based because oil-based products degrade latex.

For individuals sensitive to latex, condoms made from lamb intestines are effective, but they do not provide infection protection. Instead, nonallergenic condoms made of polyurethane or of synthetic elastomers are available. Polyurethane condoms are effective against STDs but have a higher breakage and slippage rate compared with latex condoms (Gallo, 2015).

Female Condom

The only female condom available in the United States is marketed as the *FC2 Female Condom*. It contains a nitrile sheath and outer ring and a flexible polyurethane inner ring. Its open ring remains outside the vagina, whereas its closed internal ring is fitted under the symphysis like a diaphragm (Fig. 38-3). The inner and outer sheath are covered with silicone-based lubricant, and other-based lubricants can be added. Male condoms should not be used concurrently because simultaneous use creates friction that leads to condom slipping, tearing, and displacement. Following use, the female condom outer ring should be twisted to seal the condom so that no semen spills. As an added value, the female condom may offer some protection against STDs (Minnis, 2005).

Diaphragm plus Spermicide

The diaphragm consists of a latex dome of various diameters supported by a circular latex-covered metal spring. It is effective when used in combination with water-based spermicidal jelly or cream, which is applied into the dome cup and along the device rim. The diaphragm is then positioned so that the cup faces the cervix and the cervix is partitioned effectively from the remainder of the vagina and the penis. In this fashion, the centrally placed spermicide is held against the cervix. When appropriately positioned, one rim is lodged deep in the posterior vaginal fornix, and the opposite rim fits behind the inner surface of the symphysis and immediately below the urethra. If a diaphragm is too small, it will not remain in place. If it is too large, it is uncomfortable when forced into position. Coexistent pelvic organ prolapse typically leads to instability and expulsion. Because size and spring flexibility must be individualized, the diaphragm is fitted by providers and available only by prescription.

The diaphragm and spermicide can be inserted hours before intercourse. If more than 6 hours elapse, the diaphragm can remain but additional spermicide is placed in the vagina for maximum protection. Spermicide is reapplied before each coital episode. The diaphragm is not removed for at least 6 hours after intercourse. Because toxic shock syndrome has been described following its use, it may be worthwhile to remove the diaphragm at 6 hours, or at least the next morning, to minimize this rare event. Diaphragm use is associated with a slightly greater rate of urinary infections, presumably from urethral irritation by the ring under the symphysis.

Cervical Cap

FemCap is the only cervical cap currently available in the United States. Made of silicone rubber, it has a sailor-cap shape with a dome that covers the cervix and a flared brim, which allows the cap to be held in place by the upper vagina's muscular walls. Available in 22-, 26-, and 30-mm sizes, it is used with a spermicide applied once at insertion to both

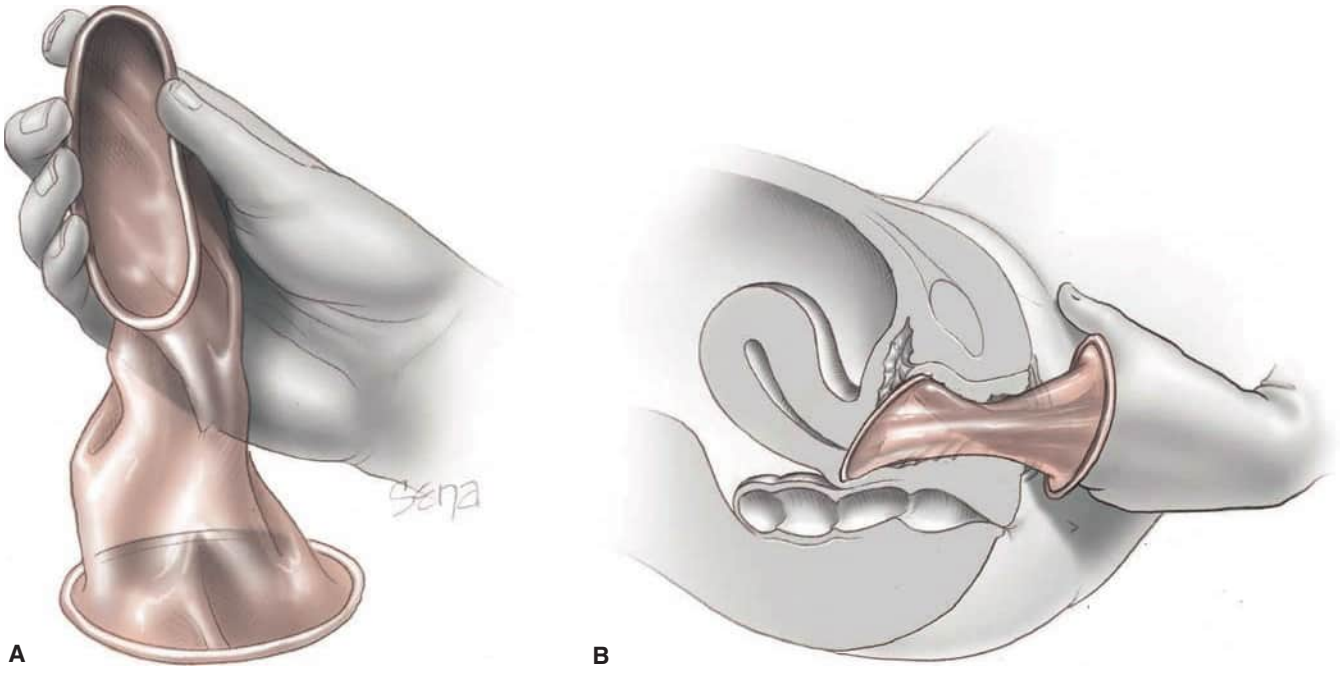

FIGURE 38-3 *FC2 Female Condom* insertion and positioning. **A.** The inner ring is squeezed for insertion. The sheath is inserted similarly to a diaphragm. **B.** The inner ring is pushed inward with an index finger.

sides of the dome cup. For contraception, it should remain in place for 6 hours following coitus and may remain for up to 48 hours. Even with proper fitting and correct use, pregnancy rates with this method are higher than those with the diaphragm (Gallo, 2012).

FERTILITY AWARENESS–BASED METHODS

These attempt to identify the fertile days each cycle and advise sexual abstinence during these days. Fertility awareness–based methods (FABMs) as a group have a 15-percent pregnancy rate with typical use (Trussell, 2018). Some smartphone applications aim to assist these practices (Berglund Scherwitzl, 2017; Jennings, 2019).

The *Standard Days Method* counsels women to avoid unprotected intercourse during cycle days 8 through 19. For successful use, women must have regular monthly cycles of 26 to 32 days. Those who use this method can mark a calendar or can use *Cycle-Beads*, which is a ring of counting beads, to keep track of their days.

The *TwoDay Method* relies on awareness of vaginal wetness, which reflects changes in the amount and quality of cervical mucus at different times in the menstrual cycle. Intercourse is considered safe if a woman did not note mucus on the day of planned intercourse or the day prior.

The *Symptothermal Method* combines changes in cervical mucus—onset of the fertile period; changes in basal body temperature—end of the fertile period; and calculations to estimate ovulation. A sustained 0.4°F rise in the basal body temperature usually precedes ovulation. For maximum efficacy, the woman must abstain from intercourse from the first day of menses through the third day after the temperature increase. Overall, this method is more complex to learn and apply, and it does not appreciably improve efficacy.

SPERMICIDES

Most spermicides contain nonoxynol-9 and are sold over-the-counter as creams, jellies, suppositories, films, and foams. They are a less effective method but provide a chemical spermicidal action and a physical barrier to sperm penetration. Their duration of maximal effectiveness is usually no more than 1 hour, and these do not offer STD protection. If pregnancy does occur, nonoxynol-9 is not teratogenic (Briggs, 2017).

In 2020, a vaginal contraceptive gel containing lactic acid, citric acid, and potassium bitartrate was FDA approved as *Phexxi*. As an acidifying agent, it resists the buffering effect of semen and thereby allows the vagina's normally acidic pH to work as a spermicide (Garg, 2001; Nelson, 2018). This pH effect also has potential as a microbicide, which warrants additional study.

Ideally, either agent is deposited high in the vagina up to 1 hour before coitus. Thereafter, each must be reinserted before repeat intercourse.

■ Contraceptive Sponge

The *Today* contraceptive sponge is an over-the-counter, one-size-fits-all device. The nonoxynol-9–impregnated polyurethane disc is 2.5 cm thick and 5.5 cm wide. One side has a dimple that faces the cervix, and the other has a satin loop for removal. The sponge can be inserted up to 24 hours prior to intercourse, and while in place, it provides contraception regardless of coital frequency. It should remain in place for 6 hours after intercourse. Pregnancy is prevented primarily by the spermicide and to a lesser extent by covering the cervix and absorbing semen.

Although the sponge is possibly more convenient than the diaphragm or condom, it is less effective than either (Kuyoh, 2013). Most common causes for method discontinuance are pregnancy, discomfort, or vaginitis (Beckman, 1989). Although toxic shock syndrome has been reported with the contraceptive sponge, it is rare, and evidence suggests that the sponge may actually limit production of the responsible staphylococcal exotoxin (Remington, 1987). Still, it is recommended that the sponge not be used during menses or the puerperium.

EMERGENCY CONTRACEPTION

Following unprotected sexual intercourse, several emergency contraception (EC) regimens substantially lower the likelihood of an unwanted pregnancy. Current methods include COCs, a progestin, a selective progesterone-receptor modulator (SPRM), and the Cu-IUD (Table 38-7). Notably, the single-dose LNG pill is available over-the-counter without a prescription to all reproductive-aged individuals. Patients can obtain information regarding EC by calling 888-NOT-2-LATE or accessing The Emergency Contraception Website: http://not-2-late.com. Although not yet adopted as EC, early efficacy data find the LNG-IUS not inferior to the Cu-IUD for EC (Turok, 2021).

Hormonal Emergency Contraception

Except for allergy to a particular component, no conditions in the US MEC contraindicate hormonal EC methods. Moreover, clinical examination or pregnancy testing is not required before EC provision (American College of Obstetricians and Gynecologists, 2019c). With all methods, dosing begins as early as possible and ideally within 72 hours of unprotected coitus. It may be given up to 120 hours after coitus (Fine, 2010; Rodrigues, 2001; von Hertzen, 2002).

The major mechanism with all hormonal regimens is inhibition or delay of ovulation. Of oral methods, failure rates are lowest with ulipristal (1 to 2 percent) and greatest with the Yuzpe method (2 to 3.5 percent) (Cleland, 2014). If EC fails to prevent pregnancy or is mistimed, no associations with major congenital malformation or pregnancy complications have been noted with these hormonal methods (Jatlaoui, 2016; Levy, 2014). With EC administration, nausea and vomiting can be an important side effect. Accordingly, an oral antiemetic may be prescribed at least 1 hour before each dose (Rodriguez, 2013). If a woman vomits within 2 hours of a dose, the dose is repeated.

For subsequent coitus, a barrier method is recommended until long-term contraception is begun. If not, EC can be repeated within a given menstrual cycle. Quick start initiation of contraceptive methods is suitable and is discussed in the respective method sections. Notably, because ulipristal competes at the progesterone receptor, a 5-day delay is recommended before starting progestin-containing contraceptives.

Copper-containing Intrauterine Devices

For women who are candidates, Cu-IUD insertion is the most effective EC method and provides an effective 10-year form of contraception. If an IUD is placed up to 5 days after unprotected coitus, the pregnancy rate approximates only 0.1 percent (Cleland, 2012; Wu, 2010).

TABLE 38-7. Emergency Contraception Methods and Some Brand-Name Examples

Method	Formulation	Pills per Dose	Number of Doses[a]
Progestin-only Pill			
Plan B One-Step	1.5 mg LNG	1	1
PRM Pill			
Ella	30 mg ulipristal acetate	1	1
COC Pills[b]			
Ogestrel	50 μg EE + 0.5 mg norgestrel[c]	2	2
Cryselle, Low-Ogestrel	30 μg EE + 0.3 mg norgestrel[c]	4	2
Enpresse (orange), Trivora (pink)	30 μg EE + 0.125 mg LNG	4	2
Levora, Seasonale	30 μg EE + 0.15 mg LNG	4	2
Aviane, LoSeasonique (orange)	20 μg EE + 0.1 mg LNG	5	2
Copper-containing IUD			
Paragard T380A			

[a]Doses taken 12 hours apart.
[b]COCs method, also known as the Yuzpe method, aims to provides a minimum of 100 μg of EE and 0.5 mg of LNG or 1.0 mg of norgestrel in each of the two doses. A listing of other suitable COCs and dosing is found at https://ec.princeton.edu/questions/dose.html#dose.
[c]Norgestrel contains two isomers, and only one of these isomers is bioactive, namely levonorgestrel. Thus, the amount of norgestrel needed for efficacy is twice that of the levonorgestrel-based regimens.
COC = combination oral contraceptive; EE = ethinyl estradiol; IUD = intrauterine device; LNG = levonorgestrel; PRM = progesterone-receptor modulator.

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CHAPTER 39

Sterilization

Among women using contraception in the United States, 28 percent rely on either male or female sterilization (Kavanaugh, 2018). Tubal interruption or excision is suitable for those requesting sterilization and who clearly understand its permanence and its difficult and often unsuccessful reversal. Alternative contraceptive choices also should be presented. Ultimately, following provision of information, patient autonomy and her decision for sterilization should be respected (American College of Obstetricians and Gynecologists, 2017, 2019).

Female sterilization is usually accomplished by occlusion, excision, or division of the fallopian tubes. *Puerperal sterilization* procedures follow cesarean or vaginal delivery and approximately 7 percent of all live births in the United States (Moniz, 2017). *Nonpuerperal tubal sterilization* is done at a time unrelated to recent pregnancy and is also termed *interval sterilization*. More recently, consideration of total salpingectomy for sterilization and for ovarian cancer risk reduction is now recommended (p. 682).

PUERPERAL TUBAL STERILIZATION

Timing

Several days postpartum, the uterine fundus lies at the level of the umbilicus, and fallopian tubes are accessible directly beneath the abdominal wall. Moreover, abdominal laxity allows easy repositioning of the incision over each uterine cornu.

On our service, puerperal tubal ligation is performed the morning after delivery by a surgical team designated solely to this role. This timing minimizes hospital stay but lowers the likelihood that postpartum hemorrhage would complicate recovery following surgery. The status of the newborn also can be better ascertained before surgery. In contrast, some prefer to perform sterilization immediately following delivery and use neuraxial analgesia already placed for labor. Designating these postpartum surgeries as nonelective can help lessen barriers. This is especially so for high-volume labor and delivery units, which typically prioritize their limited operating-room availability for intrapartum procedures (American College of Obstetricians and Gynecologists, 2021). From one large series, postpartum tubal ligation was a safe, reasonable option, regardless of body mass index (Byrne, 2020).

Method Selection

In general for postpartum sterilization, a midtubal segment of tube is excised, and the severed ends seal by fibrosis and peritoneal regrowth. Commonly used methods include the Parkland, Pomeroy, and modified Pomeroy techniques. Less often, Filshie clips are used, and evidence points to slightly decreased efficacy (Madari, 2011; Rodriquez, 2011, 2013). Also, in the absence of uterine or other pelvic disease, hysterectomy solely for sterilization is difficult to justify because of its significantly higher risk for surgical morbidity compared with tubal sterilization.

Most pelvic serous cancers are thought to originate from the distal fallopian tube (Erickson, 2013). Because of this, although currently theoretical, evidence suggests that bilateral salpingectomy may lower these ovarian cancer rates (Falconer, 2015; Lessard-Anderson, 2014). With this knowledge, the Society of Gynecologic Oncologists (Walker, 2015) and American College of Obstetricians and Gynecologists (2019b) recommend consideration of salpingectomy to lower these

cancer risks. Specifically, for women at average risk of ovarian cancer, risk-reducing salpingectomy should be discussed and considered with abdominopelvic surgery, with hysterectomy, or in lieu of tubal ligation.

In the discussion of salpingectomy, several points are instructive. First, the lifetime risk for ovarian cancer approximates 1 percent (National Cancer Institute, 2019). Data from epidemiologic studies show that tubal interruption alone offers an approximate 30-percent decline in ovarian cancer rates (Rice, 2012; Sieh, 2013). Salpingectomy may reduce the risk by 42 to 78 percent (Gockley, 2018). However, no prospective studies of sufficient size or duration have yet been done to demonstrate the true risk and benefit ratio for women at low risk of ovarian cancer. Also, few data describe the effects on ovarian reserve from tubal blood supply disruption. In small studies comparing the two surgeries, no differences in antimüllerian hormone levels, which are a measure of ovarian reserve, were found (Findley, 2013; Ganer Herman, 2017). In other comparisons, total salpingectomy at cesarean delivery takes 5 to 10 minutes longer than partial salpingectomy (Ferrari, 2019; Powell, 2017). Blood loss rates are comparable or slightly higher but do not lead to higher transfusion rates or greater postsurgical declines in hematocrit values. Only a few small studies have evaluated salpingectomy following vaginal delivery (Danis, 2016; Powell, 2017).

Technique

Spinal analgesia is typically selected for cases scheduled on the first postpartum day. General anesthesia may be less desirable due to residual pregnancy-related aspiration risks (Bucklin, 2003). If done more proximate to delivery, the same epidural catheter used for labor analgesia can be used for sterilization analgesia. Generally, with thrombocytopenia-related conditions, platelet levels should be >70,000 for spinal blockade (Chap. 25, p. 478). The bladder is emptied before surgery to avoid its laceration. A full bladder can also push the fundus and tubes above the umbilicus and incision. Considered a clean case, antibiotic prophylaxis is not required.

To begin, a small infraumbilical incision is ideal for several reasons. As noted, the fundus in most cases lies near the umbilicus. Second, the umbilicus usually remains the thinnest portion of the anterior abdominal wall and requires less subcutaneous dissection to reach the linea alba fascia. Third, an infraumbilical incision offers fascia with sufficient integrity to provide a closure with minimal risk for later incisional hernia. Last, incisions that follow the natural curve of the lower umbilical skin fold yield suitable cosmesis. A 2- to 3-cm transverse or vertical skin incision is usually sufficient for normal-weight women. For obese women, a 4- to 5-cm incision may be needed for adequate abdominal access.

Beneath this incision, the subcutaneous tissue is bluntly separated to reach the linea alba fascia. For this, an Allis clamp can be opened and closed as downward pressure is exerted. Similarly, the blades of two army-navy retractors both pulling in downward yet opposite directions can part the subcutaneous layer. Clearing this fatty tissue away from the fascia isolates the fascia for incision and for later closure without intervening fat, which may impede wound healing.

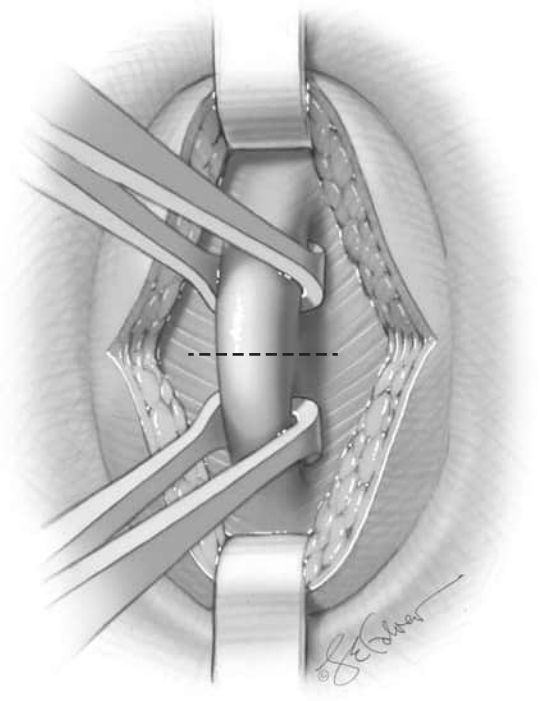


FIGURE 39-1 Fascia is grasped by two Allis clamps and elevated away from viscera beneath. Planned fascial incision is marked by dashed line. (Modified and reproduced with permission from Kho KA: Diagnostic and operative laparoscopy. In Yeomans ER, Hoffman BL, Gilstrap, III, et al [eds]: Cunningham and Gilstrap's Operative Obstetrics, 3rd ed. New York, NY: McGraw Hill; 2017.)

The fascial incision may be transverse or vertical and follows the same orientation of the skin incision. For this, once the linea alba is reached, it is grasped with two Allis clamps—one placed on either side of the planned fascial incision (Fig. 39-1). The purchase of tissue with each clamp should be substantial and creates a small roll of fascia to be incised. Often, the peritoneum is incorporated simultaneously and entered. If not, the peritoneum is grasped with two hemostats and sharply cut. Others may prefer to bluntly enter with a single index finger. Notably, if the initial fascial incision is too small, it can be extended with curved Mayo scissors.

Adequate exposure is critical, and army-navy or appendiceal retractors are suitable. For obese women, a slightly larger incision and narrow deeper retractors may be needed. If bowel or omentum is obstructing, Trendelenburg position can help displace these cephalad. Digitally packing with a single, moist, fanned-out piece of surgical gauze also can be used, but a hemostat should always be attached to the distal end to avert its intraabdominal retention. At times, mechanically tilting the entire table to the opposite side of the tube being exposed also can assist tube isolation.

The fallopian tube is identified and grasped at its midportion with a Babcock clamp. A second slightly more distal clamp grasps the tube, which is similarly lifted. This allows the fimbriated end to be seen. Such confirmation prevents confusing the round ligament for the fallopian tube. A common reason for sterilization failure is ligation of the wrong structure, typically the round ligament. If the tube is inadvertently dropped, it is mandatory to repeat this identification process. Surgical steps for ligation are outlined in Figures 39-2 and 39-3.

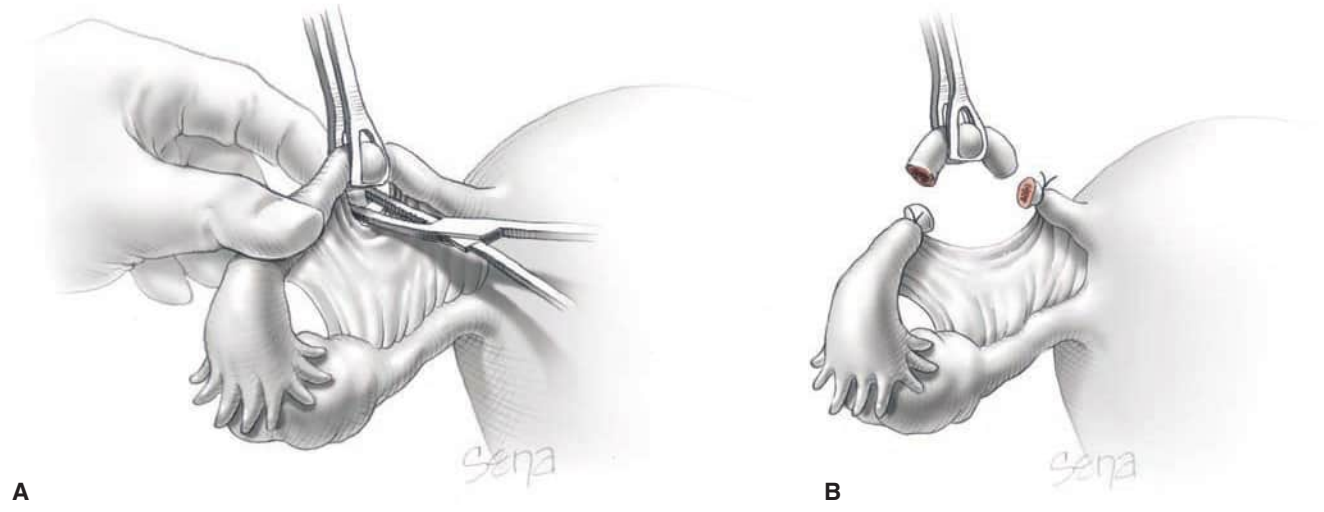


FIGURE 39-2 Parkland method. **A.** An avascular site in the mesosalpinx adjacent to the fallopian tube is perforated with a small hemostat. The jaws are opened to separate the fallopian tube from the adjacent mesosalpinx for approximately 2.5 cm. **B.** The isolated tubal portion is ligated proximally and distally with 0-chromic suture. The intervening segment of approximately 2 cm is excised, and the excision site is inspected for hemostasis. This method was designed to avoid the initial intimate proximity of the cut ends of the fallopian tube inherent with the Pomeroy procedure. (Reproduced with permission from Hoffman BL, Hamid CA, Corton MM: Surgeries for benign gynecologic conditions. In Hoffman BL, Schorge JO, Halvorson LM, et al: Williams Gynecology, 4th ed. New York, NY: McGraw Hill; 2020.)

For total salpingectomy, the umbilical incision generally will need to be larger to allow an adequate view of the tube and mesosalpinx and to place clamps (Fig. 39-4). The entire mesosalpinx must be divided to free the fallopian tube. Thus, risks include bleeding from the often large, congested mesosalpingeal veins, control of which requires extension of the laparotomy incision or even an adnexectomy. Some prefer to use a bipolar electrosurgical coagulation device (LigaSure, ENSEAL), which seals and divides the mesosalpinx simultaneously. This may add speed but also expense.

After surgery, diet is given as tolerated, and walking is encouraged. Ileus is infrequent and should prompt concern for bowel injury, albeit rare. Most women have an uncomplicated course and are discharged on the first postoperative day.

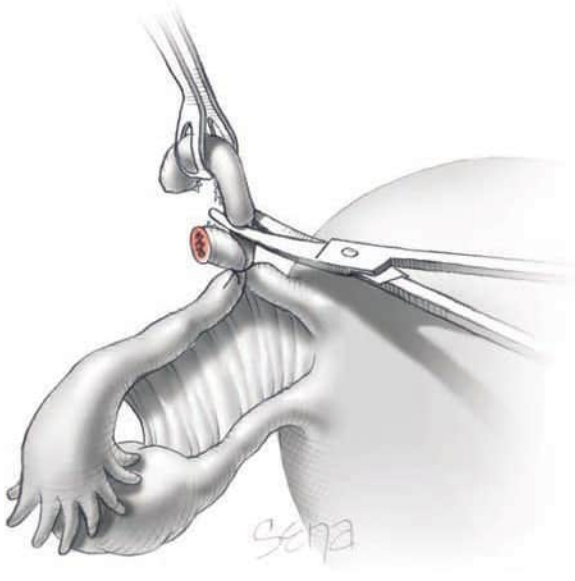


FIGURE 39-3 Pomeroy method. During ligation of a midsegment tubal loop, plain catgut is used to ensure prompt absorption of the ligature and subsequent separation of the severed tubal ends. (Reproduced with permission from Hoffman BL, Hamid CA, Corton MM: Surgeries for benign gynecologic conditions. In Hoffman BL, Schorge JO, Halvorson LM, et al: Williams Gynecology, 4th ed. New York, NY: McGraw Hill; 2020.)

NONPUERPERAL TUBAL STERILIZATION

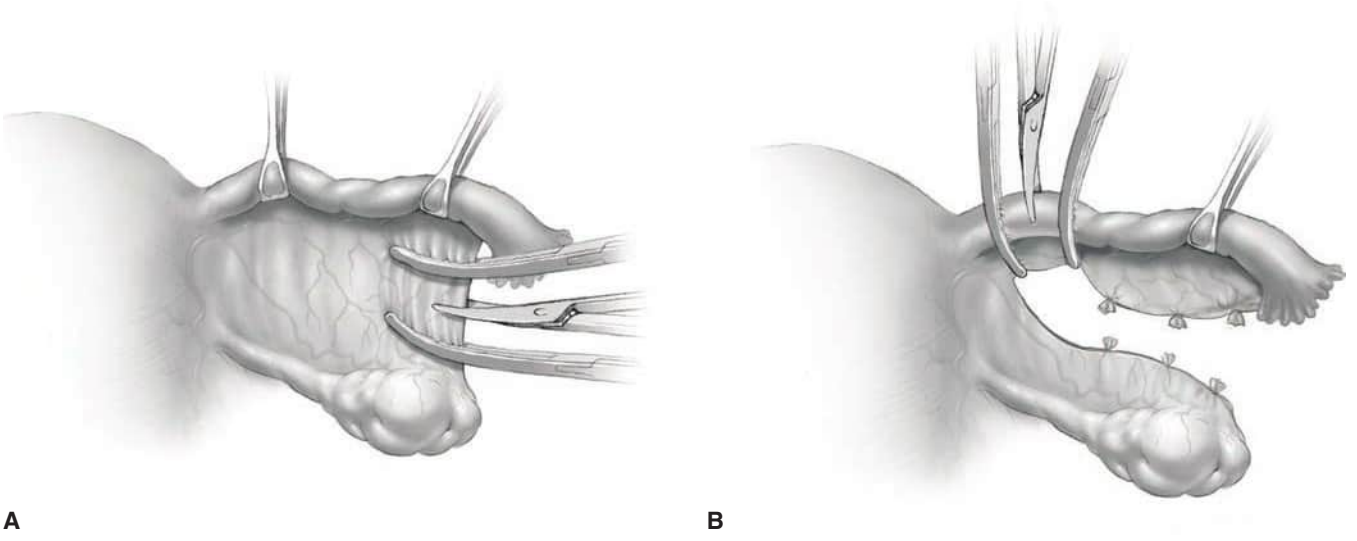
These techniques and other modifications basically consist of (1) ligation and resection at laparotomy as described earlier for puerperal sterilization; (2) application of permanent rings, clips, or inserts to the fallopian tubes by laparoscopy or hysteroscopy; or (3) electrocoagulation of a tubal segment, usually through a laparoscope. A detailed description and illustration of these can be found in *Williams Gynecology*, 4th edition (Kho, 2020).

In the United States, a laparoscopic approach to interval tubal sterilization is the most common. The procedure is frequently performed in an ambulatory surgical setting under general anesthesia. In almost all cases, the patient can be discharged within several hours. Minilaparotomy using a 3-cm suprapubic incision also is popular, especially in resource-poor countries. Major morbidity is rare with either minilaparotomy or laparoscopy. Although not often used, the peritoneal cavity can be entered through the posterior vaginal fornix via colpotomy to perform tubal interruption.

LONG-TERM COMPLICATIONS

Contraceptive Failure

Pregnancy following sterilization is infrequent. The Collaborative Review of Sterilization (CREST) study followed 10,863 women



A B

FIGURE 39-4 A. With salpingectomy, the mesosalpinx is sequentially clamped, cut, and ligated. **B.** At the cornu, clamps are placed across the fallopian tube and its adjacent mesosalpinx prior to tubal transection. (Reproduced with permission from Stuart GS: Puerperal sterilization. In Yeomans ER, Hoffman BL, Gilstrap, III, et al [eds]: Cunningham and Gilstrap's Operative Obstetrics, 3rd ed. New York, NY: McGraw Hill; 2017.)

who had undergone tubal sterilization from 1978 through 1986 (Peterson, 1996). The cumulative failure rate for the various tubal procedures was 18.5 per 1000 or approximately 0.5 percent. The study found puerperal sterilization to be highly effective. The 5-year failure rate was 5 per 1000, and at 12 years, it was 7 per 1000.

Puerperal sterilization fails for two major reasons. First, surgical errors include transection of the round ligament or only partial transection of the tube. For this reason, both tubal segments are submitted for pathological confirmation. Second, a fistulous tract or spontaneous reanastomosis may form between the severed tubal stumps.

Approximately 30 percent of pregnancies that follow failed tubal sterilization are ectopic. This rate is 20 percent for those following a postpartum procedure (Peterson, 1996, 1997). Thus, any symptoms of pregnancy in a woman after tubal sterilization must be investigated to exclude ectopic pregnancy.

Other Effects

Women who have undergone tubal sterilization are highly unlikely to subsequently have salpingitis (Levgur, 2000). Most studies also find that rates of heavy menstrual or intermenstrual bleeding are not increased following the procedure (DeStefano, 1985; Peterson, 2000; Shy, 1992). Moreover, in the CREST study, Costello (2002) found that tubal ligation did not change sexual interest or pleasure in 80 percent of women. In most of the 20 percent of women who did report a change, positive effects were 10 to 15 times more likely.

Invariably, some women express regrets regarding sterilization, and this is especially true if it is performed at a younger age (Curtis, 2006; Kelekçi, 2005). In the CREST study, Jamieson (2002) reported that 7 percent of women who had undergone tubal ligation had regrets by 5 years. This is not limited to their own sterilization, because 6.1 percent of women whose husbands had undergone vasectomy had similar regrets.

Tubal Sterilization Reversal

No woman should undergo tubal sterilization believing that subsequent fertility is guaranteed either by surgery or by assisted reproductive technologies. Both approaches are technically difficult, expensive, and not always successful. In general, pregnancy rates after tubal reversal favor women with 7 cm of remaining tube, with age younger than 35 years, with a short time from antecedent sterilization, and with isthmic–isthmic repairs. With reanastomosis via laparotomy, rates of live births range from 44 to 82 percent (Deffieux, 2011; Malacova, 2015). The rate of ectopic pregnancy is 2 to 10 percent after reanastomosis (American Society for Reproductive Medicine, 2015). With reanastomosis to reverse *Essure* sterilization, the subsequent live birth rates range from 0 to 27 percent (Fernandez, 2014; Monteith, 2014).

TRANSCERVICAL STERILIZATION

A transcervical approach to reach the tubal ostia can be used for sterilization. However, no methods using this approach are currently approved in the United States.

Mechanical methods employ insertion of a device into the proximal fallopian tubes via hysteroscopy. Both the Essure system and the Adiana Permanent Contraception system have been removed from the U.S. market. The Adiana is a cylindrical, nonabsorbent silicone elastomer matrix that once inserted stimulates tissue ingrowth to occlude the tubal lumen (Hologic, 2012).

The Essure Permanent Birth Control System is a long, slender, coiled, metallic tubal insert. Once placed, fibroblastic proliferation within the device similarly causes tubal occlusion. With this method, contraceptive failure rates range from <1 percent to 5 percent (Gariepy, 2014; Munro, 2014).

Chronic pelvic pain after hysteroscopic sterilization may develop in 2 to 6 percent of those with Essure inserts (Chudnoff, 2015; Kamencic, 2016; Yunker, 2015). Pain may stem

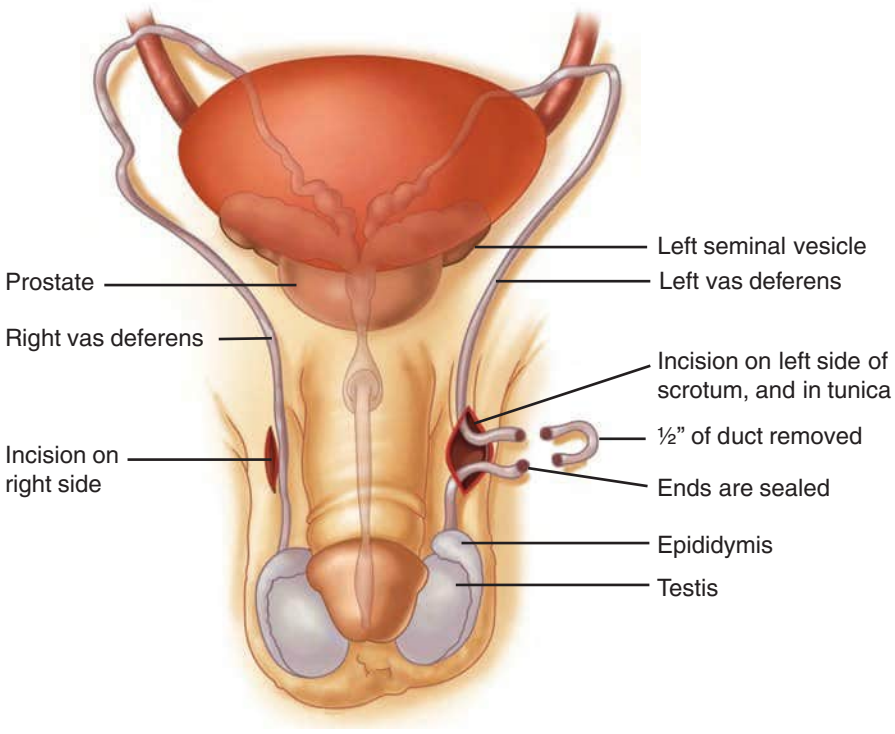


FIGURE 39-5 Anatomy of male reproductive system showing procedure for vasectomy.

from tubal perforation, device migration, or the device itself (Adelman, 2014). For those desiring removal, proximal linear salpingostomy and device removal is feasible (Kho, 2020). Importantly, device removal is not curative in all symptomatic patients (Clark, 2017; Maassen, 2019). Other cited adverse events include abnormal bleeding and allergy or hypersensitivity reaction to its components (Al-Safi, 2013; Mao, 2015).

Chemical agents may also be placed into the uterine cavity or tubal ostia to incite an inflammatory response to cause tubal occlusion. Used in lower-resource areas, one method employs an intrauterine device–type inserter to place quinacrine pellets into the uterine fundus. From randomized trials, pregnancy rates were 1 and 12 percent at 1 and 10 years, respectively (Sokal, 2008). The World Health Organization (2009) has recommended against quinacrine use because of carcinogenesis concerns. Evidence is contradictory, and some consider it a potential option for resource-poor countries (Lippes, 2015).

VASECTOMY

Currently, up to a half million men in the United States undergo vasectomy each year (Barone, 2006; Eisenberg, 2010). And, 5 percent of women rely on this method for contraception (Daniels, 2015). For sterilization, the vas deferens lumen is disrupted to block the passage of sperm from the testes (Fig. 39-5).

Vasectomy is safer than female tubal sterilization because it is less invasive and is performed with local analgesia (American College of Obstetricians and Gynecologists, 2019a). In a review that compared the two, female tubal sterilization had a 20-fold higher complication rate and a 10- to 37-fold higher failure rate (Hendrix, 1999).

One disadvantage is that sterilization following vasectomy is not immediate. Sperm stored in the reproductive tract beyond the interrupted vas deferens takes approximately 3 months or 20 ejaculations for complete release. The American Urological Association recommends a postprocedural semen analysis at 8 to 16 weeks to document sterility (Sharlip, 2012). Before azoospermia is documented, another form of contraception should be used.

The failure rate for vasectomy during the first year is 9.4 per 1000 procedures but only 11.4 per 1000 at 2, 3, and 5 years (Jamieson, 2004). Failures result from unprotected intercourse too soon after ligation, incomplete vas deferens occlusion, or recanalization (Awsare, 2005; Deneux-Tharaux, 2004).

Reanastomosis of the vas deferens can be completed most effectively using microsurgical techniques. Conception rates following reversal are adversely affected by longer duration from vasectomy, poor sperm quality found at reversal, and type of reversal procedure required (American Society for Reproductive Medicine, 2008).

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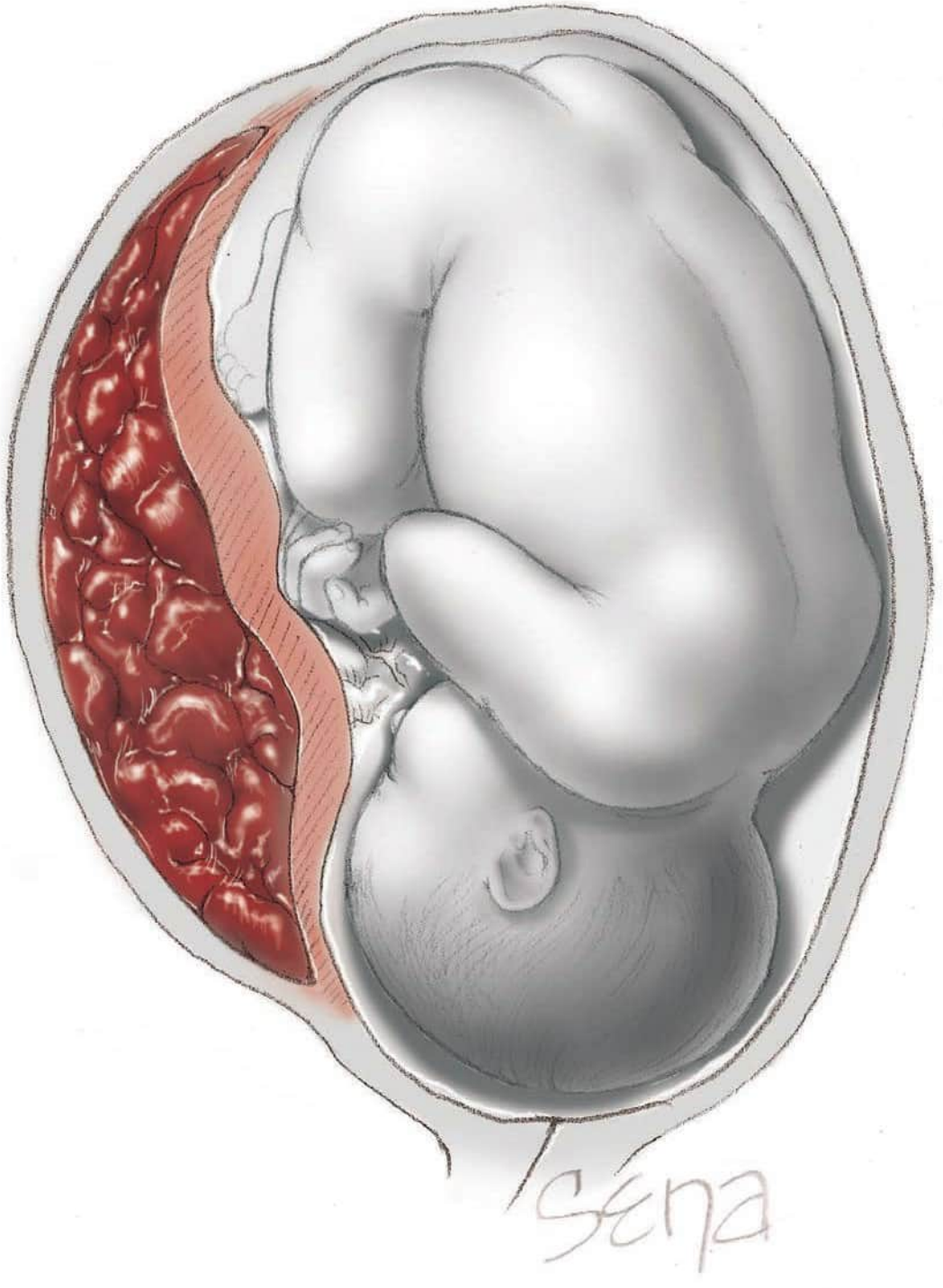
SECTION 11

OBSTETRICAL COMPLICATIONS



CHAPTER 40

Preeclampsia Syndrome

Hypertensive disorders include preeclampsia, gestational hypertension, and chronic hypertension and complicate up to 10 percent of pregnancies. As a group, they are one member of the deadly triad—along with hemorrhage and infection—that contributes greatly to maternal morbidity (Judy, 2019).

Preeclampsia, either alone or superimposed on chronic hypertension, is the most dangerous. In the United States from 2011 to 2015, 7 percent of pregnancy-related maternal deaths were caused by preeclampsia or eclampsia (Petersen, 2019). Most hypertension-related deaths are deemed preventable (Katsuragi, 2019). In response, Joint Commission (2019) accredited hospitals are now required to track their recognition and timely treatment of hypertension.

In 2018, a workshop to study preeclampsia was convened by the National Heart, Lung, and Blood Institute. This builds on the prior work of the American College of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy (2013). Its purpose was to review topics regarding all aspects of preeclampsia and to recommend future research areas. Many of these topics are discussed throughout this chapter and Chapter 41.

TERMINOLOGY AND DIAGNOSIS

To codify the classification of hypertensive disorders of pregnancy, the American College of Obstetricians and Gynecologists (2013, 2020) describes four types of hypertensive disease:

1. Preeclampsia and eclampsia syndrome
2. Chronic hypertension of any etiology
3. Preeclampsia superimposed on chronic hypertension
4. Gestational hypertension, in which definitive evidence for the preeclampsia syndrome does not develop and hypertension resolves by 12 weeks postpartum.

This classification aims to differentiate preeclampsia syndrome, which is potentially more ominous, from other hypertensive disorders.

Diagnosis of Hypertensive Disorders

Hypertension is diagnosed empirically when systolic and diastolic blood pressures exceed 140 mm Hg and 90 mm Hg, respectively. Korotkoff phase V is used to define diastolic pressure.

Previously for pregnant women, increases of 30 mm Hg systolic or 15 mm Hg diastolic above blood pressure values taken at midpregnancy had also been used as diagnostic criteria, even when absolute values were <140/90 mm Hg. These incremental changes are no longer used to define hypertension. However, blood pressure surveillance in these gravidas is reasonable because eclamptic seizures develop in some whose blood pressures have stayed below 140/90 mm Hg (Alexander, 2006).

In other cases, mean arterial pressures that suddenly rise but that still lie in normal range—"delta hypertension"—may signify preeclampsia (Macdonald-Wallis, 2012; Zeeman, 2007). We use this term to describe a relatively acute rise in blood pressure in individual patients, albeit some still with pressures <140/90 mm Hg (Fig. 40-1). Some of these

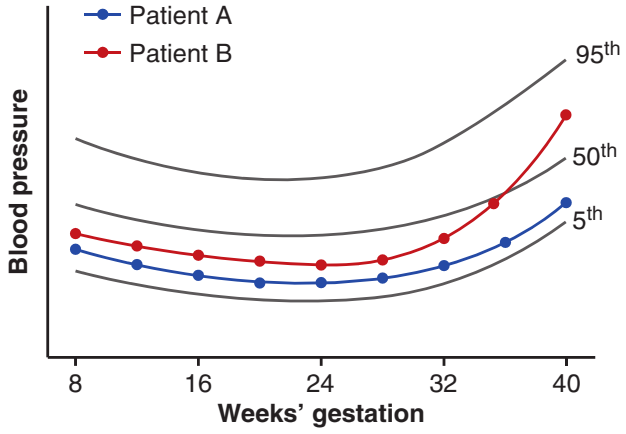


FIGURE 40-1 Schematic of normal reference ranges for mean arterial blood pressure changes across pregnancy. Patient A (*blue*) has mean blood pressures near the 20th percentile throughout pregnancy. Patient B (*red*) has a similar pattern with mean pressures at the 25th percentile until approximately 36 weeks' gestation, at which time her blood pressure begins to rise. By term, it is substantively higher and in the 75th percentile, but she is still considered "normotensive." This increase from the 25th to 75th percentile can be termed "delta hypertension."

women will go on to have obvious preeclampsia, and some even develop eclamptic seizures or hemolysis, elevated liver enzyme levels, and low platelet count (HELLP) syndrome.

Historically, systolic and diastolic blood pressure levels of 140/90 mm Hg have been arbitrarily used since the 1950s to define "hypertension" in nonpregnant individuals. However, these levels were selected by insurance companies to characterize a population of middle-aged men. It seems more realistic to define normal-range blood pressures for specific populations—such as young, healthy, pregnant women (Lu, 2019; Reddy, 2020). To provide such data, >1000 women were recently studied longitudinally through pregnancy (Green, 2020). Data of this type may shape future thresholds.

Gestational Hypertension

Women with gestational hypertension have blood pressures that reach 140/90 mm Hg or greater for the first time after midpregnancy but lack proteinuria. Almost half of affected women subsequently develop preeclampsia (Jim, 2017). Even so, when blood pressure rises appreciably, it is dangerous to both mother and fetus to ignore this elevation only because proteinuria has not yet developed (Fishel Bartal, 2020). As Chesley (1985) emphasized, 10 percent of eclamptic seizures develop before overt proteinuria can be detected. Gestational hypertension is reclassified by some as *transient hypertension* if preeclampsia does not develop and blood pressure returns to normal by 12 weeks postpartum.

Preeclampsia Syndrome

Preeclampsia is best described as a pregnancy-specific syndrome that can affect virtually every organ system. Although preeclampsia is more than simply gestational hypertension with proteinuria, the appearance of protein remains a primary diagnostic criterion. It is an objective marker and reflects the system-wide endothelial leak that characterizes the preeclampsia syndrome. Last, preeclampsia can be divided into early onset, <34 weeks; late onset, ≥34 weeks; preterm onset, <37 weeks; and term onset, ≥37 weeks (Burton, 2019; Poon, 2019).

In some women with preeclampsia, neither overt proteinuria nor fetal-growth restriction are features (Sibai, 2009). Because of this, the Task Force (2013) suggests other diagnostic criteria, some of which are shown in Table 40-1. Multiorgan involvement may be reflected by thrombocytopenia, renal dysfunction, hepatocellular necrosis, central nervous system perturbations, or pulmonary edema.

The markers listed in Table 40-1 help also to classify preeclampsia syndrome severity. Although many use a dichotomous "mild" and "severe" classification, the Task Force (2013) discourages the use of "mild preeclampsia." It is problematic

TABLE 40-1. Classification and Diagnosis of Pregnancy-Associated Hypertension

Condition	Criteria Required
Gestational hypertension	BP >140/90 mm Hg after 20 weeks in previously normotensive women
Preeclampsia: Hypertension plus	
Proteinuria	≥300 mg/24h, or Urine protein: creatinine ratio ≥0.3, or Dipstick 1+ persistent[a]
	or
Thrombocytopenia	Platelets <100,000/μL
Renal insufficiency	Creatinine >1.1 mg/dL or doubling of baseline[b]
Liver involvement	Serum transaminase levels[c] twice normal
Cerebral symptoms	Headache, visual disturbances, convulsions
Pulmonary edema	—

[a]Recommended only if sole available test.
[b]No prior renal disease.
[c]Aspartate transaminase (AST) or alanine transaminase (ALT).
BP = blood pressure.

TABLE 40-2. Indicators of Severity of Gestational Hypertensive Disorders[a]

Abnormality	Nonsevere[b]	Severe
Diastolic BP	<110 mm Hg	≥110 mm Hg
Systolic BP	<160 mm Hg	≥160 mm Hg
Proteinuria[c]	None to positive	None to positive
Headache	Absent	Present
Visual disturbances	Absent	Present
Upper abdominal pain	Absent	Present
Oliguria	Absent	Present
Convulsion (eclampsia)	Absent	Present
Serum creatinine	Normal	Elevated
Thrombocytopenia (<100,000/μL)	Absent	Present
Serum transaminase elevation	Minimal	Marked
Fetal-growth restriction	Absent	Present
Pulmonary edema	Absent	Present
Gestational age	Late	Early

[a]Compare with criteria in Table 40-1.
[b]Includes "mild" and "moderate" hypertension not specifically defined.
[c]Most disregard degrees of proteinuria to classify as nonsevere or severe.
BP = blood pressure.

that there are criteria for the diagnosis of "severe" preeclampsia, but the binary default classification is either implied or specifically termed "mild," "less severe," or "nonsevere" (Alexander, 2003; Lindheimer, 2008). No consensus criteria define "moderate" preeclampsia, which is an elusive third category. We use the criteria recommended by the American College of Obstetricians and Gynecologists (2020), some of which are listed in Table 40-2 and categorize disease as "severe" versus "nonsevere."

Some symptoms are considered ominous. *Headaches* or *visual disturbances* can precede *eclampsia*, which is a convulsion in a woman with preeclampsia that is not attributable to another cause. The seizures are generalized and may appear before, during, or after labor. The proportion that develops seizures later—after 48 hours postpartum—approximates 10 percent (Sibai, 2005; Zwart, 2008). Another symptom, *epigastric or right upper quadrant pain*, frequently accompanies hepatocellular necrosis, ischemia, and hepatic edema. Elevated serum hepatic transaminase levels can be one marker. Last, *thrombocytopenia* also signifies worsening preeclampsia. It represents platelet activation and aggregation and microangiopathic hemolysis. Other factors indicative of severe preeclampsia include renal or cardiac involvement. When these signs and symptoms are profound, they likely cannot be temporized, and delivery will more likely be required. Importantly, differentiating nonsevere and severe gestational hypertension or preeclampsia can be misleading because what might be apparently mild disease may progress rapidly to severe disease.

Preeclampsia Superimposed on Chronic Hypertension

Any chronic hypertensive disorder predisposes a woman to develop superimposed preeclampsia syndrome. Chronic underlying hypertension is diagnosed in women with documented blood pressures ≥140/90 mm Hg before pregnancy or before 20 weeks' gestation, or both. Thus, in women who are not first seen until after midpregnancy, hypertensive disorders can be difficult to classify. For example, a woman with previously undiagnosed chronic vascular disease who is seen before 20 weeks frequently has blood pressures within normal range. During the third trimester, however, as blood pressures return to their originally hypertensive levels, it may be difficult to determine whether hypertension is chronic or induced by pregnancy. Even a careful search for evidence of preexisting end-organ damage may be futile, as many of these women have mild disease and no evidence of ventricular hypertrophy, retinal vascular changes, or renal involvement.

In 20 to 50 percent of women with chronic hypertension, blood pressure rises to obviously abnormal levels, typically after 24 weeks' gestation. If new-onset or worsening baseline hypertension is accompanied by new-onset proteinuria or other findings listed in Table 40-1, superimposed preeclampsia is diagnosed (American College of Obstetricians and Gynecologists, 2019a). Compared with "pure" preeclampsia, superimposed preeclampsia commonly develops earlier in pregnancy. It tends to be more severe and more often is accompanied by fetal-growth restriction. The same criteria shown in Table 40-2 also further characterize the severity of superimposed preeclampsia.

INCIDENCE AND RISK FACTORS

Preeclampsia is identified in 5 to 8 percent of all pregnancies (Jim, 2017; Poon, 2019). Young and nulliparous women are particularly vulnerable, whereas older women are at greater risk for chronic hypertension with superimposed preeclampsia (Sheen, 2020). In one review of global studies, the incidence of preeclampsia in nulliparas ranged from 3 to 10 percent (Staff, 2015). In multiparas, the incidence ranges from 2 to 5 percent (Jim, 2017; Poon, 2019).

The incidence of preeclampsia is also influenced by race, ethnicity, and genetic predisposition. In one study by the Maternal–Fetal Medicine Units (MFMU) Network, the incidence of preeclampsia was 5 percent in white, 9 percent in Hispanic, and 11 percent in African American nulliparas (Myatt, 2012a,b). In addition, black women carry higher risk for associated severe adverse outcomes (Gyamfi-Bannerman, 2020).

For several clinical factors, Bartsch and associates (2016) extracted data from more than 25 million pregnancies and calculated relative risks (Table 40-3). Major risks include older age, nulliparity, obesity, diabetes, and chronic hypertension. Another is preeclampsia and especially HELLP syndrome in a prior pregnancy (Malström, 2020). Underlying metabolic syndrome, hyperhomocysteinemia, or chronic kidney disease are others (Masoudian, 2016; Wiles, 2020).

Of lesser factors, human immunodeficiency virus (HIV) seropositivity, sleep-disordered breathing, and a male fetus

TABLE 40-3. Selected Clinical Risk Factors for Preeclampsia

Risk Factor	Pooled Unadjusted Relative Risk[a]
Nulliparity	2.1 (1.9–2.4)
Age >35	1.2 (1.1–1.3)
BMI >30	2.8 (2.6–3.1)
Multifetal gestation	2.9 (2.6–3.1)
Prior abruption	2.0 (1.4–2.7)
Diabetes	3.7 (3.1–4.3)
Prior preeclampsia	8.4 (7.1–9.9)
CHTN	5.1 (4.0–6.5)
Prior stillbirth	2.4 (1.7–3.4)
Chronic kidney disease	1.8 (1.5–2.1)
ART	1.8 (1.6–2.1)
SLE	2.5 (1.0–6.3)
APA	2.8 (1.8–4.3)

[a]95% confidence interval.
APA = antiphospholipid antibody; ART = assisted reproductive technology; BMI = body mass index; CHTN = chronic hypertension; SLE = systemic lupus erythematosus.

pose a slightly higher risk (Facco, 2017; Jaskolka, 2017; Sansone, 2016). Previously affected family members are another, and maternal and fetal genetics are assuming greater predictive importance (Burton, 2019; Gray, 2018; Phipps, 2019). Last, preeclampsia frequently complicates the "mirror syndrome" (Chap. 18, p. 364) (Trad, 2021). Although smoking during pregnancy causes various adverse pregnancy outcomes, ironically, it lowers the risk for hypertension during pregnancy.

For eclampsia, seizure incidence has declined in areas where health care is more readily available. In countries with adequate resources, the incidence averages 1 case in 2000 to 3000 deliveries (Jaatinen, 2016; O'Connor, 2013; Schaap, 2019). At Parkland Hospital, the incidence has declined appreciably during the past decade and approximates 1 case in 2000 births (Fig. 40-2). This frequency may be related to improved access to prenatal care and our active management approach (Chap. 41, p. 717).

ETIOPATHOGENESIS

The mechanisms by which pregnancy incites or aggravates hypertension remain unsolved. Any satisfactory theory concerning the origins of preeclampsia must account for the observation that gestational hypertensive disorders are more likely to develop in women with the following characteristics:

- Exposure to chorionic villi for the first time
- Exposure to a superabundance of chorionic villi, as with twins or hydatidiform mole
- Preexisting conditions associated with endothelial cell activation or inflammation
- Genetic predisposition to hypertension developing during pregnancy.

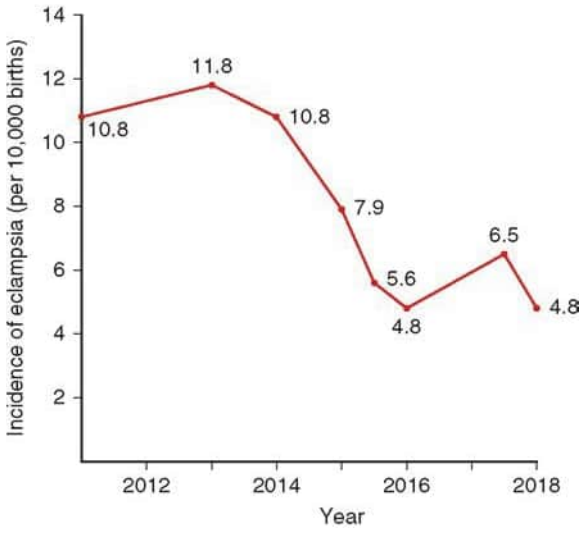


FIGURE 40-2 Incidence of eclampsia per 10,000 deliveries at Parkland Hospital ($p < 0.05$ for trend).

A fetus is not a requisite for preeclampsia to develop. Although chorionic villi are essential, they need not be intrauterine. For example, preeclampsia can develop with an advanced abdominal pregnancy (Worley, 2008). Regardless of precipitating etiology, the cascade of promoting events leads to systemic vascular endothelial damage, vasospasm, plasma transudation, and ischemic and thrombotic sequelae.

Phenotypic Expression

This varies widely for preeclampsia, and phenotype is affected by the degree of remodeling of uterine spiral arterioles by endovascular trophoblasts. This process underlies the "two-stage disorder" theory of preeclampsia pathogenesis. According to Redman and coworkers (2015), stage I—the placental syndrome—is caused by faulty endovascular trophoblastic remodeling that downstream causes stage II—the maternal syndrome. Importantly, stage II can be modified by maternal conditions that also manifest endothelial cell activation or inflammation. These include chronic hypertension, renal disease, obesity, immunological or connective tissue disorders, and diabetes.

Such staging is artificial, and preeclampsia syndrome presents a spectrum of disease (Burton, 2019). Moreover, "isoforms" likely exist and are discussed subsequently. Differences include maternal and fetal characteristics, placental findings, genetic factors, and early- versus late-onset disease (Gray, 2018; Phipps, 2019; Poon, 2019).

Etiology

Of suggested mechanisms to explain the cause of preeclampsia, primary ones include:

- Placental implantation with abnormal trophoblastic invasion of uterine vessels
- Dysfunctional immunological tolerance between maternal, paternal (placental), and fetal tissues

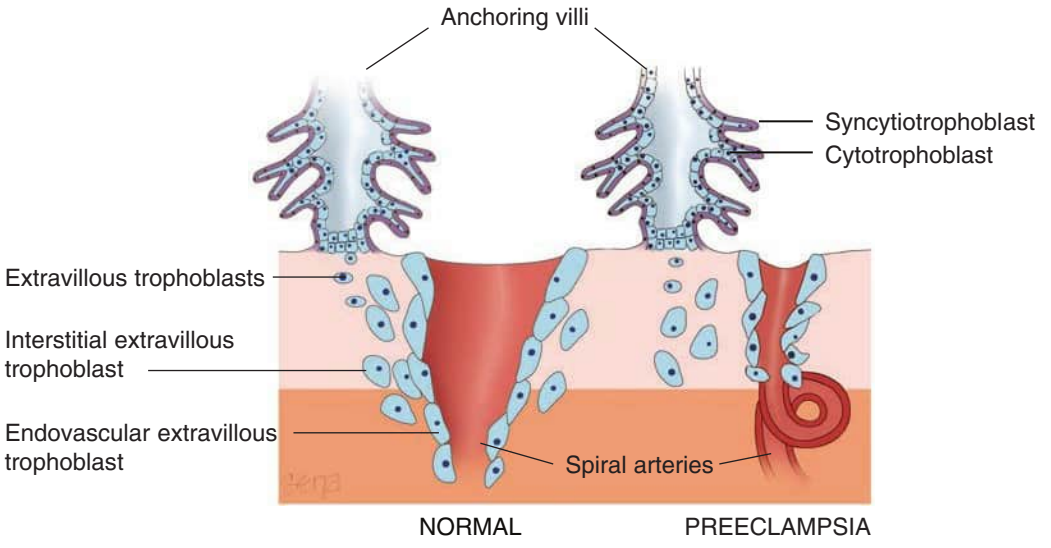


FIGURE 40-3 Schematic representation of normal placental implantation shows proliferation of extravillous trophoblasts from an anchoring villus. These trophoblasts invade the decidua and extend into the walls of the spiral arteriole to replace the endothelium and muscular wall to create a dilated low-resistance vessel. With preeclampsia, there is defective implantation characterized by incomplete invasion of the spiral arteriolar wall by extravillous trophoblasts. This results in a small-caliber vessel with high resistance to flow.

- Maternal maladaptation to cardiovascular or inflammatory changes of normal pregnancy
- Genetic factors that include predisposing genes and epigenetic influences.

Stage I—Placental Syndrome

Normal placental implantation, as discussed in Chapter 5 (p. 90), is characterized by extensive remodeling of the spiral arterioles within the decidua basalis (Fig. 40-3). In this "placental bed," endovascular trophoblasts replace the vascular endothelial and muscular linings. This advantageously enlarges arteriole diameter (Brosens, 2019). Veins are invaded only superficially. In some preeclampsia cases, but not all, trophoblastic invasion may be incomplete. With this, decidual vessels, but not myometrial vessels, become lined with endovascular trophoblasts. The deeper myometrial arterioles thus do not lose their endothelial lining and musculoelastic tissue. As a result, their mean external diameter is only half that of corresponding vessels in normal placentas (Fisher, 2015). This mechanism is more prevalent in women with early-onset preeclampsia (Khodzhaeva, 2016). Evidence suggests a critical role for soluble antiangiogenic growth factors in this faulty endovascular remodeling (McMahon, 2014).

From placental electron microscopy studies, early preeclamptic changes include endothelial damage, insudation of plasma constituents into vessel walls, myointimal cell proliferation, and medial necrosis (De Wolf, 1980). Hertig (1945) referred to lipid accumulation in myointimal cells and macrophages as *atherosis*. These findings are more common in placentas from women diagnosed with preeclampsia before 34 weeks' gestation (Nelson, 2014). Acute placental vascular atherosis may also identify a group of women at greater risk for atherosclerosis and cardiovascular disease later in life (Staff, 2015) (Chap. 41, p. 726). In pregnancy, abnormally narrow spiral arteriole lumens likely impair placental blood flow, reduce perfusion, and create a hypoxic environment (Burton, 2019).

At this point, these changes incite a systemic inflammatory response, which is stage II or the maternal syndrome. Defective placentation is posited to further predispose affected women to gestational hypertension, preeclampsia syndrome, preterm delivery, fetal growth-restriction, and placental abruption (Brosens, 2019; Labarrere, 2017; Nelson, 2014).

Immunological Factors

Maternal immune tolerance to paternally derived placental and fetal antigens is discussed in Chapter 5 (p. 85). Loss of this tolerance is another cited theory for preeclampsia (Erlebacher, 2013). Certainly, histological changes at the maternal–placental interface in those with preeclampsia suggest acute graft rejection.

Tolerance dysregulation might also explain the elevated risk when the paternal antigenic load is increased. One example is complete molar pregnancies, which have diploid complement of chromosomes solely from the father. Those with later-stage moles, have a high incidence of early-onset preeclampsia.

Women with a trisomy 13 fetus also have a 30- to 40-percent incidence of preeclampsia. The gene for one preeclampsia-linked factor, *soluble fms-like tyrosine kinase 1*, is on chromosome 13 (Bdolah, 2006). These women have elevated serum levels of antiangiogenic factors, which can affect the placenta (p. 694). Last, women previously exposed to paternal antigens, such as a prior pregnancy with the same partner, may be "immunized" against preeclampsia. Conversely, multiparas impregnated by a new partner have a greater risk of preeclampsia (Mostello, 2002).

Burton and colleagues (2019) reviewed the possible role of immune maladaptation in preeclampsia pathophysiology. In women destined to have preeclampsia, extravillous trophoblasts early in pregnancy express reduced amounts of immunosuppressive nonclassic human leukocyte antigen G (HLA-G). Black women more commonly have the 1597ΔC gene allele,

which is associated with incomplete HLA-G expression and may predispose to preeclampsia (Loisel, 2013). This immune maladaptation may contribute to the defective placental vascularization seen with preeclampsia.

As discussed in Chapter 4 (p. 61), T-helper (Th) lymphocytes during normal pregnancy are produced so that type 2 activity is increased in relation to type 1. This is the so-called *type 2 bias* (Phipps, 2019; Redman, 2015). Th2 cells promote humoral immunity, whereas Th1 cells stimulate inflammatory cytokine secretion (Ma, 2019). Beginning in the early second trimester in women who develop preeclampsia, Th1 action is increased.

Genetic Factors

Preeclampsia appears to be a multifactorial, polygenic disorder. In one study of almost 1.2 million Swedish births, a genetic association was found for gestational hypertension and for preeclampsia (Nilsson, 2004). Ward and Taylor (2015) cite an incident risk for preeclampsia of 20 to 40 percent for daughters of preeclamptic mothers; 11 to 37 percent for sisters of preeclamptic women; and 22 to 47 percent for twins. Ethnoracial factors are important and evidenced by the high incidence of preeclampsia in African American women. Latina women have a lower incidence because of interactions of American Indian and white race genes (Shahabi, 2013).

The hereditary predisposition for preeclampsia likely stems from interactions of literally hundreds of inherited genes—both maternal and paternal—that control many enzymatic and metabolic functions throughout every organ system (Burton, 2019; Triche, 2014). Plasma-derived factors may induce some of these genes in preeclampsia (Leseva, 2020; Mackenzie, 2012). Thus, the clinical manifestation in any given woman with the preeclampsia syndrome will reflect a spectrum. In this regard, phenotypic expression will differ among similar genotypes depending on interactions with environmental components (Yang, 2013).

Hundreds of genes have been studied for their possible association with preeclampsia (Buurma, 2013; Sakowicz, 2016; Ward, 2015). However, because of the complex phenotypic expression of preeclampsia, it is doubtful that any one candidate gene will be found responsible. Last, a preeclampsia predisposition has also been linked to genes of the fetus (Burton, 2019; Gray, 2018; Leseva, 2020).

■ Stage II—Maternal Syndrome

Endothelial Cell Activation

Inflammatory changes are believed to be a continuation of the placental syndrome. In response to ischemia or other inciting causes, placental factors are released and initiate a series of events (Burton, 2019; Davidge, 2015). Thus, antiangiogenic and metabolic factors and other inflammatory leukocyte mediators are thought to provoke the systemic *endotheliopathy*, which is used synonymously here with *endothelial cell activation or dysfunction*. Injury to systemic endothelial cells is seen as a centerpiece of preeclampsia pathogenesis (Burton, 2019; Phipps, 2019).

Cellular dysfunction may result from an extreme activated state of leukocytes in the maternal circulation (Gervasi, 2001). Briefly, cytokines such as tumor necrosis factor α (TNF-α) and the interleukins may contribute to the systemic oxidative stress associated with preeclampsia. This is characterized by generation of highly toxic oxygen radicals. These injure systemic vascular endothelial cells, lower nitric oxide production by these cells, and interfere with prostaglandin balance. Other sequelae include production of the lipid-laden macrophage foam cells seen in placental atherosis; activation of systemic microvascular coagulation, which is manifested by thrombocytopenia; and greater systemic capillary permeability, which is reflected by edema and proteinuria.

Intact endothelium has anticoagulant properties. Also, systemic endothelial cells, by releasing nitric oxide, blunt the response of vascular smooth muscle to agonists. Injured or activated endothelial cells may produce less nitric oxide and may secrete substances that promote coagulation and vasopressor sensitivity. Further evidence of endothelial activation includes changes in glomerular capillary endothelial morphology, greater capillary permeability, and elevated blood concentrations of substances associated with endothelial activations. Likely, multiple factors in the plasma of preeclamptic women combine to exert these vasoactive effects (Myers, 2007; Walsh, 2009).

Vasospasm and Hypertension

Vasospasm has long been associated with preeclampsia. Systemic endothelial activation causes vasospasm, which elevates resistance to produce hypertension. Concurrently, systemic endothelial cell injury promotes interstitial leakage, and platelets and fibrinogen are deposited in the subendothelial space. Endothelial junctional proteins are also disrupted, and the subendothelial region of resistance arteries undergoes ultrastructural change (Suzuki, 2003; Wang, 2002). The much larger venous circuit is similarly involved.

With diminished blood flow because of maldistribution from vasospasm and interstitial leakage, ischemia of the surrounding tissues can cause necrosis, hemorrhage, and other end-organ disturbances. One important clinical correlate to these changes is the markedly attenuated blood volume seen in women with severe preeclampsia (Zeeman, 2009).

Increased Pressor Responses

As discussed in Chapter 4 (p. 53), pregnant women normally develop refractoriness to infused vasopressors (Abdul-Karim, 1961). Women with early preeclampsia, however, have enhanced vascular reactivity to infused norepinephrine and angiotensin II (Raab, 1956; Talledo, 1968). Moreover, increased sensitivity to angiotensin II clearly precedes the onset of gestational hypertension (Gant, 1974). Paradoxically, women who develop preterm preeclampsia have lower circulating levels of angiotensin II (Chase, 2017).

Numerous *prostaglandins* are thought to be central to preeclampsia syndrome pathophysiology. Specifically, the blunted pressor response seen in normal pregnancy is at least partially due to diminished vascular responsiveness mediated by endothelial prostaglandin synthesis. For example, compared with normal pregnancy, endothelial prostacyclin (PGI_2) production is lower in preeclampsia. This action appears to be mediated by

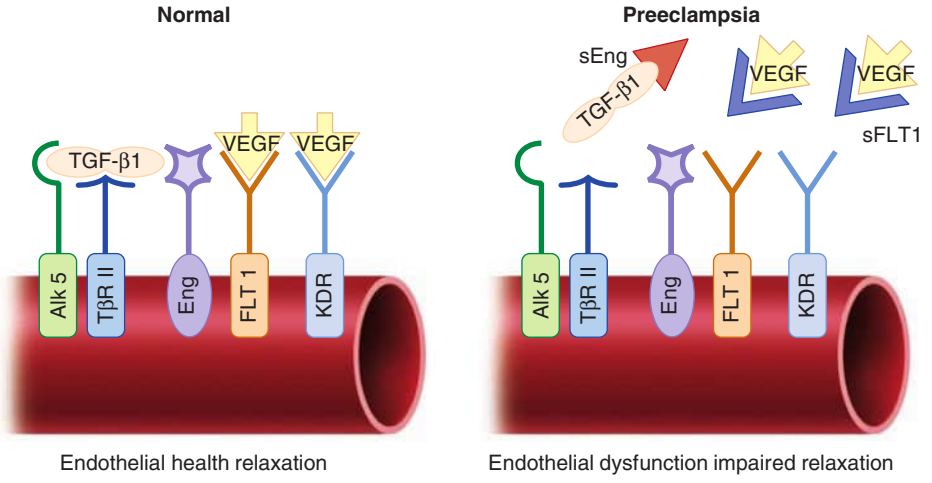


FIGURE 40-4 Schematic of receptor blocking action of soluble fms-like tyrosine kinase 1 (sFlt-1) and soluble endoglin (sENG).

phospholipase A_2 (Davidge, 2015). At the same time, thromboxane A_2 secretion by platelets is increased, and the prostacyclin: thromboxane A_2 ratio declines. The net result favors greater sensitivity to infused angiotensin II and vasoconstriction (Spitz, 1988). These changes appear as early as 22 weeks in gravidas who later develop preeclampsia (Chavarria, 2003).

Nitric oxide is a potent vasodilator and is synthesized from l-arginine by endothelial cells. Inhibition of nitric oxide synthesis raises mean arterial pressure, lowers heart rate, and reverses the pregnancy-induced refractoriness to vasopressors. Nitric oxide likely is the compound that maintains the normal low-pressure vasodilated state characteristic of normal fetoplacental perfusion (Myatt, 1992). Nitric oxide mediates the effects of placental growth factor (PlGF) and vascular endothelial growth factor (VEGF) in vitro (Zhang, 2017). The effects of nitric oxide production in preeclampsia are unclear. It appears that the syndrome is associated with decreased endothelial nitric oxide synthase expression and thus lower nitric oxide activity (Davidge, 2015).

Endothelins are 21-amino-acid peptides and potent vasoconstrictors. Endothelin l (ET-1) is the primary isoform produced by human endothelium (Karumanchi, 2016a). Plasma ET-1 levels are elevated in normotensive pregnant women. Women with preeclampsia have even higher levels, and these peptides may mediate renal injury (Phipps, 2019). Woman with preeclampsia develop functional autoantibodies to the endothelin and angiotensin II receptors (Buttrup, 2018). Interestingly, treatment of preeclamptic women with magnesium sulfate lowers ET-1 concentrations (Sagsoz, 2003). In animal studies, sildenafil reduces ET-1 concentrations (Gillis, 2016).

Angiogenic and Antiangiogenic Factors

Placental vasculogenesis is evident by 21 days after conception. The list of pro- and antiangiogenic substances involved in placental vascular development is extensive, and the VEGF and angiopoietin families are the most studied. Angiogenic imbalance describes excessive amounts of antiangiogenic factors, which are thought to be stimulated by worsening hypoxia at the uteroplacental interface. Trophoblast of women destined to develop preeclampsia overproduce at least two antiangiogenic peptides that enter the maternal circulation (Karumanchi, 2016b).

First, *soluble fms-like tyrosine kinase 1 (sF1t-1)* is a soluble variant of the membrane-bound receptor for VEGF. As depicted in Figure 40-4, elevated maternal sFlt-1 levels inactivate and reduce circulating PlGF and VEGF concentrations, leading to endothelial dysfunction (Phipps, 2019). As shown in data from Myatt and coworkers (2013), sFlt-1 levels begin to rise in maternal serum months before preeclampsia is evident (Fig. 40-5). These high levels in the second trimester are associated with a much higher risk for preeclampsia development (Haggerty, 2012; March, 2015). This elevation from normal levels appears even sooner with early-onset disease (Vatten, 2012). These factors are also

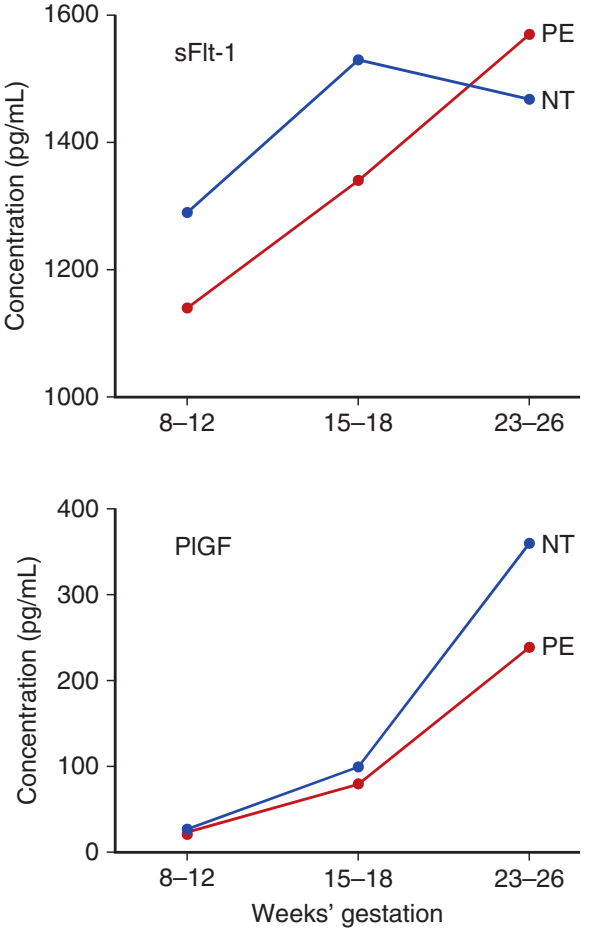


FIGURE 40-5 Angiogenic and antiangiogenic factors in normotensive (NT) and preeclamptic (PE) women across pregnancy. Both pairs of factors are significantly divergent by 23 to 26 weeks' gestation. sFlt-1 = soluble fms-like tyrosine kinase 1; PlGF = placental growth factor.

operative in pregnancies complicated by fetal-growth restriction (Herraiz, 2012).

A second antiangiogenic peptide, *soluble endoglin (sEng)*, inhibits various transforming growth factor beta (TGF-β) isoforms from binding to endothelial receptors (see Fig. 40-4). Endoglin is one of these receptors. Decreased binding to endoglin diminishes endothelial nitric oxide-dependent vasodilation. Serum levels of sEng also begin to rise months before clinical preeclampsia develops (Haggerty, 2012).

Simultaneously elevated levels of sFlt-1 and sEng are associated with more severe forms of preeclampsia (Phipps, 2019). In one systematic review, third-trimester increases in sFlt-1 levels and lower PlGF concentrations were found to correlate with preeclampsia development after 25 weeks' gestation (Widmer, 2007). From another study, doubling of sFlt-1 and sEng expression increased the preeclampsia risk by 39 and 74 percent, respectively (Haggerty, 2012). The cause of placental overproduction of antiangiogenic proteins remains an enigma. Concentrations of the soluble forms are not higher in fetal circulation or amnionic fluid of preeclamptic women, and their levels in maternal blood dissipate after delivery (Staff, 2007).

Clinical use of antiangiogenic protein levels to predict and diagnosis preeclampsia is being evaluated (p. 703). Moreover, one preliminary report described therapeutic apheresis to reduce sFlt-1 levels (Thadhani, 2016).

PATHOPHYSIOLOGY

Cardiovascular System

Disturbances in the cardiovascular system are common with preeclampsia syndrome. These are related to: (1) greater cardiac afterload imposed by hypertension; (2) cardiac preload, which is reduced by a pathologically diminished volume expansion during pregnancy and which is increased by administration of intravenous crystalloid or oncotic solutions; and (3) endothelial activation leading to leakage of intravascular fluid into the extracellular space.

Hemodynamic Changes and Cardiac Function

The cardiovascular aberrations of pregnancy-related hypertensive disorders vary. Modifying factors include preeclampsia severity, degree of hypertension, presence of underlying chronic disease, and the point in the clinical spectrum in which these are studied. In some women, these cardiovascular changes may precede hypertension (Easterling, 1990; Khalil, 2012; Melchiorre, 2013). Nevertheless, with the clinical onset of preeclampsia, cardiac output declines, due at least in part to greater peripheral resistance (Ferrazzi, 2018).

Myocardial Function

Serial echocardiographic studies document diastolic dysfunction in up to 45 percent of women with preeclampsia (Guirguis, 2015; Vaught, 2018). With this dysfunction, ventricles do not properly relax and cannot fill appropriately. In some affected women, functional differences persist up to 4 years after delivery (Evans, 2011; Orabona, 2017). Diastolic dysfunction stems from ventricular remodeling, which is a maladaptive response to the increased afterload of preeclampsia and aims to maintain normal contractility. High levels of antiangiogenic proteins may be contributory (Shahul, 2016). In otherwise healthy gravidas, these changes are usually inconsequential. But in those with underlying ventricular dysfunction—for example, concentric ventricular hypertrophy from chronic hypertension—further diastolic dysfunction may cause cardiogenic pulmonary edema (Wardhana, 2018). This is discussed further in Chapters 50 (p. 883) and 52 (p. 916).

Ventricular Function

Despite the relatively high frequency of diastolic dysfunction with preeclampsia, clinical cardiac function in most affected women is appropriate (Hibbard, 2015). In some preeclamptic women, high-sensitivity cardiac troponin levels are slightly elevated (Morton, 2018). With severe preeclampsia, amino-terminal pro–brain natriuretic peptide (NT–pro-BNP) levels are increased (Zachary, 2017).

Women with preeclampsia syndrome usually have slightly hyperdynamic ventricular function (Fig. 40-6). Both these and normotensive pregnant women have a cardiac output that is appropriate for left-sided filling pressures. This pressure can be altered by intravenous fluid volumes. Thus, aggressive hydration results in overtly *hyperdynamic* ventricular function. This is accompanied by elevated pulmonary capillary wedge pressures, and pulmonary edema may develop despite normal ventricular function. This is partly because of an alveolar endothelial-epithelial leak, and it is compounded by decreased oncotic pressure from a low serum albumin concentration. In sum, aggressive fluid administration to otherwise normal women with severe preeclampsia substantially elevates normal left-sided filling

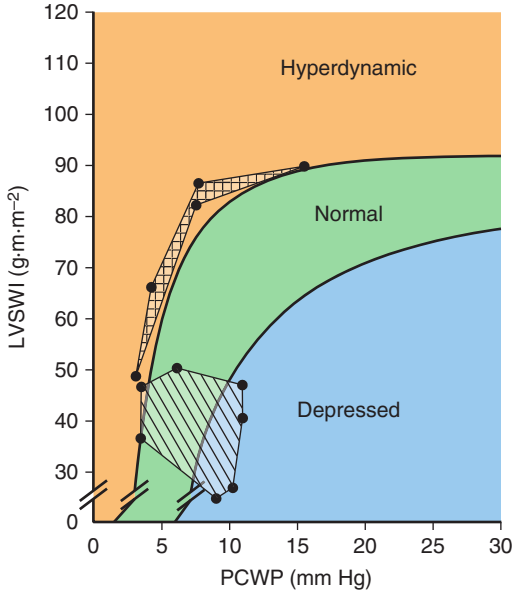


FIGURE 40-6 Ventricular function in normally pregnant women (*striped area*) and in women with eclampsia (*boxed area*) is plotted on a Braunwald ventricular function curve. Normal values are from Clark, 1989, and those for eclampsia are from Hankins, 1984. PCWP = pulmonary capillary wedge pressure; LVSWI = left ventricular stroke work index.

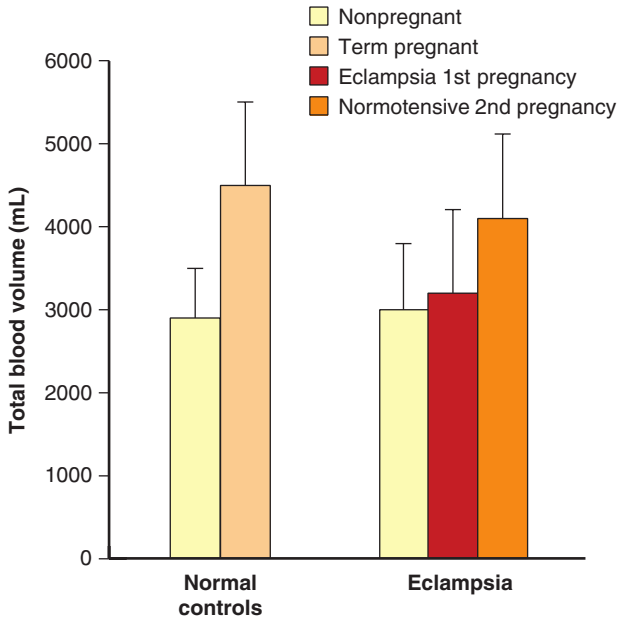


FIGURE 40-7 Total blood volumes in normotensive women compared with those with eclampsia. The vertical extensions are one standard deviation from the mean. In the eclamptic women, note the minimally increased blood volume compared with a subsequent normotensive pregnancy.

pressures and raises a physiologically normal cardiac output to hyperdynamic levels.

Blood Volume

In those with eclampsia, *hemoconcentration* is a hallmark feature (Pritchard, 1984). Data from Zeeman and associates (2009) show that normally expected pregnancy blood volume expansion is severely curtailed (Fig. 40-7). Women of average size have a nonpregnant blood volume of 3000 mL, and during the last several weeks of a normal pregnancy, this averages 4500 mL (Chap. 4, p. 59). With eclampsia, however, much or all of the anticipated 1500 mL excess is lost. Such hemoconcentration results from generalized vasospasm that follows endothelial activation and then from leakage of plasma into the interstitial space. In women with preeclampsia—depending on its severity—hemoconcentration is usually not as marked.

These changes have substantial clinical consequences. Women with severe hemoconcentration are unduly sensitive to blood loss at delivery that otherwise may be considered normal. Vasospasm and endothelial leakage of plasma persist for a variable time after delivery as the endothelium is restored to normal. As this takes place, vasoconstriction reverses, and as the blood volume reexpands, the hematocrit usually falls from dilution. *Importantly, a substantive cause of this fall in hematocrit frequently is the blood loss incurred at delivery.*

Hematological Changes

Thrombocytopenia

The platelet count is routinely measured in women with any form of gestational hypertension. The frequency and intensity of thrombocytopenia vary and are dependent on the severity and duration of preeclampsia (Hellmann, 2007; Hupuczi, 2007). Overt thrombocytopenia—defined by a platelet count <100,000/μL—reflects severe disease (see Table 40-2). In general, the lower the platelet count, the higher the likelihood of maternal and fetal morbidity and mortality. In most cases, delivery is advisable because thrombocytopenia usually worsens.

After delivery, the platelet count may continue to decline for the first day or so. It then usually rises progressively to reach a normal level within 3 to 5 days. As discussed later, in some instances with HELLP syndrome, the platelet count continues to fall after delivery. If this nadir is delayed until 48 to 72 hours, preeclampsia syndrome may be incorrectly attributed to one of the thrombotic microangiopathies (Chap. 59, p. 1060).

Another platelet alteration is platelet activation and increased α-degranulation. This leads to release of β-thromboglobulin and factor 4 and to enhanced platelet clearance (Kenny, 2015). Platelet volume concomitantly increases as young platelets are released (Bellos, 2018). Paradoxically, in most studies, in vitro platelet aggregation is reduced compared with the normal increase that is characteristic of pregnancy. This likely is due to platelet "exhaustion" following in-vivo activation. Although the cause is unknown, immunological processes or simply platelet deposition at sites of endothelial damage may be implicated. Levels of platelet-bound and circulating platelet-bindable immunoglobulins are elevated, which suggests platelet surface alterations. Abnormally low platelet levels do not develop in the fetuses of women with preeclampsia despite severe maternal thrombocytopenia (Kenny, 2015; Pritchard, 1987). Thus, thrombocytopenia in a hypertensive woman is not a fetal indication for cesarean delivery.

Hemolysis

Severe preeclampsia is frequently accompanied by hemolysis, which manifests as elevated serum lactate dehydrogenase levels and reduced haptoglobin levels (Burwick, 2018). Other evidence comes from schizocytosis, spherocytosis, and reticulocytosis in peripheral blood (Cunningham, 1985; Pritchard, 1954, 1976). Red cell distribution width (RDW) reflects variability in the size of circulating red blood cells, and RDW is higher in preeclamptic women (Adam, 2019). These derangements result in part from *microangiopathic hemolysis* caused by endothelial disruption with platelet adherence and fibrin deposition. Cunningham and coworkers (1995) postulated that erythrocyte morphological changes were partially caused by serum lipid alterations. Related, substantively decreased long-chain fatty acid content is found in erythrocytes of women with preeclampsia (Mackay, 2012).

After early reports of hemolysis and thrombocytopenia with severe preeclampsia, descriptions were added of abnormally elevated serum liver transaminase levels that indicated hepatocellular necrosis (Chesley, 1978). Weinstein (1982) referred to this combination of events as the *HELLP syndrome* (p. 699).

Coagulation Changes

Subtle changes consistent with intravascular coagulation commonly are found with preeclampsia and eclampsia (Cunningham, 2015; von Dadelszen, 2018). Some include elevated factor VIII

consumption, increased levels of fibrinopeptides A and B and of D-dimers, and reduced concentrations of the regulatory proteins—antithrombin III and proteins C and S. Coagulation aberrations generally are mild and seldom clinically significant (Kenny, 2015; Pritchard, 1984). Unless placental abruption is comorbid, plasma fibrinogen levels do not differ remarkably from levels found in normal pregnancy (Cunningham, 2015). As preeclampsia worsens, so do abnormal findings with *thromboelastography*, which is described in Chapter 44 (p. 774) (Pisani-Conway, 2013). Despite these changes, routine laboratory assessments of coagulation, such as prothrombin time (PT), activated partial thromboplastin time (aPTT), and plasma fibrinogen level, are not required in the management of pregnancy-associated hypertensive disorders.

Endocrine and Hormonal Alterations

Plasma levels of *renin*, *angiotensin II*, *aldosterone*, *deoxycorticosterone*, and *atrial natriuretic peptide (ANP)* are substantively augmented during normal pregnancy. ANP is released during atrial wall stretching from blood volume expansion, and it responds to cardiac contractility (Chap. 4, p. 65). Serum ANP levels rise in pregnancy, and its secretion is further enhanced in preeclampsia (Gu, 2018). Levels of its precursor—*proatrial natriuretic peptide*—also are elevated in preeclampsia. *Vasopressin* levels are similar in nonpregnant, in normally pregnant, and in preeclamptic women, although its metabolic clearance is elevated in the latter two (Dürr, 1999).

Fluid and Electrolyte Alterations

In women with severe preeclampsia, the volume of *extracellular fluid*, which manifests as edema, is usually much greater than that in normal pregnant women. The mechanism responsible for pathological fluid retention is endothelial injury and subsequent extravasation of intravascular fluid. Affected women also have reduced plasma oncotic pressure. This further displaces intravascular fluid into the surrounding interstitium. In women with preeclampsia, electrolyte concentrations do not differ appreciably from those of normal pregnant women.

Following an eclamptic convulsion, the *serum pH* and *bicarbonate concentration* are lowered due to lactic acidosis and compensatory respiratory loss of carbon dioxide. The intensity of acidosis relates to the amount of lactic acid produced—metabolic acidosis—and the rate at which carbon dioxide is exhaled—respiratory acidosis.

Kidney

During normal pregnancy, renal blood flow and glomerular filtration rate (GFR) rise appreciably (Chap. 4, p. 68). With preeclampsia, several reversible physiological changes ensue. Of clinical importance, renal perfusion and GFR are slightly reduced. Most of the decrement in GFR is from increased renal afferent arteriolar resistance that may be elevated up to fivefold (Conrad, 2015; Cornelis, 2011).

Morphological changes are characterized by *glomerular endotheliosis*, which blocks filtration (Phipps, 2019). Diminished filtration causes serum creatinine levels to rise to values seen in nonpregnant individuals, that is, 1 mg/mL, and sometimes higher. Acute kidney injury is discussed subsequently.

Plasma uric acid concentration is typically elevated in preeclampsia. The elevation exceeds that attributable to the reduced GFR and likely is also due to enhanced tubular reabsorption (Chesley, 1945). At the same time, preeclampsia is associated with diminished urinary excretion of calcium, perhaps because of greater tubular reabsorption (Taufield, 1987).

Proteinuria

Detection of proteinuria helps to establish the diagnosis of preeclampsia (see Table 40-1). Abnormal protein excretion is empirically defined by 24-hour urinary excretion exceeding 300 mg; a spot urine protein: creatinine ratio ≥0.3; or persistent protein values of 30 mg/dL (1+ dipstick) in random urine samples. Although worsening or nephrotic-range proteinuria was in the past considered by most to be a sign of severe disease, this does not appear to be the case (American College of Obstetricians and Gynecologists, 2013; Bartal, 2020).

Problematically, the optimal method of establishing abnormal levels of either urine protein or albumin remains to be defined. For a 24-hour quantitative specimen, the consensus threshold value is ≥300 mg/24 h (American College of Obstetricians and Gynecologists, 2013; Bartal, 2020). Using a urinary protein excretion threshold of 165 mg in a 12-hour sample shows equivalent efficacy (Stout, 2015).

Determination of urinary protein: creatinine ratio may supplant the cumbersome 24-hour quantification (Morris, 2012). In one systematic review, random urine protein:creatinine ratios <130 to 150 mg/g, that is, 0.13 to 0.15, indicate a low likelihood of proteinuria exceeding 300 mg/d (Papanna, 2008). Ratios <0.08 or >1.19 have negative and positive predictive values of 86 and 96 percent, respectively (Stout, 2013). However, midrange ratios, for example, 300 mg/g or 0.3, have poor sensitivity and specificity. Any midrange ratio should be repeated, and if persistent, a 24-hour urine collection for measurement of protein excretion should be considered.

With urine dipstick assessment, results depend on urine concentration and are notorious for false-positive and -negative results. A concentrated urine specimen may show a dipstick value of 1+ to 2+ in women who actually excrete <300 mg/d.

Importantly, proteinuria may develop late, and some women may already be delivered or have had an eclamptic convulsion before it appears. At presentation, 10 to 15 percent of women with HELLP syndrome do not have proteinuria (Sibai, 2004). In another report, 17 percent of women with eclampsia did not have proteinuria by the time of seizures (Zwart, 2008).

Anatomical Changes

Sheehan and Lynch (1973) frequently found microscopic changes that were identified at autopsy in the kidneys of eclamptic women. Glomeruli are enlarged by approximately 20 percent, they are "bloodless," and capillary loops variably are dilated and contracted. Endothelial cells are swollen—termed *glomerular capillary endotheliosis* (Spargo, 1959). Such swelling may be severe enough to block or partially block the capillary

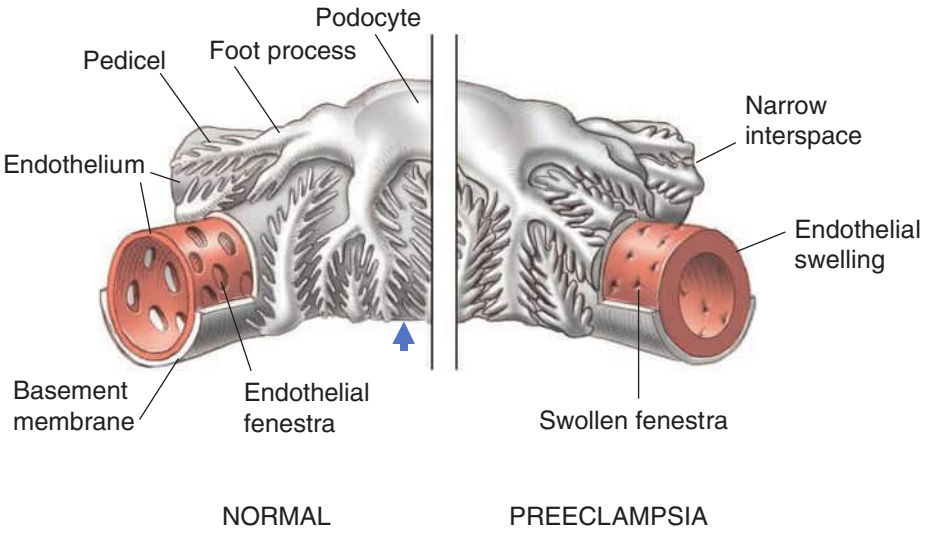


FIGURE 40-8 Schematic showing glomerular capillary endotheliosis. The capillary of the normal glomerulus shown on the left has wide endothelial fenestrations, and the pedicels emanating from the podocytes are widely spaced (*arrow*). The illustration on the right is of a glomerulus with changes induced by the preeclampsia syndrome. The endothelial cells are swollen and their fenestrae narrowed, as are the pedicels that now abut each other.

lumens (Fig. 40-8). Last, homogeneous subendothelial deposits of proteins and fibrin-like material are seen (Hecht, 2017).

Endothelial swelling may result from angiogenic protein "withdrawal." This is caused by the complexing of free angiogenic proteins with a compatible circulating antiangiogenic protein receptor (see Fig. 40-4). The angiogenic proteins are crucial for podocyte health, and their inactivation leads to podocyte dysfunction and endothelial swelling (Conrad, 2015; Phipps, 2019). Eclampsia is characterized by greater excretion of these epithelial podocytes (White, 2014).

Acute Kidney Injury

In one study, preeclampsia syndrome caused acute kidney injury (AKI) in 5 percent of patients and in 14 percent of those with HELLP syndrome (Novotny, 2020). With severe preeclampsia, Rodriguez and colleagues (2021) reported AKI in 15 percent of women in a study from Parkland Hospital. In most, AKI was stage 1. In another study of 72 women with preeclampsia and renal failure, half had HELLP syndrome, and a third had placental abruption (Drakeley, 2002). In a review of 183 women with HELLP syndrome, 5 percent had AKI (Haddad, 2000). Of those with renal injury, half had placental abruption, and most had postpartum hemorrhage. Abnormal renal values usually begin to normalize 10 days or later after delivery (Cornelis, 2011; Spaan, 2012). Although mild degrees of AKI are encountered, clinically apparent acute tubular necrosis is almost invariably induced by comorbid hemorrhage and subsequent hypovolemia and hypotension (Chap. 43, p. 753).

To evaluate AKI etiology clinically, urine electrolytes may be obtained. Results with preeclampsia reflect an *intrarenal* cause. In most with preeclampsia, the urine sodium concentration is elevated. Instead, changes that indicate a *prerenal* mechanism include increase urine osmolality, elevated urine: plasma creatinine ratio, and low fractional excretion of sodium.

In response to oliguria, sodium-containing crystalloid temporarily improves urine output. However, rapid infusions may cause clinically apparent pulmonary edema (p. 695). Intensive intravenous fluid therapy is not indicated as "treatment" for women with preeclampsia and oliguria, unless urine output is diminished from hemorrhage or fluid loss from vomiting or fever. In nonpregnant individuals, intravenous saline infusions have demonstrated a negative impact on renal function. However, at Parkland Hospital, transition from Ringer lactate to normal saline did not significantly impair renal function in women with preeclampsia (Yule, 2020).

Liver

Hepatic changes are common in women with severe preeclampsia syndrome. Several gross and microscopic anatomical derangements lead to elevated serum hepatic transaminase levels. This *transaminitis* indicates hepatocellular injury and is a marker for severe preeclampsia. Values are seldom more than 500 U/L, but levels exceeding 2000 U/L have been reported (Chap. 58, p. 1031). In general, serum concentrations inversely follow platelet levels, and they both usually return to normal levels within 3 days after delivery.

Anatomical Changes

Regions of periportal hemorrhage in the liver periphery typify the hepatic lesions of eclampsia (Hecht, 2017; Sheehan, 1973). Extensive involvement such as shown in Figure 40-9 is

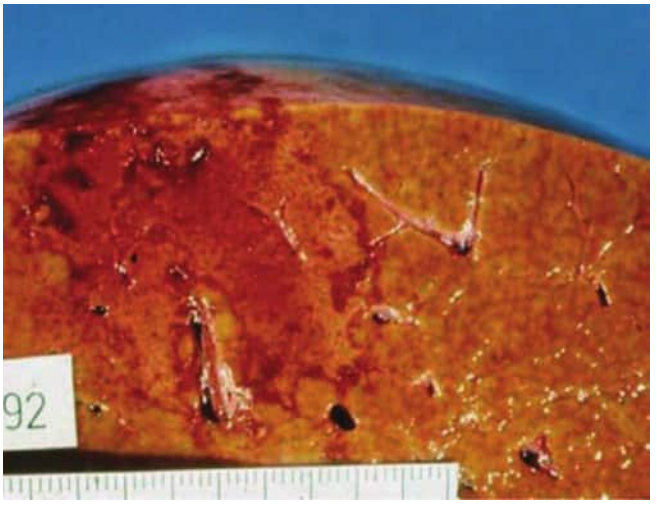


FIGURE 40-9 Hepatic section from a woman with HELLP syndrome who died of aspiration pneumonia. There are areas of ischemia and infarction, and histopathological examination showed periportal hemorrhages.

unusual. Sheehan and Lynch (1973) described that some degree of hepatic infarction accompanied hemorrhage in almost half of women who died with eclampsia. These findings corresponded with reports during the 1960s that described elevated serum hepatic transaminase levels. Pritchard and associates (1954) described hemolysis and thrombocytopenia with eclampsia. This constellation of hemolysis, hepatocellular necrosis, and thrombocytopenia was later termed HELLP syndrome. Similarities with hepatic sinusoidal obstruction are reviewed by von Salmuth and coworkers (2020).

Liver involvement with preeclampsia may clinically display several manifestations. First, pain is considered a sign of severe disease. It typically manifests as moderate to severe right upper quadrant or midepigastric pain and tenderness. These women usually have elevated serum aspartate transaminase (AST) or alanine transaminase (ALT) levels. In some cases, however, the amount of hepatic tissue involved with infarction may be surprisingly extensive yet still clinically insignificant. To study this, we performed magnetic resonance (MR) imaging in 16 women with HELLP syndrome (Nelson, 2018). All but two had evidence of acute liver injury, and the volume of involvement correlated with serum AST levels. Frank infarction is unusual, and in our experiences, it may be worsened or precipitated by hypotension from obstetrical hemorrhage. It occasionally causes hepatic failure—also called *shock liver* (Morgan, 2019; Yoshihara, 2016).

Hepatic Hematoma

In another presentation, periportal hemorrhage and infarction may extend to develop a hepatic hematoma. This in turn can extend to form a subcapsular hematoma that may rupture. Computed tomography (CT) scanning or MR imaging greatly aids diagnosis (Fig. 40-10). Unruptured hematomas are probably more common than clinically suspected and are more likely to be found with HELLP syndrome (Nelson, 2018). Although once considered a surgical condition, current management of a hepatic hematoma is usually observation unless bleeding is ongoing. In some cases, however, prompt surgical intervention or angiographic embolization may be lifesaving (Chandrasekaran, 2020). In one review of 180 cases of hepatic hematoma or rupture, 94 percent of affected gravidas had HELLP syndrome, and in 90 percent of the total, the capsule had ruptured (Vigil-De Gracia, 2012). The maternal mortality rate was 22 percent, and the perinatal mortality rate was 31 percent. Another review of 73 cases found similar outcomes (Gupta, 2021). In rare cases, liver transplantation is necessary (Escobar Vidarte, 2019).

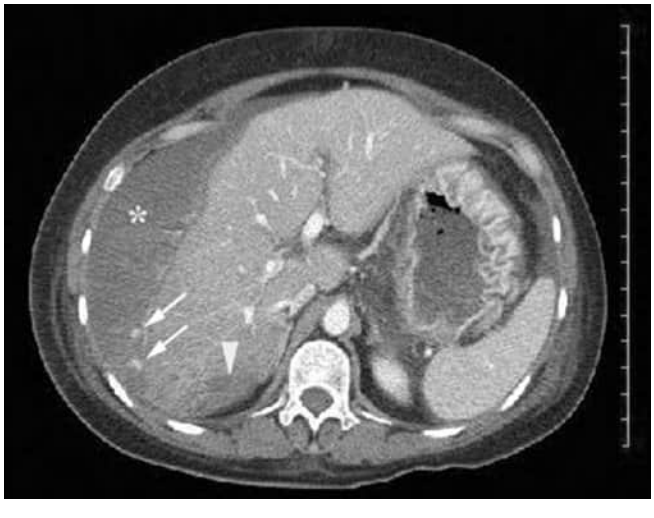


FIGURE 40-10 Abdominal CT imaging performed postpartum in a woman with severe HELLP syndrome and right-upper quadrant pain. A large subcapsular hematoma (*asterisk*) is seen confluent with intrahepatic infarction and hematoma (*arrowhead*). Numerous flame-shaped hemorrhages are seen at the hematoma interface (*arrows*).

Acute fatty liver of pregnancy is sometimes confused with preeclampsia (Byrne, 2020; Nelson, 2013). It too has an onset in late pregnancy, and often hypertension, elevated serum transaminase and creatinine levels, and thrombocytopenia are comorbid. In distinction, the hallmark of acute fatty liver is marked liver dysfunction. Liver function overall is usually normal in HELLP syndrome. Table 58-1 (p. 1031) highlights these clinical differences.

No convincing data link *pancreatic involvement* with preeclampsia syndrome. In 407 women with severe preeclampsia, the incidence was 1 percent (Sang, 2019). That said, the occasional case of concurrent hemorrhagic pancreatitis is likely unrelated (Lynch, 2015). In our experiences from Parkland Hospital, lipase and amylase levels are seldom elevated in women with preeclampsia (Nelson, 2018).

HELLP Syndrome

This acronym stands for hemolysis, elevated liver enzyme levels, and low platelet count. No strict definition of the syndrome is universally accepted, and thus its reported incidence varies.

In women with preeclampsia, those with HELLP syndrome typically have worse outcomes than those without it (Martin, 2012, 2013). In the previously noted study of 183 women with HELLP syndrome, 40 percent had adverse outcomes, and two mothers died (Haddad, 2000). Complications included eclampsia in 6 percent, placental abruption—10 percent, AKI—5 percent, and pulmonary edema—10 percent. Stroke, hepatic hematoma, coagulopathy, acute respiratory distress syndrome, and sepsis were other complications. In one review of 693 women with HELLP syndrome, 10 percent had concurrent eclampsia (Keiser, 2011). Obstetrical outcomes also may suffer. In one study comparing women with HELLP against those with preeclampsia, rates of eclampsia were greater with HELLP—15 versus 4 percent; preterm birth—93 versus 78 percent; and perinatal mortality—9 versus 4 percent, respectively (Sep, 2009). Because of these marked clinical differences, some postulate that HELLP syndrome has a distinct pathogenesis (Reimer, 2013; Vaught, 2016).

■ Central Nervous System

Headaches and visual symptoms are common with severe preeclampsia, and associated convulsions define eclampsia. The earliest anatomical descriptions of brain involvement came from autopsy specimens, but CT and MR imaging and Doppler studies have added important insights.

Neuroanatomical Lesions

From early anatomical descriptions, brain pathology accounted for only approximately a third of fatal cases, such as the one shown in Figure 40-11. In fact, most deaths were from pulmonary edema, and brain lesions were coincidental. Thus, although gross intracerebral hemorrhage was seen in up to 60 percent of eclamptic women, it was fatal in only half of these (Richards, 1988). With data from Sheehan and Lynch (1973) shown in Figure 40-12, cortical and subcortical petechial hemorrhages are other principal lesions found at autopsy in women with eclampsia. The classic microscopic vascular lesions consist of fibrinoid necrosis of the arterial wall and perivascular microinfarcts and hemorrhages. Other lesions include nonhemorrhagic areas of "softening" throughout the brain, hemorrhages in the white matter, and subcortical edema (Hecht, 2017; Willard, 2018). Hemorrhage in the basal ganglia or pons, often with rupture into the ventricles, may develop.

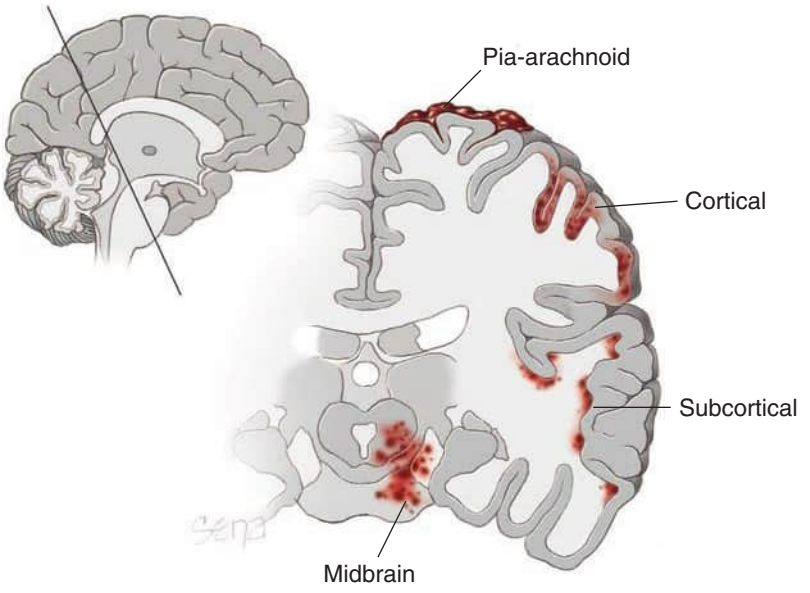


FIGURE 40-12 Composite illustration showing location of cerebral hemorrhages and petechiae in women with eclampsia. Insert shows the level of the brain from which the main image was constructed.

Cerebrovascular Pathophysiology

Clinical, pathological, and neuroimaging findings have led to two general theories to explain cerebral abnormalities with eclampsia. Endothelial cell dysfunction likely plays a key role in both. The first theory suggests that in response to acute and severe hypertension, cerebrovascular overregulation leads to vasospasm and eventual tissue infarction (Trommer, 1988). Little objective evidence supports this mechanism.

The second theory is that sudden elevations in systemic blood pressure exceed the normal cerebrovascular autoregulatory capacity (Schwartz, 2000). Regions of forced vasodilation and vasoconstriction develop, especially in arterial boundary zones. At the capillary level, disruption of end-capillary pressure causes increased hydrostatic pressure, hyperperfusion, and extravasation of plasma and red cells through endothelial tight-junction openings. This leads to *vasogenic edema*.

Most likely, the true mechanism combines these two. Thus, a preeclampsia-associated interendothelial cell leak develops at blood pressure levels much lower than those that usually cause vasogenic edema, and this is coupled with a loss of upper-limit autoregulation (Fugate, 2015; Zeeman, 2009). As shown in Figure 40-13, these abnormalities manifest as the *posterior reversible encephalopathy syndrome (PRES).* Lesions principally involve the occipital and parietal cortices, but other areas are often involved, although less extensively (Edlow, 2013; Zeeman, 2004a).

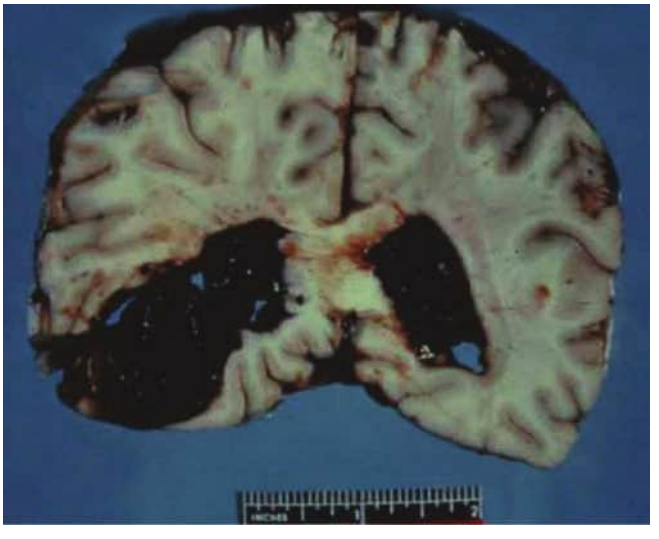


FIGURE 40-11 This autopsy brain slice shows a fatal hypertensive hemorrhage in a primigravida with eclampsia.

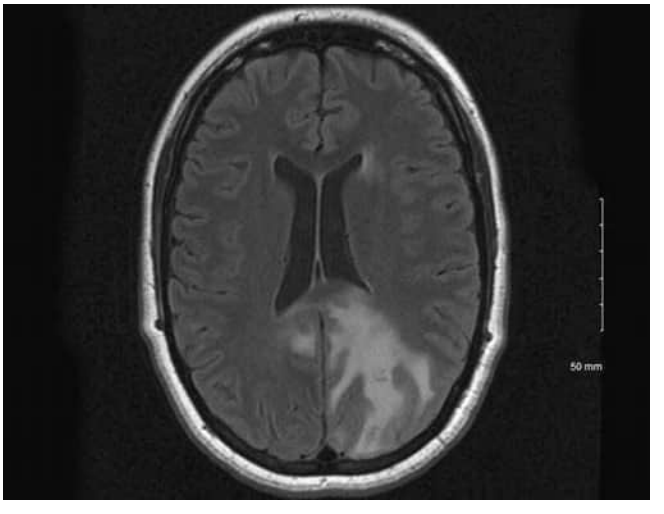


FIGURE 40-13 Cranial magnetic resonance imaging in a nullipara with eclampsia. This T2-FLAIR image shows an occipital lesion consistent with posterior reversible encephalopathy syndrome (PRES). FLAIR = fluid-attenuated inversion recovery.

Cerebral Blood Flow

Autoregulation is the mechanism by which cerebral blood flow remains relatively constant despite alterations in cerebral perfusion pressure. In nonpregnant individuals, this mechanism protects the brain from hyperperfusion when mean arterial pressures increase up to 160 mm Hg. These pressures are far greater than those seen in most women with eclampsia. Thus, to explain eclamptic seizures, it was theorized that autoregulation must be altered by pregnancy. Some investigators have shown impaired autoregulation in women with preeclampsia (Bergman, 2021b; Janzarik, 2014). When studied 2 to 3 years postpartum, women who had preeclampsia had returned to normal autoregulation (Janzarik, 2018).

Zeeman and associates (2003) showed that cerebral blood flow during the first two trimesters of normal pregnancy is similar to nonpregnant values. But during the last trimester, flow significantly drops by 20 percent. They found greater cerebral blood flow in this trimester in women with severe preeclampsia compared with flow in normotensive pregnant women (Lee, 2019; Zeeman, 2004b). Taken together, these findings suggest that eclampsia occurs when cerebral hyperperfusion forces capillary fluid interstitially because of endothelial damage. This leak leads to perivascular edema. Some data suggest that the blood-brain barrier is not impaired, but in-vitro studies may indicate increased permeability (Bergman, 2021a; Burwick, 2018).

Neurological Manifestations

Several neurological manifestations typify the preeclampsia syndrome. Each signifies severe involvement and requires immediate attention.

First, *headache and scotomata* are thought to arise from cerebrovascular hyperperfusion that has a predilection for the occipital lobes. In women preceding an eclamptic convulsion, up to 75 percent have headaches, and 20 to 30 percent have visual changes (Sibai, 2005; Zwart, 2008). The headaches vary in severity and persistence. In our experiences, they are unique in that they do not usually respond to traditional analgesia but frequently improve after magnesium sulfate infusion.

Convulsions are diagnostic for eclampsia. These are caused by abnormal excessive or synchronous neural activity in the brain. Evidence suggests that extended seizures can cause significant brain injury and later brain dysfunction.

Blindness and *generalized cerebral edema* are discussed in subsequent sections. Last, women with eclampsia have been shown to have some cognitive decline when studied 5 to 10 years following the involved pregnancy (Bergman, 2021c). This is discussed further in Chapter 41 (p. 727).

Neuroimaging Studies

With CT imaging, localized hypodense lesions are frequently seen with eclampsia at the gray- and white-matter junction and primarily in the parietooccipital lobes. Frontal and inferior temporal lobes, the basal ganglia, and thalamus are other sites (Brown, 1988). These hypodense areas correspond to petechial hemorrhages and local edema. Edema of the occipital lobes or diffuse cerebral edema may cause blindness, lethargy, and confusion (Cunningham, 2000). Widespread edema can appear as marked compression or even obliteration of the cerebral ventricles. Such women may develop signs of impending life-threatening transtentorial herniation.

Several MR imaging acquisitions are used to study women with eclampsia (Singh, 2021). Common findings are hyperintense T2 lesions in the subcortical and cortical regions of the parietal and occipital lobes, which reflect PRES (see Fig. 40-13). The basal ganglia, brainstem, and cerebellum are other involved sites (Brewer, 2013; Zeeman, 2004a). PRES lesions are almost universal in women with eclampsia, and their incidence in women with severe preeclampsia approximates 20 percent (Hosapatna Basavarajappa, 2020; Mayama, 2016). Although usually reversible, a fourth of these hyperintense lesions with eclampsia have restricted diffusion that signify cerebral infarctions. These have persistent MR imaging findings (Loureiro, 2003; Zeeman, 2004a).

Visual Changes and Blindness

Retinal artery and venular calibers are decreased in women with preeclampsia (Soma-Pillay, 2018). These changes, along with visual cortex involvement, can cause scotomata, blurred vision, or diplopia, which is common with severe preeclampsia and eclampsia. These symptoms usually improve with magnesium sulfate therapy, or lowered blood pressure, or both.

Blindness is rare with preeclampsia alone, but it complicates up to 15 percent of women with eclampsia (Cunningham, 1995). It can develop a week or more following delivery. Blindness is usually reversible and may arise from three potential areas. These are the occipital lobe's visual cortex, the lateral geniculate nuclei, and the retina.

Occipital blindness is also called *amaurosis*. With MR imaging, affected women usually have evidence of extensive occipital lobe vasogenic edema. Of 15 women cared for at Parkland Hospital, occipital blindness lasted from 4 hours to 8 days, but it resolved completely in all cases (Cunningham, 1995). Rarely, extensive cerebral infarctions may result in total or partial visual defects.

In the retina, ischemia, infarction, or serous detachment may occur (Handor, 2014). Retinal infarction, termed *Purtscher retinopathy*, is rare (Fig. 40-14). *Serous retinal detachment* is usually unilateral and seldom causes total visual loss. Asymptomatic serous retinal detachment is relatively common with preeclampsia (Gupta, 2019). In most cases of eclampsia-associated blindness, visual acuity subsequently improves (Mandura, 2021). If blindness is caused by retinal artery occlusion, vision may be permanently impaired (Roos, 2012).

Cerebral Edema

Manifestations that suggest widespread cerebral edema are worrisome. During 13 years at Parkland Hospital, 10 of 175 women with eclampsia were diagnosed with symptomatic cerebral edema (Cunningham, 2000). Symptoms ranged from lethargy, confusion, and blurred vision to obtundation and coma. In most cases, symptoms waxed and waned. Of these 10, three became comatose and had imaging findings of transtentorial herniation. One woman died.

Mental status changes generally correlated with the degree of involvement seen with CT and MR imaging studies. *These women are very susceptible to sudden and severe blood pressure*

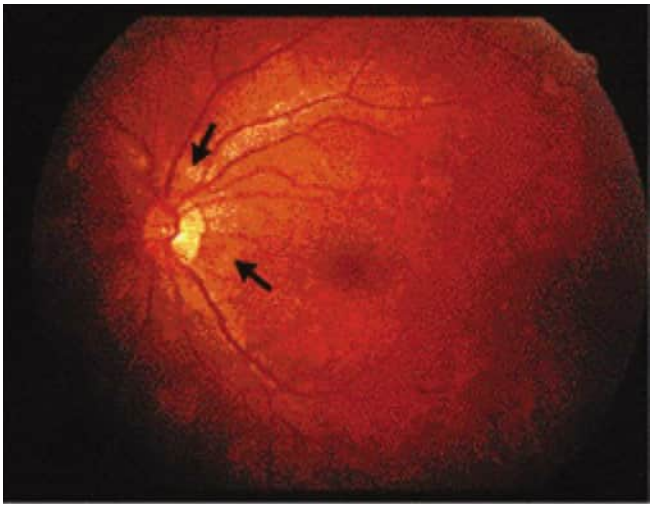


FIGURE 40-14 Purtscher retinopathy caused by choroidal ischemia and infarction in preeclampsia syndrome. Ophthalmoscopy shows scattered yellowish, opaque lesions of the retina (*arrows*). (Reproduced with permission from Lam, DS, Chan W: Images in clinical medicine. Choroidal ischemia in preeclampsia. N Engl J Med 344(10):739, 2001).

elevations, which can acutely worsen the already widespread vasogenic edema. Thus, careful blood pressure control is essential.

■ Uteroplacental Perfusion

Compromised uteroplacental perfusion is almost certainly a major contributor to the increased perinatal morbidity and mortality rates associated with preeclampsia syndrome (Harmon, 2015). Contributing defects in endovascular trophoblastic invasion were discussed earlier (p. 692). Thus, measurement of uterine, intervillous, and placental blood flow would likely be informative. Attempts to assess these in humans have been hampered. Barriers include the placenta's inaccessibility, the complexity of its venous effluent, and the need for invasive techniques or radioisotopes.

As a surrogate, sonographic measurement of uterine artery blood flow velocity can estimate resistance to uteroplacental blood flow. Vascular resistance is estimated by comparing arterial systolic and diastolic velocity waveforms (Chap. 14, p. 262). By the completion of placentation, impedance to uterine artery blood flow is markedly decreased, but with abnormal placentation, abnormally high resistance persists (Everett, 2012; Napolitano, 2012). In earlier studies, peak systolic:diastolic velocity ratios from uterine and umbilical arteries in preeclamptic pregnancies were measured. In some cases, but not all, resistance was higher (Ferrazzi, 2018; Trudinger, 1990).

Another Doppler waveform, termed uterine artery "notching," has been linked with increased risks for preeclampsia or fetal-growth restriction (Groom, 2009). However, in one MFMU Network study, notching had a low predictive value except for early-onset, severe disease (Myatt, 2012a).

Resistance in *uterine spiral arteries* also has been measured. In one study, mean resistance values were greater in all women with preeclampsia compared with those in normotensive controls (Matijevic, 1999). Another study used MR imaging and other techniques to assess placental perfusion ex vivo in the myometrial arteries removed from women with preeclampsia or fetal-growth restriction (Ong, 2003). In both conditions, myometrial arteries exhibited similar vascular responses.

Despite these findings, evidence for compromised uteroplacental circulation is found in only a few women who later develop preeclampsia. Indeed, when preeclampsia develops during the third trimester, only a third of women with severe disease have abnormal uterine artery velocimetry (Li, 2005). In a study of 50 women with HELLP syndrome, only a third had abnormal uterine artery waveforms (Bush, 2001). In general, the extent of abnormal waveforms correlates with severity of fetal involvement (Ghidini, 2008; Groom, 2009).

These sonographic findings have value for prediction of fetal-growth restriction but not preeclampsia (American College of Obstetricians and Gynecologists, 2019b; Demers, 2019). Several other flow velocity waveforms have been investigated for preeclampsia prediction. However, none is suitable for clinical use (De Kat, 2019; Townsend, 2018).

Fetal-growth Restriction

Discussed in detail in Chapter 47, this potential consequence of preeclampsia can serve as one severity indicator (see Table 40-2). Namely, poor growth is usually confined to fetuses of women destined to develop severe preeclampsia (Mateus, 2019). Perry and colleagues (2020) reported that pregnancies complicated by fetal-growth restriction more likely had maternal hemodynamic indices similar to preeclampsia. Measures showed higher mean arterial pressure, greater systemic vascular resistance, lower cardiac output, and elevated uterine artery pulsatility index. Fetuses born to preeclamptic mothers have cardiac remodeling similar to growth-restricted fetuses (Youseff, 2020).

PREDICTION

Some biological markers implicated in the genesis of the preeclampsia syndrome have been measured to help predict its development. Although most have been evaluated in the first half of pregnancy, some have been tested as predictors of severity in the third trimester. Still others have been used to forecast recurrent preeclampsia. Overall, these efforts have resulted in testing strategies with poor sensitivity and poor positive predictive values for preeclampsia (Conde-Agudelo, 2015; De Kat, 2019). *Currently, no screening tests for preeclampsia are predictably reliable, valid, and economical.*

Because combinations of tests and risk factors might be superior to single predictors, some have developed multivariable screening algorithms (Boutin, 2021; Brunelli, 2020; Copel, 2020; Serra, 2020; Snell, 2020). One first-trimester screening protocol using serum sFlt-1 levels has been proposed (Pihl, 2020). Other examples are midpregnancy algorithms (Black, 2020; Peguero, 2021; Stepan, 2020). None has been adequately verified sufficiently for widespread clinical use (Capriglione, 2020).

■ Vascular Resistance Testing and Placental Perfusion

Most tests in this category are cumbersome, time consuming, and inaccurate. To evaluate blood pressure changes, three tests

assess the blood pressure rise in response to a stimulus. In one, women at 28 to 32 weeks' gestation rest in the left lateral decubitus position and then roll to lie supine. With this *roll-over test*, rising blood pressure in response to the maneuver signifies a positive test. The *isometric exercise* test employs the same principle by squeezing a handball. The *angiotensin II infusion test* provides incrementally higher doses intravenously, and the hypertensive response is quantified. Sensitivities of all three tests range from 55 to 70 percent, and specificities approximated 85 percent (Conde-Agudelo, 2015).

Uterine artery Doppler velocimetry is posited to reflect faulty trophoblastic invasion of the spiral arteries. The poor predictive value of this for preeclampsia was described in the Uteroplacental Perfusion section (p. 702).

Fetal-Placental Unit Endocrine Function

Several serum analytes have been proposed to help predict preeclampsia. Newer ones are continually added. In general, none of these tests is clinically beneficial for hypertension prediction.

Renal Function Tests

Hyperuricemia results from reduced uric acid clearance caused by diminished glomerular filtration, increased tubular reabsorption, and decreased secretion. In one study, the sensitivity of serum uric acid levels to detect preeclampsia ranged from 0 to 55 percent, and specificity was 77 to 95 percent (Cnossen, 2006). These are seldom used to diagnose preeclampsia (Chescheir, 2019).

Isolated gestational proteinuria is a risk factor for preeclampsia (Jayaballa, 2015; Morgan, 2016). But, as a predictive test for preeclampsia, microalbuminuria has sensitivities ranging from 7 to 90 percent and specificities spanning 29 to 97 percent (Conde-Agudelo, 2015).

Endothelial Dysfunction and Oxidative Stress

Endothelial activation and inflammation are major participants in preeclampsia pathophysiology. Levels of some implicated compounds are elevated in the blood of affected women and have been assessed as predictors.

Fibronectins are high-molecular-weight glycoproteins released from endothelial cells and extracellular matrix following endothelial injury. In one systematic review, however, neither cellular nor total fibronectin levels were clinically useful to predict preeclampsia (Leeflang, 2007).

Thrombocytopenia and *platelet dysfunction* are integral features of preeclampsia. Platelet activation causes their augmented destruction and lower blood concentrations. Platelet volume is increased because of platelet immaturity, and platelet volume has been described to be an early predictor of preeclampsia (Bellos, 2019; Mayer-Pickel, 2021). Although markers of coagulation activation described earlier (p. 696) are elevated, they substantively overlap with levels in normotensive pregnant women (von Dadelszen, 2018).

Of *oxidative stress markers*, higher levels of lipid peroxides coupled with decreased antioxidant activity can be seen with preeclampsia. Other markers are *iron*, *transferrin*, *and ferritin*; *resistin*; *hyperhomocysteinemia*; *blood lipids*; and antioxidants such as *ascorbic acid* and *vitamin E* (Christiansen, 2015; Conde-Agudelo, 2015; Mackay, 2012; Mignini, 2005). However, none has sufficient predictive value.

Angiogenic and Antiangiogenic Factor Imbalance

An imbalance in angiogenic and antiangiogenic factors is convincingly linked to preeclampsia pathogenesis (p. 694). Serum levels of VEGF and PlGF begin to drop before clinical preeclampsia develops. At the same time, levels of some antiangiogenic factors, such as sFlt-1 and sEng, begin to rise. Factor levels and ratios differ significantly between women with preeclampsia and those who are normotensive. These show especially good predictive performance with early-onset preeclampsia (Burton, 2019; Cerdeira, 2019; Phipps, 2019; Stepan, 2020).

These tests also can serve as diagnostic adjuncts (Duhig, 2019; Zeisler, 2016). First, they may aid differentiating between preeclampsia and mimics that include chronic hypertension, chronic kidney disease, systemic lupus erythematosus, and immunological thrombocytopenia. These tests can also help differentiate mild and severe disease. These plus other multiple markers will likely have a future role in first-trimester preeclampsia screening (Sovio, 2019).

Other Markers

Cell-free DNA (cfDNA) of placental origin can be detected in maternal plasma (Chap. 16, p. 327). It is hypothesized that cfDNA is released in preeclampsia by accelerated apoptosis of cytotrophoblasts. However, one MFMU Network study found no correlation between total cfDNA levels and preeclampsia prediction (Silver, 2017).

Other investigated markers include glycosylated hemoglobin A1c, serum cystatin-c, and first-trimester estimated placental volume (Bellos, 2019; Cavero-Redondo, 2018; Kim, 2021). Proteomic, metabolomic, and transcriptomic technologies can be employed to study serum and urinary proteins and cellular metabolites. Preliminary studies indicate their potential predictive value (Bahado-Singh, 2013; Ma, 2014).

PREVENTION

Various strategies used to prevent or modify preeclampsia severity have been evaluated. Some are listed in Table 40-4. With the possible exception of aspirin, none is convincingly and reproducibly effective.

Dietary and Lifestyle Modifications

A *low-salt* diet was one of the earliest researched preventions but is not supported by data (De Snoo, 1937). Of studies, one randomized trial showed that a sodium-restricted diet was ineffective in preventing preeclampsia (Knuist, 1998).

Regular exercise during pregnancy is linked to a lower risk of developing preeclampsia (Barakat, 2016; Morris, 2017). In one

TABLE 40-4. Some Methods to Prevent Preeclampsia That Have Been Evaluated in Randomized Trials

Dietary manipulation: low-salt diet, calcium or fish oil supplementation
Exercise: physical activity, stretching
Cardiovascular drugs: diuretics, antihypertensive drugs
Antioxidants: ascorbic acid (vitamin C), α-tocopherol (vitamin E), vitamin D
Antithrombotic drugs: low-dose aspirin, aspirin/dipyridamole, aspirin + heparin, aspirin + ketanserin

Modified from Jim, 2017; Staff, 2015.

systematic review, a similar trend toward risk reduction with exercise was noted (Kasawara, 2012). Only a few studies have been randomized.

Somewhat related, one retrospective cohort study of 677 nonhypertensive women were hospitalized for bed rest because of threatened preterm delivery (Abenhaim, 2008). When outcomes of these women were compared with those of the general obstetrical population, bed rest was associated with a significantly reduced risk of developing preeclampsia (relative risk 0.27). From two small randomized trials, prophylactic bed rest for 4 to 6 hours daily at home was successful in significantly lowering the preeclampsia incidence in women with normal blood pressures (Meher, 2006). Currently, the Society for Maternal-Fetal Medicine (2020) does not recommend reduced activity for women with hypertensive disorders or for prevention of preeclampsia.

Calcium supplementation has been studied, but in one trial of more than 4500 low-risk nulliparas, supplementation failed to decrease the risk for preeclampsia or pregnancy-associated hypertension (Levine, 1997). Similar findings were reported from another trial (Hofmeyer, 2019). In aggregate, most trials show that unless women are calcium deficient, supplementation offers no benefits (Palacios, 2019; Sanchez-Ramos, 2017).

Subclinical hypothyroidism is associated with increased preeclampsia risk. This insufficiency has been postulated to stem from iodine deficiency, but a recent metaanalysis found no association between iodine sufficiency and preeclampsia (Businge, 2021). *Folic acid* was evaluated in a randomized trial (Wen, 2018). Nearly 2500 high-risk women were given a 4-mg folic acid dose daily or placebo. The incidence of preeclampsia in both groups approximated 14 percent.

Cardioprotective fatty acids found in some fish likely prevent inflammation-mediated atherogenesis. Thus, it was posited that they might also prevent preeclampsia. However, randomized trials conducted thus far show no such benefits from fish oil supplementation (Zhou, 2012). In one longitudinal cohort study, a seafood diet, compared with a western one, provided a protective effect against preeclampsia (Ikem, 2019).

Antihypertensive Drugs

Because of the prior purported benefits of sodium restriction for preeclampsia prevention, diuretic therapy became popular with the advent of chlorothiazide in 1957 (Flowers, 1962). In one metaanalysis of nine randomized trials with more than 7000 pregnancies, women given diuretics had a lower incidence of edema and hypertension but not of preeclampsia (Churchill, 2007). Because women with chronic hypertension are at high risk for preeclampsia, several randomized trials have evaluated various antihypertensive drugs to reduce the incidence of superimposed preeclampsia (Chap. 41, p. 713). A critical analysis of these trials by Staff and coworkers (2015) failed to demonstrate benefits for this goal.

Antioxidants

Data imply that an imbalance between oxidant and antioxidant activity plays a role in preeclampsia pathogenesis. Thus, naturally occurring antioxidants—vitamins C, D, and E—might reduce such oxidation. Several randomized studies have assessed antioxidant vitamin supplementation for women at high risk for preeclampsia (Burton, 2019; Villar, 2009). The Combined Antioxidant and Preeclampsia Prediction Studies (CAPPS) by the MFMU Network included almost 10,000 low-risk nulliparas (Roberts, 2010). None of these studies showed reduced preeclampsia rates in women supplemented with vitamins C and E compared with those given placebo.

Statins were proposed to prevent preeclampsia because they stimulate heme oxygenase-1 expression, which inhibits sF1t-1 release. Early animal data suggest that statins may prevent hypertensive disorders of pregnancy (Lewis, 2017). The MFMU Network plans a randomized trial to test pravastatin for prevention, and a pilot study is completed (Costantine, 2016).

Metformin inhibits *hypoxic inducible factor 1α* by lowering mitochondrial electron transport chain activity. It reduces sFlt-1 and sEng activity and thus has potential to prevent preeclampsia (Brownfoot, 2016). In a preliminary study, prediabetic women were given metformin or placebo throughout pregnancy, and metformin-treated women had a lower incidence of severe preeclampsia (Racine, 2021). However, other clinical studies are lacking.

Antithrombotic Agents

Preeclampsia is characterized by vasospasm, endothelial cell dysfunction, inflammation, and activation of platelets and the coagulation–hemostasis system. Other sequelae include placental infarction and spiral artery thrombosis (Nelson, 2014). Thus, antithrombotic agents have been evaluated to prevent preeclampsia. Low-molecular-weight heparin has been studied in randomized trials. In a subsequent metaanalysis using individual data from 963 women, the risk for recurrent preeclampsia, abruption, or fetal-growth restriction was similar in women receiving heparin or placebo (Rodger, 2016).

Low-dose Aspirin

In low doses of 50 to 150 mg daily, *aspirin* effectively inhibits platelet thromboxane A_2 biosynthesis. It has minimal effects on vascular prostacyclin production. Still, several clinical trials have shown limited benefits in preeclampsia prevention. In a randomized trial from the MFMU Network, risks for adverse outcomes were not significantly reduced with aspirin therapy (Caritis, 1998). This study was followed by numerous similar studies and metaanalyses.

In another randomized trial of more than 1600 women at high risk for preterm preeclampsia, oral low-dose aspirin was given daily from 11 to 14 weeks' gestation until 36 weeks to prevent recurrence (Rolnik, 2017). The rate of preterm preeclampsia recurrence was 1.6 percent in the aspirin group compared with 4.3 percent in the placebo arm. In a metaanalysis, Roberge and colleagues (2017) found that aspirin prophylaxis initiated before 16 weeks' gestation was associated with a significant risk reduction—approximately 60 percent—of preeclampsia and fetal-growth restriction. At the same time, however, Meher and associates (2017) performed an individual participant data metaanalysis and reported a much lower—approximately 10 percent—risk reduction. Effects were significant whether therapy was initiated before or after 16 weeks' gestation.

In a subsequent metaanalysis, Roberge and coworkers (2018) found that aspirin prophylaxis given starting ≤16 weeks' gestation reduced the risk of preterm, but not term, preeclampsia. Turner and colleagues (2020) reported that aspirin improved some perinatal outcomes independent of effects on preeclampsia risk. But to the contrary, the review by Chaemsaithong and coworkers (2020) found no benefits even when low-dose aspirin was given before 11 weeks' gestation.

Based on these data, the U.S. Preventive Services Task Force (2021) recommends low-dose aspirin prophylaxis for women at high risk for preeclampsia. The American College of Obstetricians and Gynecologists (2018, 2020) now recommends low-dose aspirin be given between 12 and 28 weeks' gestation to help prevent preeclampsia in high-risk women. Candidates include those with ≥1 of the following: prior preeclampsia, chronic hypertension, overt diabetes, renal disease, autoimmune disorders, and multifetal gestation. Supplementation may be *considered* for those with more than one of these qualities: nulliparous, aged older than 35 years, obese, family history of preeclampsia, vulnerable sociodemographics, and prior low-birthweight or growth-restricted neonate. These results have also raised the question as to whether all pregnant women should be given aspirin (Ayala, 2019).

Low-dose aspirin coupled with heparin mitigates thrombotic sequelae in women with lupus anticoagulant (Chap. 62, p. 1116). Because of a similarly high prevalence of placental thrombotic lesions found with severe preeclampsia, trials have assessed the possible merits of such treatments for women with prior preeclampsia. In two randomized trials, women with a history of early-onset preeclampsia were given aspirin alone or a regimen of enoxaparin plus aspirin (Groom, 2017; Haddad, 2016). Outcomes were similar. Low-molecular-weight heparin, with or without aspirin, may decrease the risk for preeclampsia in high-risk women (de Vries, 2012; Wang, 2020).

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CHAPTER 41

Clinical Management of the Preeclampsia Syndrome

Preeclampsia remains one of the leading causes of death and severe maternal morbidity. This chapter discusses many clinical aspects of the preeclampsia syndrome and its management after recognition. Also presented are the long-term consequences that may accrue in affected women. The pathophysiology of preeclampsia was detailed in Chapter 40.

DIAGNOSIS AND EVALUATION

Diagnosis

In routine prenatal care, gravidas are seen more often during the third trimester, and this aids early detection of preeclampsia. However, it cannot always be diagnosed definitively. Increases in systolic and diastolic blood pressure can be either normal physiological changes or signs of developing pathology.

Women without overt hypertension, but in whom the early development of preeclampsia is suspected, are seen more frequently. Heightened surveillance permits recognition of ominous changes in blood pressure, critical laboratory findings, and clinical signs and symptoms. Outpatient surveillance continues unless overt hypertension, proteinuria, headache, visual changes, or epigastric pain supervene. At Parkland Hospital, women with new-onset overt hypertension—either diastolic pressures ≥90 mm Hg or systolic pressures ≥140 mm Hg—are admitted to exclude preeclampsia or to define its severity.

Evaluation

With hospitalization, a systematic evaluation begins:

- Detailed examination, which is coupled with daily scrutiny for headache, visual changes, or epigastric pain
- Daily weight measurement to identify rapid weight gain
- Quantification of proteinuria or a urine protein: creatinine ratio
- Blood pressure readings with an appropriate-size cuff every 4 hours, unless previously elevated, which would mandate more frequent readings
- Measurements of serum creatinine and hepatic transaminase levels and a hemogram that includes a platelet count. The frequency of testing is determined by hypertension severity. Although some recommend assessment of serum uric acid and lactate dehydrogenase levels and coagulation, their value has been questioned (Chescheir, 2019; Conde-Agudelo, 2015)
- Evaluation of fetal size and well-being and amnionic fluid volume
- Reduced physical activity may have benefits, although evidence is not robust.

Still investigational as a clinical tool, measurements of *placental growth factor (PlGF)* and *soluble fms-like tyrosine kinase 1 (sF1t-1)* levels will likely be available to help predict preeclampsia (Barton, 2020; Chappell, 2013; Zeisler, 2016). Chapter 40 (p. 694) describes their role in preeclampsia genesis.

In sum, evaluation goals are early identification of preeclampsia and then management until timely delivery. Complete

abatement of all signs and symptoms is uncommon until after delivery. If severe preeclampsia is diagnosed using the criteria in Table 40-2 (p. 690), further management is subsequently described.

Consideration for Delivery

With gestational hypertension, its morbidity and management vary depending on hypertension severity, presence of preeclampsia, and gestational age of the fetus. The basic management objectives for any pregnancy complicated by preeclampsia are: (1) termination of pregnancy with the least possible trauma to mother and fetus, (2) birth of a healthy newborn that subsequently thrives, and (3) complete restoration of health to the mother. In many with preeclampsia, especially those at or near term, all three objectives are served equally well by induction of labor.

Termination of pregnancy is the only known cure for preeclampsia. Headache, visual changes, or epigastric pain are indicative that convulsions may be imminent, and oliguria is another ominous sign. Severe preeclampsia almost always demands anticonvulsant and antihypertensive therapy, followed by delivery. Treatment for eclampsia is identical. Prime objectives are to forestall convulsions, control blood pressure to prevent intracranial hemorrhage and serious damage to other organs, and deliver a healthy newborn. This is true even when the cervix is unfavorable. Labor induction is carried out, usually with preinduction cervical ripening (Chap. 26, p. 488).

Concerns stemming from an unfavorable cervix, a perceived sense of urgency because of preeclampsia severity, and a need to coordinate neonatal intensive care have led some to advocate for cesarean delivery. In an earlier study from Parkland Hospital, Alexander and colleagues (1999) reviewed 278 singleton liveborn neonates weighing 750 to 1500 g delivered of women with severe preeclampsia. In half of the women, labor was induced, and induction was successful in accomplishing vaginal delivery in a third. Similar data were reported from the Consortium on Safe Labor (Coviello, 2019). In this study, half of 914 women with severe preeclampsia underwent induction, and half of these were delivered vaginally. Others have reported similar observations (Alanis, 2008; Roland, 2017). For these reasons, we attempt labor induction and reserve cesarean delivery for other obstetrical indications.

With preeclampsia without severe features, optimal delivery timing has not been widely studied. A randomized trial of 756 women with mild preeclampsia supported delivery after 37 weeks' gestation (Koopmans, 2009). This practice is also supported by the American College of Obstetricians and Gynecologists (2020a). At Parkland Hospital, we deliver women with preeclampsia without severe features at 38 weeks' gestation.

With a preterm fetus, the tendency is to delay delivery to help reduce the risk of neonatal death or serious morbidity from prematurity. Such a policy certainly is justified in milder cases. Assessments of fetal well-being and placental function are performed, especially when the fetus is immature. To assess these, most recommend frequent performance of nonstress testing or biophysical profiles, which are described in Chapter 20 (p. 392). The American College of Obstetricians and Gynecologists (2021a,b) recommends consideration for antenatal surveillance twice weekly for those with gestational hypertension and nonsevere features and daily testing for those with severe features.

With late-preterm fetuses, that is, those between 34 and 36 weeks' gestation, the decision to deliver is less clear (Barton, 2011; Langenveld, 2011). The Dutch HYPITAT-II study randomly assigned women with nonsevere hypertension between 34 and 37 weeks to immediate delivery or to expectant management (Broekhuijsen, 2015). Immediate delivery reduced the risks for adverse maternal outcomes—1.1 versus 3.1 percent. However, it increased the risk for neonatal respiratory distress syndrome— 5.7 versus 1.7 percent.

In a more recent study, 901 women at 34 to <37 weeks' gestation with nonsevere preeclampsia were randomly assigned to early delivery or expectant management (Chappell, 2019). A third of each group self-stratified into intervals of 34, 35, and 36 weeks' gestation. For women in the immediate delivery group, rates of the primary maternal outcomes, which were features of severe preeclampsia, were significantly lower than in the expectant group. Conversely, rates of adverse perinatal outcomes, which were perinatal deaths or neonatal unit admission, were significantly greater in the immediate delivery group. Similar findings were reported by other (Bernardes, 2019; Chatzakis, 2021). Last, the PEACOCK study found that angiogenic biomarkers did not help determine the need for delivery in late-preterm preeclampsia (Duhig, 2021). At Parkland Hospital, we favor an active management approach given the maternal risks of expectant management. However, if preeclampsia is nonsevere, we routinely induce after 38 completed weeks.

Inpatient or Outpatient Care

For women with mild to moderate stable hypertension, whether or not preeclampsia has been confirmed, monitoring is continued. During surveillance, reduced physical activity throughout much of the day, at least intuitively, seems reasonable. Complete bed rest was not recommended in the prior consensus work of the American College of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy (2013). Also, the Society for Maternal-Fetal Medicine (2020b) suggests that activity restriction not be prescribed for women with hypertensive disorders. Complete bed rest is pragmatically unachievable because of the severe restrictions it places on otherwise well women. It likely also predisposes to thromboembolism (Knight, 2007; McCarty-Singleton, 2014).

To reduce activity, several studies have addressed the benefits of inpatient care and outpatient management. The concept of prolonged hospitalization for women with hypertension arose during the 1970s. At Parkland Hospital, an inpatient antepartum unit was established in 1973 by Dr. Peggy Whalley to provide care for such women. Initial results from this unit were reported by Hauth (1976) and Gilstrap (1978) and their coworkers. Most hospitalized women have a beneficial response characterized by amelioration or improvement of hypertension. *These women are not "cured," and nearly 90 percent have recurrent hypertension before or during labor.* By 2020, more than 10,000 nulliparas with mild to moderate, early-onset hypertension during pregnancy had

TABLE 41-1. Randomized Clinical Trials Comparing Hospitalization Versus Routine Care for Women with Mild Gestational Hypertension or Preeclampsia

	Maternal Characteristics—Admission					Maternal Characteristics—Delivery				Perinatal Outcomes		
Study Groups	No.	$Para_0$ (%)	Chronic HTN (%)	EGA (wk)	Prot (%)	EGA (wk)	<37 wk (%)	<34 wk (%)	Mean Hosp (d)	Mean BW (g)	SGA (%)	PMR (%)
Crowther (1992)	218[a]											
Hospitalization	110	13	14	35.3	0	38.3	12	1.8	22.2	3080	14	0
Outpatient	108	13	17	34.6	0	38.2	22	3.7	6.5	3060	14	0
Turnbull (2004)	374[b]											
Hospitalization	125	63	0	35.9	22	39	—	—	8.5	3330	3.8	0
Day Unit	249	62	0	36.2	22	39.7	—	—	7.2	3300	2.3	0

[a]Excluded women with proteinuria at study entry.
[b]Included women with ≤1+ proteinuria.
BW = birthweight; EGA = estimated gestational age; Hosp = hospital; HTN = hypertension; $Para_0$= nulliparas; PMR = perinatal mortality rate; Prot = proteinuria; SGA = small for gestational age.

been managed successfully in this unit. This relatively simple unit requires modest nursing care, no drugs other than iron and folate supplements, and few essential laboratory tests. Provider costs—not charges—for this care are minimal compared with the cost of neonatal intensive care for a preterm neonate. Importantly, thromboembolic disease has been rare in these women.

Many clinicians believe that further hospitalization is not warranted if hypertension abates within a few days, and this has emboldened third-party payers to deny inpatient reimbursement. Consequently, many women with mild to moderate hypertension are managed at home. For women in vulnerable sociodemographic home situations, this strategy may not be feasible. In other groups, outpatient management may continue as long as preeclampsia syndrome does not worsen and fetal jeopardy is not suspected. Decreased activity is recommended, and women are encouraged to report symptoms. Home blood pressure and urine protein monitoring or frequent evaluations by a visiting nurse may be beneficial.

To assess this approach, 1182 nulliparas with mild gestational hypertension—20 percent had proteinuria—were managed with home care (Barton, 2002). Their mean gestational ages were 32 to 33 weeks at enrollment and 36 to 37 weeks at delivery. Severe preeclampsia developed in approximately 20 percent, two women had eclampsia, and 3 percent developed hemolysis, elevated liver enzyme levels, and low platelet count (HELLP) syndrome. Perinatal outcomes were generally good. In approximately 20 percent, fetal growth was restricted, and the perinatal mortality rate was 4.2 deaths in 1000 births.

Table 41-1 presents two studies that compare continued hospitalization and outpatient care. In the first trial, after hospital evaluation, 218 women with mild gestational nonproteinuric hypertension were randomly assigned to continued hospitalization versus home care (Crowther, 1992). The mean hospitalization duration was 22.2 days for women with inpatient management compared with only 6.5 days in the home care group. Severe hypertension and preterm delivery before 34 and before 37 weeks' gestation were significantly increased twofold in the outpatient group. Despite this, maternal and newborn outcomes were otherwise similar.

Another approach, popular in Europe, is day care. In the second trial (Table 41-1), 374 women with gestational hypertension were randomized to either day care or inpatient care (Turnbull, 2004). Almost 95 percent had mild to moderate hypertension and 86 women had ≥1+ proteinuria. There were no perinatal deaths, and none of the women developed eclampsia or HELLP syndrome. Costs for either scheme were not significantly different, and general satisfaction favored day care.

In sum, either inpatient or close outpatient management is appropriate for a woman with mild de novo hypertension, including those with nonsevere preeclampsia. Keys to success are close surveillance and patients with home support and access to care.

Antihypertensive Therapy for Mild to Moderate Hypertension

Antihypertensive drugs have been evaluated to prolong pregnancy or modify perinatal outcomes in pregnancies complicated by various hypertensive disorders. Treatment for women with *chronic hypertension* complicating pregnancy is discussed in Chapter 53 (p. 949). Drug treatment for early mild preeclampsia has been disappointing (Table 41-2). Sibai and associates (1987a) reported that women given labetalol had significantly lower mean blood pressures than those given a placebo. However, mean pregnancy prolongation, gestational age at delivery, and birthweights did not differ between groups. The cesarean delivery rate and the number of newborns admitted to special-care nurseries also were similar. *The frequency of growth-restricted neonates was doubled in women given labetalol compared with placebo—19 versus 9 percent.*

The three other studies listed in Table 41-2 compare labetalol or a calcium-channel blocker drugs against placebo. Except for fewer episodes of severe hypertension, none of these studies showed any benefits from antihypertensive treatment (Magee, 2015). One review of 49 randomized trials of antihypertensive therapy for mild to moderate gestational hypertension compared with either no treatment or placebo reached similar conclusions (Abalos, 2014).

TABLE 41-2. Randomized Placebo-Controlled Trials of Antihypertensive Therapy for Early Mild Gestational Hypertension

Study	Study Drug (No.)	Pregnancy Prolonged (d)	Severe HTN[a] (%)	Cesarean Delivery (%)	Placental Abruption (%)	Mean Birthweight (g)	Growth Restriction (%)	Neonatal Deaths (No.)
Sibai (1987a)[a] 200 inpatients	Labetalol (100)	21.3	5	36	2	2205	19[c]	1
	Placebo (100)	20.1	15[c]	32	0	2260	9	0
Sibai (1992)[b] 200 outpatients	Nifedipine (100)	22.3	9	43	3	2405	8	0
	Placebo (100)	22.5	18[c]	35	2	2510	4	0
Pickles (1992) 144 outpatients	Labetalol (70)	26.6	9	24	NS	NS	NS	NS
	Placebo (74)	23.1	10	26	NS	NS	NS	NS
Wide-Swensson (1995) 111 outpatients	Isradipine (54)	23.1	22	26	NS	NS	NS	0
	Placebo (57)	29.8	29	19	NS	NS	NS	0

[a]All women had preeclampsia.
[b]Includes postpartum hypertension.
[c]$p < 0.5$ when study drug compared with placebo.
HTN = hypertension; NS = not stated.

Expectant Management of Preterm Severe Preeclampsia

Up through the early 1990s, women with severe preeclampsia were usually immediately delivered. Subsequently, however, another approach for women with preterm severe preeclampsia was studied. The aim of "expectant" management was to improve neonatal outcome without compromising maternal safety. This approach always includes careful daily—and usually more frequent—inpatient monitoring of the mother and her fetus.

Theoretically, antihypertensive therapy has potential application when severe preeclampsia develops before intact neonatal survival is expected. Such management has been controversial and is potentially dangerous (Churchill, 2018). In one of the first studies, Sibai and the Memphis group (1985) attempted to prolong pregnancy because of fetal immaturity in 60 women with severe preeclampsia between 18 and 27 weeks. *The results were disastrous.* The perinatal mortality rate was 87 percent. Although no mothers died, 13 suffered placental abruption, 10 had eclampsia, three developed renal failure, two had hypertensive encephalopathy, one had an intracerebral hemorrhage, and another had a ruptured hepatic hematoma.

Because of their early study, the Memphis group redefined criteria and performed a randomized trial of aggressive versus expectant management for 95 women who had severe preeclampsia but with more advanced gestations of 28 to 32 weeks (Sibai, 1994). *Women with HELLP syndrome were excluded from this trial.* Aggressive management included glucocorticoid administration for fetal lung maturation followed by delivery in 48 hours. Expectantly managed women were observed at bed rest and given either labetalol or nifedipine orally for severe hypertension. In this study, pregnancy was prolonged for a mean of 15.4 days in the expectant management group. An overall improvement in neonatal outcomes also was reported.

In women expectantly managed at 23 to 34 weeks' gestation, serious complications have included placental abruption, HELLP syndrome, pulmonary edema, renal failure, and eclampsia (Table 41-3). Moreover, perinatal mortality rates averaged 90 per 1000 births. Fetal-growth restriction was common, and in studies from The Netherlands, it was an astounding 94 percent (Ganzevoort, 2005a,b). Perinatal mortality rates were disproportionately high in these growth-restricted neonates (Haddad, 2007; Shear, 2005).

Following these experiences, expectant management became more commonly practiced, with the caveat that women with HELLP syndrome or growth-restricted fetuses were usually excluded. More recently, a prospective comparative study reported that expectant management of women with "stable" HELLP syndrome at <34 weeks may benefit mother and fetus (Cavaignac-Vitalis, 2019). The MEXPRE Latin Study was a multicenter trial that randomly assigned 267 women with severe preeclampsia at 28 to 32 weeks' gestation to prompt delivery or to expectant management (Vigil-De Gracia, 2013). The perinatal mortality rate approximated 90 per 1000 in each group, and the composite neonatal morbidity outcome was not improved with expectant management. Conversely, fetal-growth restriction—22 versus 9 percent—and placental abruption—7.6 versus 1.5 percent—were significantly higher in the group managed expectantly.

Churchill and colleagues (2018) performed a Cochrane Database review of six randomized trials of interventionist versus

TABLE 41-3. Maternal and Perinatal Outcomes with Expectant Management of Severe Preeclampsia from 23 to 34 Weeks

			Maternal Outcomes (%)					Perinatal Outcomes (%)	
Study	No.	Days Gained	Placental Abruption	HELLP	Pulm. Edema	AKI	Eclampsia	FGR	PMR
Ganzevoort (2005a,b)	216	11	1.8	18	3.6	NS	1.8	94	18
Bombrys (2009)	66	5	11	8	9	3	0	27	1.5
Abdel-Hady (2010)	211	12	3.3	7.6	0.9	6.6	0.9	NS	48
Vigil-De Gracia (2013)	131	10.3	7.6	14	1.5	4.5	0.8	22	8.7
Mooney (2016)	108	5[b]	NS	11	NS	NS	2	~36	4.6
Hoshino (2019)	79	8.5	12	12	4	3	3	NS	0
Cavaignac-Vitalis (2019)[a]	87	6[b]	NS	100	0	NS	3.5	NS	9.3
Total	892								
Range		5-12	1.8–12	7.6–100	0.9–4.0	3–6.6	0.9–18	27–94	1.5–48

[a]All had HELLP syndrome at enrollment.
[b]Median.
AKI = acute kidney injury; EGA = estimated gestational age; FGR = fetal -growth restriction; HELLP = hemolysis, elevated liver enzyme levels, low platelet count; NS = not stated; PMR = perinatal mortality rate; Pulm. = pulmonary.

expectant care for severe preeclampsia between 24 and 34 weeks. Their review had findings similar to those in Table 41-3 and suggested that expectant management was beneficial to perinatal outcome. However, data were insufficient to establish conclusions on maternal health.

Expectant Management of Midtrimester Preeclampsia

Several small studies have focused on expectant management of severe preeclampsia syndrome before 28 weeks' gestation. In one review of eight such studies, maternal complications were common among nearly 200 women with severe preeclampsia with an onset <26 completed weeks (Bombrys, 2009). Because no neonates survived when delivered before 23 weeks, most experts recommend pregnancy termination in these cases. For women with slightly more advanced pregnancies, however, the decision is less clear. For example, at 23 weeks' gestation, the perinatal survival rate was 18 percent, but long-term perinatal morbidity is yet unknown. For women with pregnancies at 24 to 26 weeks, perinatal survival approaches 60 percent, and it averages almost 90 percent for those at 26 weeks.

As shown in Table 41-4, maternal complications—especially HELLP syndrome—were commonplace and one mother died. Perinatal mortality exceeded 50 percent. At this time, no comparative studies attest to perinatal benefits of such expectant treatment versus early delivery in the face of serious maternal complications, which approach rates of 50 percent.

Corticosteroids for Lung Maturation

To enhance fetal lung maturation, glucocorticoids have been administered to women with severe hypertension who are remote from term. Treatment does not seem to worsen maternal hypertension, and a lower incidence of respiratory distress and

TABLE 41-4. Pregnancy Outcomes with Expectant Management of Women with Severe Midtrimester Preeclampsia[a]

			Maternal Outcomes (%)						
Study	No.	EGA	Prolonged Pregnancy[b]	HELLP	Pulm. Edema	Placental Abruption	Eclampsia	Death	Perinatal Mortality
Gaugler-Senden (2006)	26	<26 wk	24 d[b]	16	4	0	5	1	23/28
Budden (2006)	31	<25 wk	~12 d[b]	20	0	0	0	0	22/31
Bombrys (2008)	46	<27 wk	6 d[c]	11	2	6	1	NS	22/51
Abdel-Hady (2010)	61	24–28 wk	12 d[b]	6	0	4	0	0	29/61
Belghiti (2011)	51	<26 wk	7 d[c]	5	2	3	0	0	31/53

[a]Includes women with superimposed preeclampsia.
[b]Mean.
[c]Median.
EGA = estimated gestational age; NS = not stated; Pulm. = pulmonary edema.

improved fetal survival rates have been cited. That said, only one randomized trial has evaluated corticosteroids given to hypertensive women for fetal lung maturation. This trial included 218 women who had severe preeclampsia between 26 and 34 weeks' gestation and who were randomly assigned to betamethasone or placebo administration (Amorim, 1999). Rates of neonatal complications that included respiratory distress, intraventricular hemorrhage, and death were reduced significantly when betamethasone was given compared with placebo. *On the heavily weighted negative side, there were two maternal deaths and 18 stillbirths.* We add these findings to buttress our unenthusiastic acceptance of attempts to prolong gestation in many of these women (Alexander, 2015; Bloom, 2003).

Corticosteroids to Ameliorate HELLP Syndrome

Several observational studies have indicated that corticosteroid therapy would ameliorate facets of the HELLP syndrome (Añez-Aguayo, 2018; Martin, 2016). Subsequently, at least three randomized trials aimed to evaluate the benefits of glucocorticoids given to improve the laboratory abnormalities associated with HELLP syndrome. Fonseca and associates (2005) randomly assigned 132 women with HELLP syndrome to either dexamethasone or placebo administration. Outcomes assessed included hospitalization length, recovery time of abnormal laboratory test results, resolution of clinical parameters, and complications that included acute renal failure, pulmonary edema, eclampsia, and death. None of these was significantly different between the two groups. In another study, 105 postpartum women with HELLP syndrome were assigned to dexamethasone or placebo treatment. Katz and colleagues (2008) found no advantage to dexamethasone (Fig. 41-1). In the third study, preeclamptic women were given either placebo or methylprednisolone if their platelet count was between 50,000 and 150,000/μL (Pourrat, 2016). Again, no benefits were gained from corticosteroid therapy. A Bolivian study did show benefits from corticosteroid therapy, however, it was not randomized (Añez-Aguayo, 2018). Because of these findings, the 2013 Task Force does not recommend corticosteroid treatment to improve thrombocytopenia with HELLP syndrome.

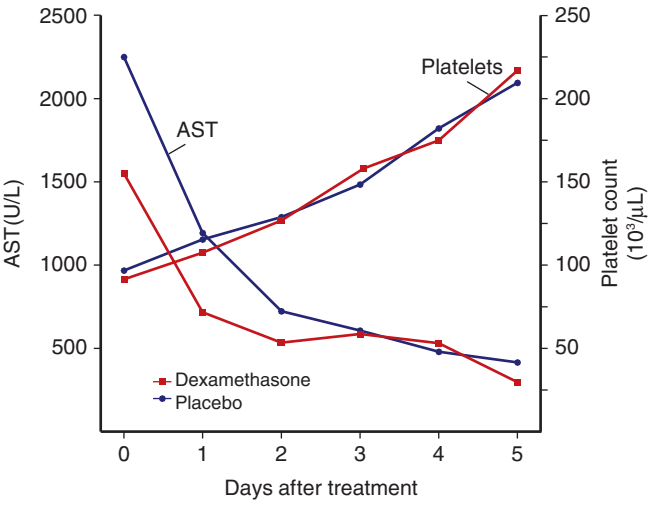

FIGURE 41-1 Recovery times for platelet counts and serum aspartate transaminase (AST) levels in women with HELLP syndrome assigned to receive treatment with dexamethasone or placebo.

Expectant Management Recommendations

Taken in toto, these studies do not show overwhelming benefits of expectant management of severe preeclampsia in women with gestations from 24 to 32 weeks compared with maternal risks. Despite these caveats, the Society for Maternal-Fetal Medicine (2011) has determined that such management is a reasonable alternative in selected women with severe preeclampsia before 34 weeks (Fig. 41-2). The Task Force

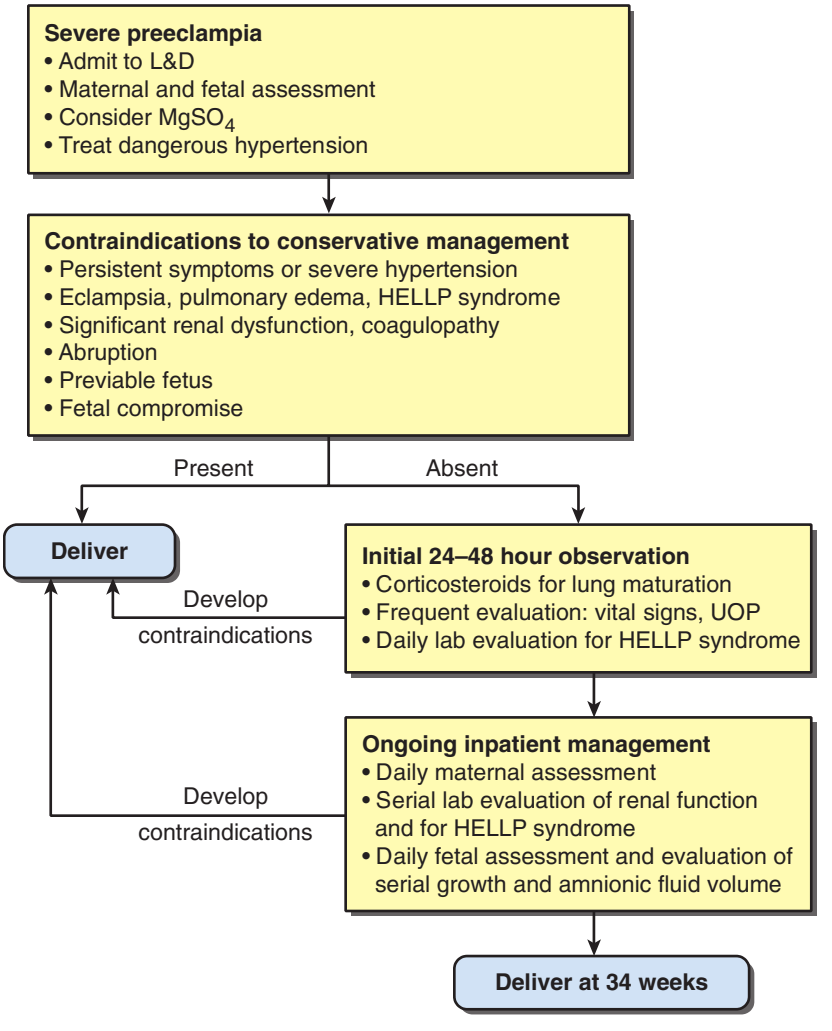

FIGURE 41-2 Clinical management algorithm for severe preeclampsia at <34 weeks. HELLP = hemolysis, elevated liver enzyme levels, low platelet count; L & D = labor and delivery; $MgSO_4$= magnesium sulfate; UOP = urine output.

TABLE 41-5. Indications for Delivery in Women <34 Weeks' Gestation Managed Expectantly

Prompt Delivery After Maternal Stabilization and After Single-dose Corticosteroid Therapy for Lung Maturation:[a]
Uncontrolled severe hypertension
Persistent headaches, refractory to treatment
Persistent epigastric pain
Eclampsia
HELLP syndrome
Pulmonary edema
Placental abruption
Disseminated intravascular coagulation
Stroke
Myocardial infarction
Nonreassuring fetal status
Fetal demise
Delay Delivery 48 hr If Possible to Allow Corticosteroid Therapy for Lung Maturation:
Preterm ruptured membranes or labor
Fetal-growth restriction
Oligohydramnios
Reversed end-diastolic Doppler flow in umbilical artery
Worsening renal dysfunction

[a]Inital dose only, do not delay delivery.
HELLP = hemolysis, elevated liver enzyme levels, low platelet count.
From American College of Obstetricians and Gynecologists, 2020b; Society for Maternal-Fetal Medicine, 2011.

(2013) supports this recommendation. As shown in Table 41-5, such management calls for inpatient maternal and fetal surveillance with delivery prompted by evidence for worsening severe preeclampsia or maternal or fetal compromise. Although attempts are made for vaginal delivery in most cases, the likelihood of cesarean delivery rises with decreasing gestational age.

Our view is more conservative. Undoubtedly, the overriding reason to terminate pregnancies with severe preeclampsia is maternal safety. Indeed, it seems obvious that a delay to prolong gestation in women with severe preeclampsia may have serious maternal consequences. These observations are even more pertinent when considered with the absence of convincing evidence that perinatal outcomes are markedly improved by the average prolongation of pregnancy by approximately 1 week. If undertaken, the caveats that mandate delivery shown in Table 41-5 should be strictly heeded.

Experimental Therapies

In preliminary studies, therapies have been used to lower serum levels of antiangiogenic factors in hopes to mitigate their adverse actions. Some of these include *therapeutic apheresis* to lower sFlt-1 levels (Thadhani, 2016; Winkler, 2018). Another novel therapy uses RNA molecules to silence placental sFlt-1 (Turanov, 2018). The *proton-pump inhibitor* esomeprazole was studied in women with early-onset preeclampsia (Cluver, 2018). *Sildenafil citrate*, a phosphodiesterase inhibitor, has been provided to promote vasodilation (Trapani, 2016; Vigil-De Gracia, 2016). Other studies compared *recombinant antithrombin infusion* with placebo (Paidas, 2020). In general, none of these therapies has shown promise.

SEVERE PREECLAMPSIA AND ECLAMPSIA

Classification of preeclampsia with severe features is summarized in Table 40-2 (p. 690). Briefly, features include systolic blood pressure ≥160 mm Hg or diastolic pressure ≥110 mm Hg; liver derangement with transaminitis; thrombocytopenia; renal insufficiency; pulmonary edema; new-onset headache; or visual changes. Eclampsia is defined by new-onset tonic-clonic, focal, or multifocal seizures in the absence of other causes.

Eclampsia

The development of eclampsia appreciably raises the risk to mother and fetus (Fishel-Bartal, 2020). In an earlier report, Mattar and Sibai (2000) described outcomes in 399 consecutive women with eclampsia from 1977 through 1998. Major maternal complications included placental abruption—10 percent, neurological deficits—7 percent, aspiration pneumonia—7 percent, pulmonary edema—5 percent, cardiopulmonary arrest—4 percent, and acute kidney injury (AKI)—4 percent. Moreover, 1 percent of these women died. Several subsequent reports similarly described excessive maternal morbidity and mortality rates with eclampsia that also included HELLP syndrome, pulmonary embolism, and stroke (Andersgaard, 2006; Knight, 2007).

Almost without exception—but at times unnoticed—preeclampsia precedes convulsions. Eclampsia is most common in the last trimester and becomes increasingly frequent as term approaches. Postpartum, the incidence of eclampsia has declined during the past decade. Improved access to prenatal care, earlier detection of antepartum preeclampsia, and prophylactic use of magnesium sulfate are explanations (Chames, 2002). Other diagnoses should be considered in women with convulsions more than 48 hours postpartum or in women with focal neurological deficits, prolonged coma, or atypical eclampsia.

Clinical Findings with Eclampsia

Eclamptic seizures may be violent, and the woman must be protected, especially her airway. So forceful are the muscular movements that the woman may throw herself out of her bed, and if not protected, her tongue is bitten by the violent action of the jaws (Fig. 41-3). This phase, in which the muscles alternately contract and relax, may last approximately a minute.

Gradually, the muscular movements become smaller and less frequent, and finally the woman lies motionless.

After a seizure, the woman is postictal, but in some, a coma of variable duration ensues. When the convulsions are infrequent, the woman usually recovers some degree of consciousness after each attack. As the woman arouses, a semiconscious combative state may ensue. In severe cases, coma persists from one convulsion to another, and death may result.

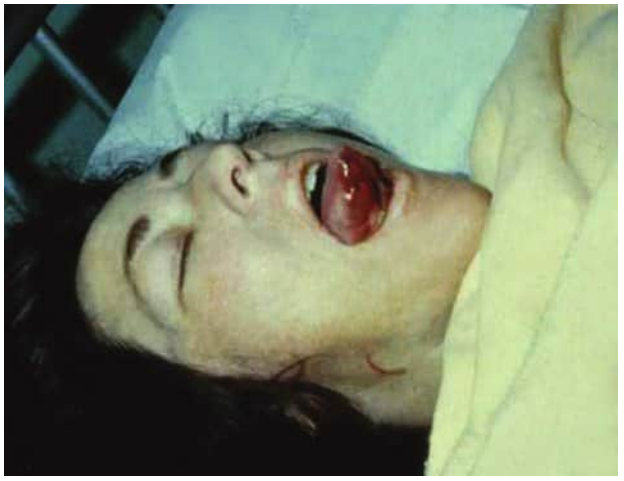

FIGURE 41-3 Hematoma of tongue from laceration during an eclamptic convulsion. Thrombocytopenia may have contributed to the bleeding.

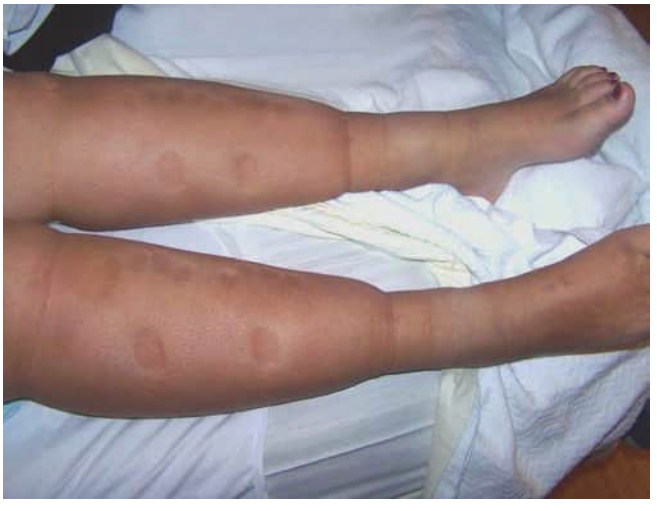

FIGURE 41-4 Severe edema in a young nullipara with antepartum preeclampsia. Fingerprint indentations from clinical assessment can be seen on both shins. Rings at the ankles formed from elastic sock bands. (Reproduced with permission from Dr. Nidhi Shah.)

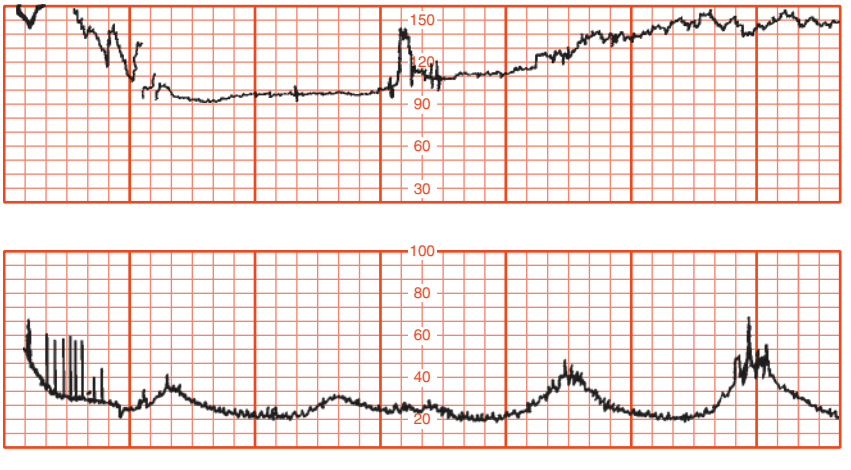

FIGURE 41-5 Fetal heart rate tracing shows fetal bradycardia following an intrapartum eclamptic convulsion. Bradycardia resolved and beat—to—beat variability returned approximately 5 minutes following the seizure.

Rarely, a single convulsion may be followed by coma from which the woman may never emerge. As a rule, however, death does not occur until after frequent convulsions. Last, and also rarely, convulsions continue unabated—*status epilepticus*—and require deep sedation and even general anesthesia to obviate anoxic encephalopathy.

The respiratory rate after an eclamptic convulsion usually rises and may reach 50 or more per minute in response to hypercarbia, lactic acidemia, and transient hypoxia. Cyanosis may be observed in severe cases. High fever is a grave sign as it likely emanates from cerebrovascular hemorrhage.

Proteinuria is usually present, and a fourth of women with severe preeclampsia have some degree of AKI (Rodriguez, 2021). Urine output may be diminished appreciably, and occasionally anuria develops. Hemoglobinuria may be seen, but hemoglobinemia is rare. Edema may be pronounced (Fig. 41-4).

With severe preeclampsia, urinary output rises after delivery and is usually an early sign of improvement. With renal dysfunction, serum creatinine levels are serially monitored. Proteinuria and edema ordinarily disappear within a week postpartum. In most cases, blood pressure returns to normal within a few days to 2 weeks after delivery (Berks, 2009). As subsequently discussed, persisting and severe hypertension likely predicts underlying chronic vascular disease.

In antepartum eclampsia, labor may begin spontaneously shortly after convulsions ensue and may progress rapidly. If the seizures develop during labor, contractions may increase in frequency and intensity, and the duration of labor may be shortened. Because of maternal hypoxemia and lactic acidemia caused by convulsions, fetal bradycardia often follows a seizure (Fig. 41-5). In our experiences, the fetal heart rate usually recovers within 2 to 10 minutes. If it persists more than 10 minutes, another cause of bradycardia, such as placental abruption, should be considered.

Pulmonary edema may follow shortly after eclamptic convulsions or several hours later. This complication is further explored on page 724.

Occasionally, sudden death occurs synchronously with an eclamptic seizure, or it follows shortly thereafter. Most often in these cases, a massive cerebral hemorrhage is the cause (Fig. 40-11, p. 700). Hemiplegia may result from sublethal hemorrhage. Cerebral hemorrhages are more likely in older women with underlying chronic hypertension. For women with a neurological deficit after an eclamptic seizure, consideration is given for emergent cranial computed tomography (CT) scanning. Up to 5 percent of women with eclampsia have altered consciousness, including persistent coma, following a seizure. This may be due to extensive cerebral edema, and associated transtentorial herniation may cause death (Cunningham, 2000). In approximately 10 percent of eclamptic women, some degree of blindness follows a seizure. The causes of impaired vision which usually improves postpartum, are discussed in Chapter 40 (p. 701).

Rarely, eclampsia is followed by psychosis, and the woman becomes violent. This may last for several days to 2 weeks. The prognosis for return to normal function is good, provided mental illness was not preexisting. It is presumed to be similar to postpartum psychosis discussed in Chapter 64 (p. 1148). Antipsychotic medications have been effective in the few cases of posteclampsia psychosis treated at Parkland Hospital.

Generally, eclampsia is more likely to be diagnosed too frequently rather than overlooked. Epilepsy, encephalitis, meningitis, brain tumor, neurocysticercosis, amnionic fluid embolism, postdural puncture cephalalgia, and ruptured cerebral aneurysm during late pregnancy or in the puerperium may simulate eclampsia. Until other such causes are excluded, however, all pregnant women with convulsions should be considered to have eclampsia. As a pragmatic rule, loading with magnesium sulfate should be considered while alternate diagnoses are explored.

MANAGEMENT OF SEVERE PREECLAMPSIA-ECLAMPSIA

Most eclampsia regimens in the United States adhere to a similar philosophy:

- Control or prevent convulsions using an intravenous loading dose of magnesium sulfate. This is followed by maintenance dosing, usually given intravenously
- Provide intermittent antihypertensive medication to lower dangerously high blood pressure
- Avoid diuretics unless pulmonary edema is obvious; limit intravenous fluid administration unless fluid loss is excessive; and avoid hyperosmotic agents
- Deliver the fetus to resolve preeclampsia.

Magnesium Sulfate

This parenterally administered agent is an effective anticonvulsant and avoids producing central nervous system depression. It may be given intravenously by continuous infusion or intramuscularly by intermittent injection (Table 41-6). A third option is intermittent, intravenous, 2-g injections (Easterling, 2018). Dosages for severe preeclampsia mirror those for eclampsia. Because labor and delivery is a more likely time for seizures to develop, women with severe preeclampsia or eclampsia usually are given magnesium sulfate during labor and for 24 hours postpartum. In the United States, magnesium sulfate is almost universally administered intravenously. Of concern, magnesium sulfate solutions, although inexpensive to prepare, are not readily available in all parts of the developing world. Even if solutions are available, the technology to infuse them may not be. Thus, the drug can be administered intramuscularly, and this is as effective as intravenous infusion (Pritchard, 1955, 1975, 1984; Salinger, 2013).

Magnesium sulfate is not given to treat hypertension. Magnesium ion most likely exerts a specific anticonvulsant action on the cerebral cortex. Typically, the mother stops convulsing after the initial 4-g loading dose. By an hour or two, she regains consciousness sufficiently to be oriented to place and time.

The magnesium sulfate dosage regimens presented in Table 41-6 usually result in increased plasma magnesium levels. Data from Brookfield and associates (2016) are illustrated in Figure 41-6. When magnesium sulfate is given to arrest an eclamptic seizure, up to 15 percent of women will have a subsequent convulsion. If so, an additional 2-g dose of magnesium sulfate in a 20-percent solution is slowly administered intravenously. In a small woman, this additional 2-g dose may be used once, but it can be given twice if needed in a larger woman. In

TABLE 41-6. Magnesium Sulfate Dosage Schedule for Severe Preeclampsia and Eclampsia

Continuous Intravenous (IV) Infusion
Give 4- to 6-g loading dose of magnesium sulfate diluted in 100 mL of IV fluid administered over 15–20 min
Begin 2 g/hr in 100 mL of IV maintenance infusion. Some recommend 1 g/hr
Monitor for magnesium toxicity:
Assess deep tendon reflexes periodically
Some measure serum magnesium level at 4–6 hr and adjust infusion to maintain levels between 4 and 7 mEq/L (4.8–8.4 mg/dL)
Measure serum magnesium levels if serum creatinine ≥1.0 mg/dL
Magnesium sulfate is discontinued 24 hr after delivery
Intermittent Intramuscular Injections
Give 4 g of magnesium sulfate ($MgSO_4 7H_2O$ USP) as a 20% solution intravenously at a rate not to exceed 1 g/min
Follow promptly with 10 g of 50% magnesium sulfate solution, one half (5 g) injected deeply in the upper outer quadrant of each buttock through a 3-inch-long 20-gauge needle. (Addition of 1.0 mL of 2% lidocaine minimizes discomfort.) If convulsions persist after 15 min, give up to 2 g more intravenously as a 20% solution at a rate not to exceed 1 g/min. If the woman is large, up to 4 g may be given slowly.
Every 4 hr thereafter, give 5 g of 50% solution of magnesium sulfate injected deeply in the upper outer quadrant of alternate buttocks, but only after ensuring that:
The patellar reflex is present,
Respirations are not depressed, and
Urine output the previous 4 hr exceeded 100 mL
Magnesium sulfate is discontinued 24 hr after delivery

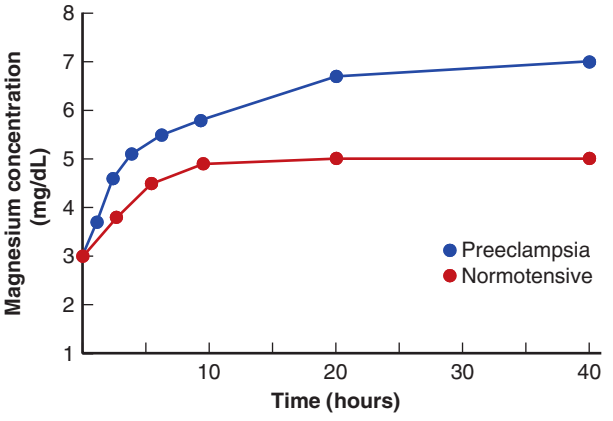

FIGURE 41-6 Serum magnesium concentration in normotensive and preeclamptic women following a 4-g loading dose of magnesium sulfate and 2 g/h infusion.

only 5 of 245 women with eclampsia at Parkland Hospital was it necessary to use alternative supplementary anticonvulsant medication to control seizures (Pritchard, 1984). For these, a small dose of a short-acting benzodiazepine such as midazolam or lorazepam is given intravenously. Their prolonged use is avoided because of an associated higher mortality rate from aspiration pneumonia (Royal College of Obstetricians and Gynaecologists, 2006).

Maintenance magnesium sulfate therapy has traditionally been continued for 24 hours after delivery. For eclampsia that develops postpartum, magnesium sulfate is administered for 24 hours after the onset of convulsions. A few investigators have truncated this therapy duration to 12 hours and reported no seizures (Anjum, 2016; Ehrenberg, 2006; Kashanian, 2016). Outcomes have also been reported when magnesium sulfate therapy was stopped after delivery (Ludmir, 2017; Vigil-De Gracia, 2018). These studies are relatively small, and the abbreviated magnesium sulfate regimens need further study before being routinely implemented.

Pharmacology and Toxicology

Parenterally administered magnesium is cleared almost totally by renal excretion, and magnesium clearance rate is approximately a third of glomerular filtration rate (GFR) determined by creatinine clearance. Magnesium intoxication is unusual when the GFR is normal or only slightly reduced. Adequate urine output usually correlates with preserved GFR. That said, magnesium excretion is not urine flow dependent, and urinary volume per unit time does not, per se, predict renal function. *Thus, serum creatinine levels must be measured to confirm a decreased GFR.*

Eclamptic convulsions are almost always prevented or arrested by plasma magnesium levels maintained at 4 to 7 mEq/L, 4.8 to 8.4 mg/dL, or 2.0 to 3.5 mmol/L. However, one review of magnesium pharmacokinetics showed that most regimens result in much lower serum magnesium levels (Okusanya, 2016). This was especially true if only 1 g/hr was infused (Yefet, 2017). Importantly, the obesity epidemic has affected these observations (Cunningham, 2016). Tudela and colleagues (2013) described our results from Parkland Hospital with magnesium administration to obese women. More than 60 percent of women who had a body mass index (BMI) >30 kg/m^2 and who were receiving a 2-g/hr dose had subtherapeutic levels at 4 hours. Thus, most obese women would require 3 g/hr to maintain effective plasma levels. That said, most currently do not recommend routine magnesium level measurements (American College of Obstetricians and Gynecologists, 2020a; Royal College of Obstetricians and Gynaecologists, 2006).

Patellar reflexes disappear when the plasma magnesium level reaches 10 mEq/L—approximately 12 mg/dL—presumably because of a curariform action. This sign serves to warn of impending magnesium toxicity. When plasma levels rise above 10 mEq/L, breathing weakens. At 12 mEq/L or higher levels, respiratory paralysis and respiratory arrest follow (Somjen, 1966). *Treating with calcium gluconate or calcium chloride, 1 g intravenously, coupled with magnesium sulfate discontinuation, usually reverses mild to moderate respiratory depression.* One of these agents should be readily available whenever magnesium is being infused. Unfortunately, the effects of intravenously administered calcium may be short-lived if a steady-state toxic magnesium level has been reached. For severe respiratory depression and arrest, prompt tracheal intubation and mechanical ventilation are lifesaving. Direct toxic effects on the myocardium from high levels of magnesium sulfate are uncommon (Morisaki, 2000).

Because magnesium is cleared almost exclusively by renal excretion, our described dosages of magnesium sulfate will become excessive if the GFR is substantially decreased. The initial 4- or 6-g loading dose of magnesium sulfate can be safely administered regardless of renal function. It is important to administer the standard loading dose and not to reduce it. A loading dose achieves the desired therapeutic level, and the infusion maintains the steady-state level. *Thus, only the maintenance infusion rate should be altered for those with a diminished GFR.* Renal function is estimated by measuring plasma creatinine. Whenever plasma creatinine levels are >1.0 mg/mL, serial serum magnesium levels are determined to guide the infusion rate (American College of Obstetricians and Gynecologists, 2020a).

After a 4-g intravenous dose is administered during 15 minutes, mean arterial pressure falls slightly and is accompanied by a 13-percent rise in cardiac index (Cotton, 1986b). Thus, magnesium lowers systemic vascular resistance and mean arterial pressure. At the same time, cardiac output is increased. These findings are coincidental with transient nausea and flushing, and the cardiovascular effects persist for only 15 minutes despite continued magnesium infusion. Magnesium-induced vasodilation is weaker in placental vessels because of diminished calcium-channel activity (Tang, 2018).

Thurnau and coworkers (1987) showed that magnesium therapy led to a small but significant rise in the cerebrospinal fluid's total magnesium concentration. The magnitude was directly proportional to the corresponding serum concentration.

Other Effects

Magnesium has anticonvulsant and neuroprotective effects in animal models. Some proposed mechanisms of action include: (1) reduced presynaptic release of the neurotransmitter glutamate, (2) blockade of glutamatergic *N*-methyl-D-aspartate (NMDA) receptors, (3) potentiation of adenosine action, (4) improved

calcium buffering by mitochondria, and (5) blockage of calcium entry via voltage-gated channels (Arango, 2008; Wang, 2012).

In the uterus, relatively high serum magnesium concentrations depress myometrial contractility. Inhibition of uterine contractility is magnesium dose dependent, and serum levels of at least 8 to 10 mEq/L are needed to inhibit uterine contractions (Watt-Morse, 1995). With the suggested magnesium sulfate regimens for seizure prevention, prolonged myometrial depression has not been observed. A transient decline in activity during and immediately after the initial intravenous loading dose can be seen (Leveno, 1998; Witlin, 1997). Blood loss at delivery is not increased by standard magnesium sulfate treatment (Graham, 2016).

■ Neuroprophylaxis—Prevention of Seizures

Several randomized trials have tested the efficacy of seizure prophylaxis for women with gestational hypertension, with or without proteinuria. In all, magnesium sulfate was superior to the comparator agent to prevent eclampsia. Four of the larger studies are summarized in Table 41-7. In the study from Parkland Hospital, magnesium sulfate therapy was superior to phenytoin to prevent seizures in women with gestational hypertension or preeclampsia (Lucas, 1995). In another study, magnesium sulfate and nimodipine, which is a calcium-channel blocking drug with specific cerebral vasodilator activity, were compared in 1650 women with severe preeclampsia (Belfort, 2003). The rate of eclampsia was more than threefold higher for women allocated to the nimodipine group—2.6 versus 0.8 percent.

The largest comparative study was *Magnesium Sulfate for Prevention of Eclampsia* reported by the Magpie Trial Collaboration Group (2002). More than 10,000 women with severe preeclampsia from 33 countries were randomly allocated to treatment with magnesium sulfate or placebo. Women given magnesium had a 58-percent significantly lower risk of eclampsia than those given placebo. Maternal mortality and placental abruption rates also were decreased. Child behavior at 18 months did not differ between groups (Smyth, 2009).

Who Should Be Given Magnesium Sulfate?

Magnesium will prevent proportionately more seizures in women with correspondingly worse disease. However, severity is difficult to quantify, and thus deciding which woman might benefit most from neuroprophylaxis is sometimes difficult. The American College of Obstetricians and Gynecologists (2020a) recommends that women with either eclampsia or severe preeclampsia should be given magnesium sulfate prophylaxis. Again, criteria that establish "severity" are not universal.

Thus, the conundrum is whether women with "nonsevere" gestational hypertension or preeclampsia should receive magnesium neuroprophylaxis. We found that approximately 1 woman in 100 who has nonsevere preeclampsia but who is not given magnesium sulfate prophylaxis can be expected to have a seizure. A fourth of these women likely will require emergent cesarean delivery and be exposed to the attendant maternal and perinatal morbidity from general anesthesia. From this, the major question regarding management of nonsevere gestational hypertension remains whether it is acceptable to avoid unnecessary treatment of 99 women to risk eclampsia in one. The answer appears to be yes, as suggested by the American College of Obstetricians and Gynecologists (2020a). At Parkland Hospital, our policy is to give magnesium neuroprophylaxis to women with preeclampsia with severe features, and conservatively to those with proteinuria hypertension (Table 40-1, p. 689).

Fetal and Neonatal Effects

Magnesium administered parenterally promptly crosses the placenta to achieve equilibrium in fetal serum and less so in amnionic fluid (Gortzak-Uzan, 2005; Narasimhulu, 2017). Magnesium sulfate has small but significant effects on the fetal heart rate pattern and specifically on beat-to-beat variability

TABLE 41-7. Randomized Comparative Trials of Prophylaxis with Magnesium Sulfate and Placebo or Another Anticonvulsant in Women with Gestational Hypertension

Study/Inclusions	No. with Seizures/Total No. Treated (%)		
	Magnesium Sulfate	Control	Comparison[a]
Lucas (1995) Gestational hypertension[b]	0/1049	Phenytoin 10/1089 (0.9)	$p < 0.001$
Coetzee (1998) Severe preeclampsia	1/345 (0.3)	Placebo 11/340 (3.2)	RR = 0.09 (0.1–0.69)
Altman (2002)[c] Severe preeclampsia	40/5055 (0.8)	Placebo 96/5055 (1.9)	RR = 0.42 (0.26 – 0.60)
Belfort (2003) Severe preeclampsia	7/831 (0.8)	Nimodipine 21/819 (2.6)	RR = 0.33 (0.14–0.77)

[a]All comparisons significant $p < 0.05$.
[b]Included women with and without proteinuria and those with all severities of preeclampsia.
[c]Magpie Trial Collaboration Group, 2002.
RR = relative risk.

(Hallak, 1999). One study showed a lower baseline heart rate that was within the normal range; decreased variability; and fewer prolonged decelerations (Duffy, 2012).

Overall, maternal magnesium therapy appears safe for perinates (Drassinower, 2015). One study of more than 1500 exposed preterm neonates found no association between the need for neonatal resuscitation and cord blood magnesium levels (Johnson, 2012). Still, a few neonatal adverse events are associated with its use. In a Parkland Hospital study of 6654 mostly term, exposed newborns, 6 percent had hypotonia (Abbassi-Ghanavati, 2012). In addition, exposed neonates had lower 1- and 5-minute Apgar scores, a higher intubation rate, and more admissions to the special care nursery. Neonatal depression occurs only if hypermagnesemia at delivery is severe.

Observational studies suggest a protective effect of magnesium against the development of cerebral palsy in very-low-birthweight newborns (Crowther, 2017). These beneficial effects may extend to growth-restricted fetuses. Randomized trials have also assessed neuroprotective effects for preterm neonates, and findings are discussed in Chapter 45 (p. 803). One review expanded this possibility to include term newborns, but data were insufficient to draw conclusions (Nguyen, 2013).

Maternal Safety and Efficacy

The multinational Eclampsia Trial Collaborative Group study (1995) involved 1687 women with eclampsia randomly allocated to one of three different anticonvulsant regimens: magnesium sulfate, diazepam, or phenytoin (Table 41-8). In aggregate, magnesium sulfate therapy was associated with a significantly lower incidence of recurrent seizures (9.7 percent) compared with women given phenytoin (28 percent) or diazepam (17 percent). Moreover, the aggregate maternal death rate of 3.2 percent with magnesium sulfate was significantly lower than that of 5.2 percent for the other two regimens.

Severe Hypertension Treatment

Dangerous hypertension can cause cerebrovascular hemorrhage and hypertensive encephalopathy, and it can trigger eclamptic convulsions. Other complications are placental abruption and congestive heart failure induced by elevated hypertensive afterload. Studies highlight the importance of treating systolic hypertension when blood pressures are >160 mm Hg (Judy, 2019; Martin, 2005, 2016).

Because of these serious sequelae, the Working Group for the National High Blood Pressure Education Program (2000) and the American College of Obstetricians and Gynecologists (2020a) recommend treatment to lower systolic pressures to a level ≤160 mm Hg and diastolic pressures to ≤110 mm Hg. Lower diastolic pressures can compromise placental perfusion.

From other observations, it seems likely that at least half of serious hemorrhagic strokes associated with preeclampsia are in women with chronic hypertension (Cunningham, 2005; Zofkie, 2018). Long-standing hypertension results in development of *Charcot–Bouchard aneurysms* in the deep penetrating arteries of the lenticulostriate branch of the middle cerebral arteries. These vessels supply the basal ganglia, putamen, thalamus, adjacent deep white matter, pons, and deep cerebellum. These unique aneurysmal weakenings predispose these small arteries to rupture during sudden hypertensive episodes.

Several drugs are available to rapidly lower dangerously elevated blood pressure in women with pregnancy-associated hypertension. Hydralazine, labetalol, and nifedipine are recommended as first-line agents by the American College of Obstetricians and Gynecologists (2020a). Evidence supports their value to decrease stroke risk (Cleary, 2018).

All three agents have equivalent efficacy. Comparative studies of hydralazine and labetalol show similar results (Mable, 1987; Umans, 2015). Hydralazine causes significantly more maternal tachycardia and palpitations, whereas labetalol more frequently leads to maternal hypotension and bradycardia. Randomized trials that compared nifedipine with labetalol found neither drug definitively superior, but nifedipine lowered blood pressure more quickly (Gainder, 2019; Zulfeen, 2019). Both drugs are associated with a reduced frequency of fetal heart rate accelerations (Cahill, 2013). Last, a study comparing nifedipine and hydralazine showed similar efficacy (Sharma, 2017).

A few other generally available antihypertensive agents have been tested in clinical trials but are not widely used (Umans, 2015). These include verapamil, nitroglycerin, nitroprusside, ketanserin, nicardipine, and nimodipine (Belfort, 2003; Cornette, 2016). Experimental antihypertensive drugs may eventually be useful for preeclampsia treatment (Lam, 2013).

Hydralazine

This antihypertensive agent is administered intravenously or intramuscularly. An initial 5- to 10-mg dose can act as rapidly

TABLE 41-8. Randomized Comparative Trials of Magnesium Sulfate versus Phenytoin and Diazepam to Prevent Recurrent Eclamptic Convulsions

	Magnesium Sulfate	Phenytoin	Diazepam
Recurrent seizures[a]	60/453 (13%)	126/452 (28%)	—
	22/388 (5.6%)	—	66/389 (17%)
Maternal deaths[b]	10/388 (2.6%)	20/387 (5.2%)	—
	17.453 (3.8%)	—	24/452 (5.3%)

[a]All comparisons $p < 0.01$.
[b]Individual comparisons nonsignificant, combined comparison $p < 0.05$.

TABLE 41-9. Antihypertensive Agents for Urgent Control of Severe Hypertension

Drug	Dose	Side Effects
Hydralazine	5 mg IV or IM followed by 10-mg doses at 15–20 min intervals for up to 3 doses ***or*** Constant infusion 0.5–10 mg/hr	Tachycardia, headaches, hypotension
Labetalol	10 mg IV followed by 20 mg IV in 20 min, then 40 mg IV, then 80 mg IV ***or*** Constant infusion 1–2 mg/min	Asthma precipitation, bradycardia, hypotension
Nifedipine	10 mg orally followed by 20 mg doses at 20 min × 2	Tachycardia, headaches

IM = intramuscular; IV = intravenous

as 10 minutes. If needed, this is followed by 10-mg doses at 15- to 20-minute intervals until a satisfactory response is achieved (Table 41-9). Although we will administer a third dose, the American College of Obstetricians and Gynecologists (2020a) recommends labetalol therapy if severe hypertension persists after the second dose. Another regimen continuously infuses hydralazine at a rate of 0.5 to 10 mg/hr.

For higher blood pressures, the tendency to give a larger initial dose of hydralazine should be avoided. The response to 5- to 10-mg doses cannot be predicted by hypertension severity. Thus, our protocol is to always administer 5 mg as the initial dose. An adverse response to exceeding this initial dose is shown in Figure 41-7. This woman had chronic hypertension complicated by severe superimposed preeclampsia, and hydralazine was injected more frequently than recommended. Her blood pressure in less than 1 hour dropped from 270/150 mm Hg to 110/80 mm Hg. Fetal heart rate decelerations characteristic of uteroplacental insufficiency became evident. Decelerations persisted until her blood pressure was raised with rapid crystalloid infusion. In some cases, this fetal response to diminished uterine perfusion may be confused with placental abruption and may result in unnecessary and potentially dangerous emergency cesarean delivery.

Labetalol

This effective intravenous antihypertensive agent is an α- and nonselective β-blocker. Some prefer its use to hydralazine because of fewer side effects. Importantly, labetalol is usually not given to asthmatic women.

At Parkland Hospital, we give 10 mg intravenously initially. If blood pressure has not declined to suitable levels in 10 minutes, 20 mg is given. The next 10-minute incremental dose is 40 mg and is followed by another 40 mg if needed. If a salutary response is not achieved, an 80-mg dose is provided (see Table 41-9). The American College of Obstetricians and Gynecologists (2020a) recommends starting with a 10- to 20-mg intravenous bolus. If not effective, this is followed by 20 to 80 mg every 10 to 30 minutes. If hypertension persists, hydralazine is then given.

Nifedipine

This calcium-channel blocking agent is given initially as a 10- to 20-mg oral dose of immediate release medication. If necessary after 20 minutes, a 10- to 20-mg oral dose is repeated. With an unsatisfactory response, labetalol is provided. *Nifedipine given sublingually is no longer recommended.* This route is associated with dangerously rapid and extensive effects.

Diuretics

Potent loop diuretics can further compromise placental perfusion. Immediate effects include redistribution of intravascular volume, which most often is already reduced in severe preeclampsia (p. 724). Thus, before delivery, diuretics are not used to lower blood pressure (Zeeman, 2009; Zondervan, 1988). Furosemide or similar drugs are used before delivery

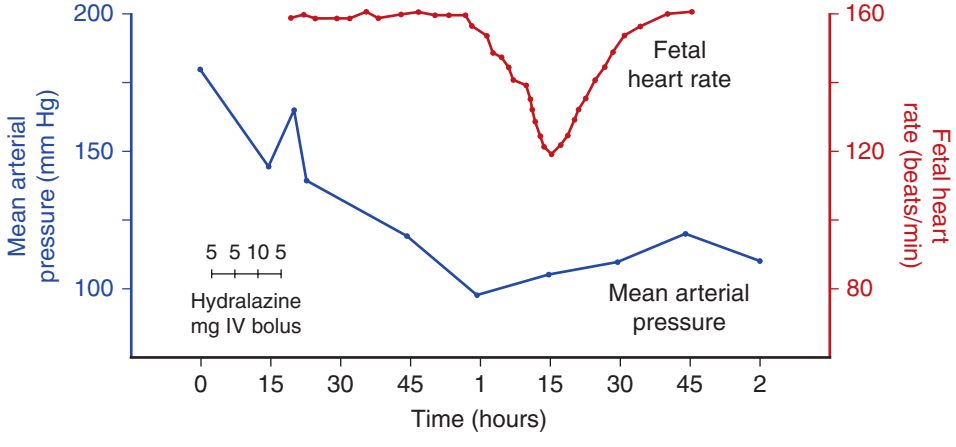

FIGURE 41-7 Hydralazine was given at 5-minute intervals instead of 15-minute intervals. The mean arterial pressure dropped from 180 to 90 mm Hg within 1 hour and was associated with fetal bradycardia. Rapid crystalloid infusion raised the mean pressure to 115 mm Hg, and the fetus recovered.

solely to treat pulmonary edema. Discussed on page 725, they may have a role in treatment of postpartum hypertension.

Fluid Therapy

Crystalloid solution is administered routinely at a rate between 60 and 125 mL per hour, unless fluid loss is unusual from vomiting, diarrhea, diaphoresis, or excessive blood loss. Oliguria is common with severe preeclampsia. Coupled with the knowledge that maternal blood volume is likely constricted compared with that of normal pregnancy, it is tempting to administer intravenous fluids more vigorously. However, controlled, conservative fluid administration is preferred for the typical woman with severe preeclampsia. These gravidas already have excessive extracellular fluid that has inappropriately extravasated from the intravascular compartment.

Infusion of large fluid volumes enhances the maldistribution and thereby elevates the risk of pulmonary and cerebral edema (Sciscioner, 2003; Zinaman, 1985). Thus, for preeclamptic women with anuria, small incremental boluses can be given to maintain urine output above 30 mL/hr. Diminished intravascular volume from hemorrhage or fluid loss from vomiting or fever can similarly be replaced by gradual incremental boluses of crystalloid. For labor analgesia with neuraxial analgesia, crystalloid solutions are infused slowly in graded amounts (Chap. 25, p. 479).

Pulmonary Edema

Women with severe preeclampsia who develop pulmonary edema most often do so postpartum (Cunningham, 1986, 2012). With pulmonary edema in the eclamptic woman, aspiration of gastric contents, which may be the result of convulsions, anesthesia, or oversedation, should be excluded. Otherwise, in women with severe preeclampsia, three common causes of pulmonary edema are pulmonary capillary permeability edema, cardiogenic edema, or their combination.

First, in women with preeclampsia, both increased capillary permeability and greater extravascular fluid oncotic pressure are found (Brown, 1989; Øian, 1986). If intravenous fluid replacement is vigorous, pulmonary congestion can follow.

Second, in some women, pulmonary edema may be caused by ventricular failure from increased afterload that results from severe hypertension. Such pulmonary edema from ventricular failure is more common in morbidly obese women and in those with chronic hypertension.

Invasive Hemodynamic Monitoring

Knowledge concerning cardiovascular and hemodynamic pathophysiological alterations associated with severe preeclampsia–eclampsia has accrued from studies done using invasive monitoring and a pulmonary artery catheter (Fig. 40-5, p. 694). Two conditions frequently cited as indications are preeclampsia associated with oliguria or with pulmonary edema (Clark, 2010). Somewhat ironically, it is usually vigorous treatment of the former that results in most cases of the latter. The Task Force (2013) recommends against routine invasive monitoring. This is best reserved for women with severe preeclampsia and with accompanying cardiac disease, renal disease, or both or with refractory hypertension, oliguria, and pulmonary edema. Preliminary data from studies using a *noninvasive cardiac monitoring system* need to be verified before widespread clinical application (Lavie, 2018).

Plasma Volume Expansion

Because the preeclampsia syndrome is associated with hemoconcentration, some have infused various fluids, starch polymers, albumin concentrates, or combinations to expand blood volume. Older studies describe serious complications—especially pulmonary edema—with volume expansion (Benedetti, 1985; Sibai, 1987b).

The Amsterdam randomized study reported by Ganzevoort and coworkers (2005a,b) was a well-designed investigation done to evaluate volume expansion. A total of 216 women with severe preeclampsia were enrolled between 24 and 34 weeks' gestation. The study included women whose preeclampsia was complicated by HELLP syndrome, eclampsia, pulmonary edema, or fetal-growth restriction. In the group randomly assigned to volume expansion, each woman was given 250 mL of 6-percent hydroxyethyl starch infused over 4 hours twice daily. Pregnancy outcomes were compared with a control group, and none of these were significantly different. Importantly, serious maternal morbidity and a substantive perinatal mortality rate accompanied their expectant management.

Analgesia and Anesthesia

During the past 25 years, the use of neuraxial analgesia for women with preeclampsia syndrome has proved ideal. Randomized studies attest to its safety, and these trials are fully described in Chapter 25 (p. 478).

Initial problems with neuraxial analgesia included hypotension and diminished uterine perfusion caused by sympathetic blockade in preeclamptic women, who already have attenuated hypervolemia. However, slow induction of epidural analgesia with dilute solutions of anesthetic agents counter the need for rapid infusion of large volumes of crystalloid or colloid to prevent maternal hypotension (Hogg, 1999; Wallace, 1995). Importantly, epidural blockade avoids general anesthesia, in which the stimulation of tracheal intubation may cause sudden severe hypertension. Such blood pressure spikes can cause pulmonary edema, cerebral edema, or intracranial hemorrhage. Last, tracheal intubation may be particularly difficult and thus hazardous in women with airway edema due to preeclampsia (American College of Obstetricians and Gynecologists, 2020b).

Judicious fluid administration is essential in women with severe preeclampsia who receive regional analgesia. Vigorous crystalloid infusion with epidural blockade in women with severe preeclampsia elevates pulmonary capillary wedge pressures (Newsome, 1986). Aggressive volume replacement in preeclamptic women raises their risk for pulmonary edema, especially in the first 72 hours postpartum (Clark, 1985; Cotton, 1986a). Last, most cases of pharyngolaryngeal edema are related to aggressive volume therapy (Heller, 1983). In sum, general anesthesia, epidural analgesia, or combined spinal-epidural analgesia are acceptable for women severe preeclampsia if steps are taken to ensure a careful approach to the selected method. At Parkland Hospital, a gentle bolus is given accompanying epidural placement (Chap. 25, p. 479).

■ Blood Loss at Delivery

Hemoconcentration or lack of normal pregnancy-induced hypervolemia is an almost predictable feature of severe preeclampsia–eclampsia (Fig. 40-7, p. 696) (Zeeman, 2009). *These women, who consequently lack normal pregnancy hypervolemia, may poorly tolerate even normal blood loss.* Thus, an appreciable fall in blood pressure soon after delivery most often means excessive blood loss and not sudden resolution of vasospasm and endothelial damage. When oliguria follows delivery, the hematocrit should be evaluated frequently to help detect excessive blood loss. If identified, hemorrhage should be treated appropriately by crystalloid and blood transfusion.

■ Persistent Severe Postpartum Hypertension

Postpartum, 8 percent of women develop de novo hypertension (Goel, 2015). At times, controlling severe hypertension may be difficult or intravenous hydralazine or labetalol or oral immediate-release nifedipine are being used repeatedly. In these cases, oral maintenance regimens can be given. Examples include labetalol or another β-blocking agent; nifedipine extended release; amlodipine; or another calcium-channel blocking agent (Sharma, 2017). Women so treated are less likely to require readmission (Stamilio, 2021; Wen, 2019). The Society for Maternal-Fetal Medicine (2020a) has developed a check list for postpartum care of women with hypertensive disorders.

Persistent hypertension is likely aggravated by pathological interstitial fluid that is now returning to the intravascular compartment, by underlying chronic hypertension, or by both (Sibai, 2012; Tan, 2002). Nonsteroidal antiinflammatory drugs do not aggravate postpartum hypertension (Anastasio, 2018; Penfield, 2019). In some women with chronic hypertension and left-ventricular hypertrophy, severe postpartum hypertension can cause pulmonary edema from cardiac failure (Cunningham, 1986, 2019; Sibai, 1987a).

Furosemide

Severe hypertension persists depending on the onset and length of extracellular fluid mobilization and diuresis. Thus, it seems logical that furosemide-augmented diuresis might serve to hasten blood pressure control (Ascarelli, 2005). In one randomized trial of 384 women with hypertensive disorders of pregnancy, a cohort that received furosemide postpartum had significantly lower blood pressures at 7 days—6 versus 14 percent—compared with women who received placebo (Lopes Perdigao, 2021). The need for antihypertensive treatment to be given at discharge in the furosemide group also was significantly reduced. In another randomized study, women with severe postpartum preeclampsia received nifedipine plus furosemide or nifedipine alone. The furosemide regimen significantly lowered the need for additional antihypertensive agents—8 versus 26 percent, respectively (Veena, 2017). Conversely, in one study, *torsemide* had no significant benefits (Viteri, 2018).

We use a simple method to estimate excessive extracellular fluid. The *postpartum weight* is compared with the most recent *prenatal weight*, either from the last clinic visit or from admission for delivery. Typically, soon after delivery, maternal weight should be reduced by at least 10 to 15 pounds depending on newborn and placental weight, amnionic fluid volume, and blood loss. Because of various interventions, especially intravenous crystalloid infusions given with labor epidural analgesia or during operative vaginal or cesarean delivery, women with severe preeclampsia often have an immediate postpartum weight *in excess of their last prenatal weight*. If this weight increase is associated with severe persistent postpartum hypertension, diuresis with intravenous furosemide can be helpful in controlling blood pressure.

Thrombotic Microangiopathy

Occasionally, women have an atypical syndrome in which severe preeclampsia–eclampsia persists despite delivery. Martin and associates (1995) described 18 such women whom they encountered during a 10-year period. They advocate single or multiple plasma exchange for these women. In some cases, 3 L of plasma was exchanged three times before a response was forthcoming. This is a 36- to 45-donor-unit exposure for each patient. Others have described plasma exchange performed in postpartum women with HELLP syndrome (Förster, 2002; Obeidat, 2002). In all of these cases, however, the distinction between HELLP syndrome and thrombotic thrombocytopenic purpura or hemolytic uremic syndrome was not clear (Tsai, 2016). In our experiences with more than 55,000 women with gestational hypertension among nearly 500,000 pregnancies cared for at Parkland Hospital through 2021, we have encountered very few women with persistent postpartum hypertension, thrombocytopenia, and renal dysfunction who were diagnosed as having a thrombotic microangiopathy (Dashe, 1998).

Reversible Cerebral Vasoconstriction Syndrome

This is another cause of persistent hypertension, "thunderclap" headaches, seizures, and central nervous system findings. *Reversible cerebral vasoconstriction syndrome* is characterized by diffuse segmental constriction of cerebral arteries and may be associated with ischemic and hemorrhagic strokes. This syndrome has several inciting causes that include pregnancy and particularly preeclampsia (Ducros, 2012). It is more frequent in women, and long-term sequelae are uncommon. However, in some cases, vasoconstriction may be so severe as to cause cerebral ischemia and infarction (Boitet, 2020). We have encountered only a few women with a stroke cause by this arteriopathy (Zofkie, 2019). The most appropriate management is unclear (Cho, 2019).

LONG-TERM CONSEQUENCES

■ Future Pregnancies

Women with preeclampsia during an index pregnancy are at risk for hypertensive and other disorders in subsequent pregnancies and later in life (Wang, 2021). In some, but not all women, the risk for hypertension is higher in the first 6 months postpartum (Giorgione, 2021; Mulder, 2021). Even in subsequent nonhypertensive pregnancies, women who had preterm preeclampsia have a higher risk for preterm birth and growth-restricted neonates (Connealy, 2014; Palatnik, 2016). Generally, the earlier preeclampsia is diagnosed during the index pregnancy, the greater the likelihood of recurrence. Women with preeclampsia

TABLE 41-10. Some Long-Term Consequences in Women with Preeclampsia Syndrome

Obstetrical
- Hypertensive disorders
- Preterm delivery
- Fetal-growth restriction

Cardiovascular
- Chronic hypertension
- Ischemic heart disease
- Atherosclerosis
- Coronary artery calcification
- Cardiomyopathy
- Thromboembolism
- Peripheral vascular disease

Renal
- Glomerular dysfunction
- Proteinuria

Neurovascular
- Stroke
- Retinal detachment
- Diabetic retinopathy
- Dementia
- Seizure disorder
- Retinopathy

Metabolic
- Type 2 diabetes
- Metabolic syndrome
- Dyslipidemia
- Obesity

TABLE 41-11. Long-Term Cardiovascular Morbidities After Recurrent Preeclampsia Compared with a Single Pregnancy with Preeclampsia and a Subsequent Normal Pregnancy

Morbidity (No. of Studies)	Recurrent (No.)	Single (No.)	Risk Ratio[a]
Hypertension (7)	2186	5589	2.33
IHD (3)	428	977	2.40
Heart failure (2)	160	298	2.88
CVA (2)	196	616	1.69
Cardiovascular event (2)	1278	5909	1.57

[a]All p values <0.0002.
CVA = cerebrovascular accident; IHD = ischemic heart disease.

near term had a recurrence risk of 23 percent, but nulliparas diagnosed with preeclampsia before 30 weeks had a recurrence risk as high as 40 percent (Bramham, 2011; Sibai 1986, 1991).

As perhaps expected, women with HELLP syndrome have a substantive risk for recurrence in subsequent pregnancies. Even if HELLP syndrome does not recur with subsequent pregnancies, again incidences of preterm delivery, fetal-growth restriction, placental abruption, and cesarean delivery are increased (Habli, 2009; Malmström, 2020).

Cardiovascular Morbidity

The preeclampsia syndrome is also a marker for subsequent long-term cardiovascular morbidity (Table 41-10) (Hammad, 2020; Stuart, 2018; Wang, 2021). Thus, women with hypertension identified during pregnancy should be evaluated during the first several months postpartum.

The Working Group of the NHBPEP (2000) concluded that hypertension attributable to pregnancy should resolve within 12 weeks of delivery, and hypertension persisting beyond this time is considered chronic (Chap. 53, p. 944). The Magpie Trial Follow-Up Collaborative Group (2007) reported that 20 percent of 3375 preeclamptic women seen at a median of 26 months postpartum had hypertension. From one metanaalysis, a 28-percent incidence of hypertension was found within 2 years of deliveries complicated by preeclampsia (Giorgione, 2021). From a Danish registry and after a mean of almost 15 years, the incidence of chronic hypertension was fivefold higher in those who had gestational hypertension, fourfold greater after mild preeclampsia, and sixfold higher after severe preeclampsia compared with women without hypertension in pregnancy (Lykke, 2009).

Any hypertension during pregnancy is a risk marker for cardiovascular morbidity in later life (Wang, 2021). As shown in data from Brouwers and coworkers (2018), the risk is greater in women with recurrent preeclampsia (Table 41-11). In a study from Iceland, the prevalence of ischemic heart disease—24 versus 15 percent, and of stroke—9.5 versus 6.5 percent, were increased in women who had gestational hypertension compared with normotensive controls (Arnadottir, 2005). In a Swedish population study of more than 400,000 women, those with recurrent preeclampsia had systolic dysfunction and a greater incidence of ischemic heart disease (Valensise, 2016). Diastolic dysfunction also is more common (Bokslag, 2018). Preeclampsia is also a risk for coronary artery calcification and idiopathic cardiomyopathy (Gammill, 2018; White, 2016).

Women who have preeclampsia and who develop chronic hypertension later in life have an increased ventricular mass index before they become hypertensive (Ghossein-Doha, 2013). Last, in at least some women with prior preeclampsia, hypertensive cardiovascular pathologies appear to have begun near the time of *their own* births. A similar phenomenon is associated with preterm birth and with fetal-growth disorders.

Other cofactors or comorbidities are related to acquisition of these long-term adverse outcomes (Gastrich, 2012; Harskamp, 2007; Hermes, 2012; Spaan, 2012). These include the metabolic syndrome, diabetes, obesity, dyslipidemia, and atherosclerosis (Catzov, 2021; Cho, 2019; Kajantie, 2017). Women with pregnancy-associated hypertension are at increased risk for type 2 diabetes (Stuart, 2018). Preeclampsia predisposes for later diabetic retinopathy and retinal detachment (Auger, 2017; Beharier, 2016).

Renal Sequelae

Preeclampsia is a marker for subsequent renal disease. Almost 15 percent of women with prior preeclampsia have renal dysfunction (Lopes van Balen, 2017). This may be related to AKI associated with preeclampsia (Novotny, 2020; Rodriquez, 2021). In a Danish study with more than a million women, the chronic renal disease rate was sixfold greater in those who had preeclampsia (Kristensen, 2019). These data need to be considered in light of the findings that 15 to 20 percent of women with preeclampsia who undergo renal biopsy have evidence of chronic renal disease (Chesley, 1978). In another long-term study, women with prior preeclampsia were significantly more likely to be chronically hypertensive—55 versus 7 percent—compared with control women. They also had higher peripheral vascular and renovascular resistance and decreased renal blood flow. These data do not permit conclusions as to cause versus effect (Spaan, 2009).

Central Nervous System Sequelae

Eclamptic seizures were once believed to have no significant long-term CNS sequelae. However, this likely is not the case (Bergman, 2021c; Theilen, 2016). Recall that almost all eclamptic women have multifocal areas of perivascular edema, and approximately a fourth also have areas of cerebral infarction (Zeeman, 2004).

In several long-term studies in women with severe preeclampsia and eclampsia, white-matter lesions in the brain that followed eclamptic convulsions persist (Aukes, 2009, 2012). Specifically, with magnetic resonance (MR) imaging, 40 percent of women with prior eclampsia had more numerous and larger aggregate white-matter lesions compared with 17 percent of normotensive control women. These white-matter lesions were also found in women with preeclampsia without convulsions (Aukes, 2012). Others found temporal lobe white-matter changes and reduced cortical volume in women with prior preeclampsia (Siepmann, 2017).

In some, but not all studies, women with prior eclampsia had subjectively impaired cognitive functioning and increased risk for dementia (Basit, 2018; Elharram, 2018). They also had a modest increase in the frequency of seizure disorders (Nerenberg, 2017). In another study, women with prior eclampsia had lower vision-related quality of life compared with control women (Wiegman, 2012).

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CHAPTER 42

Causes of Obstetrical Hemorrhage

In addition to hypertension and infection, obstetrical hemorrhage remains among the infamous triad of maternal death causes. Of more than 7000 pregnancy-related maternal deaths in the United States from 2006 to 2015, hemorrhage was a direct cause in 11 percent (Creanga, 2015, 2017; Petersen, 2019). Hemorrhage is also the single most important cause of maternal death worldwide (Goffman, 2016; Oladapo, 2016). Notably, perhaps a third of severe cases of hemorrhage are likely preventable (Lepine, 2020).

These statistics have prompted several organizations to develop programs to prevent hemorrhage-related maternal morbidity. In the United States, one example is the Alliance for Innovation on Maternal Health (AIM) (2015), with its intent to standardize recognition, response, and reporting of obstetrical hemorrhage. The Joint Commission (2019) has also implemented standards under the Provision of Care, Treatment, and Services chapter for obstetrical hemorrhage—the R3 Report. Our following three chapters align with these.

GENERAL CONSIDERATIONS

Mechanisms of Normal Hemostasis

Near term, an incredible amount of blood—at least 600 mL/min—flows through the spiral arteries and into the intervillous space (Pates, 2010). Averaging 120 in number, the spiral arteries lack a muscular layer because of their remodeling by trophoblasts and thereby form a low-pressure system. With placental separation, vessels at the implantation site are avulsed. Hemostasis is achieved first by myometrial contraction, which directly compresses the arteries. Compression is followed by clotting and eventually by obliteration of vessel lumens.

If, after delivery, the myometrium contracts vigorously, substantial hemorrhage from the placental implantation site is unlikely. *Importantly, an intact coagulation system is not necessary for postpartum hemostasis unless there are lacerations in the uterus, birth canal, or perineum.* However, fatal postpartum hemorrhage can result from uterine atony despite normal coagulation.

Definition and Incidence

Historically, postpartum hemorrhage has been defined as blood losses ≥500 mL after the third stage of labor. This is problematic because almost half of all women delivered vaginally shed that amount of blood or more when losses are carefully measured. Moreover, approximately 5 percent of women delivering vaginally lose >1000 mL of blood (Fig. 42-1) (Pritchard, 1962). Almost a third of women undergoing cesarean delivery have blood loss >1000 mL. The American College of Obstetricians and Gynecologists (2019a) now defines postpartum hemorrhage as cumulative blood loss >1000 mL or blood loss accompanied by signs and symptoms of hypovolemia.

In a Maternal-Fetal Network Units study of more than 115,000 deliveries, the incidence of hemorrhage with vaginal

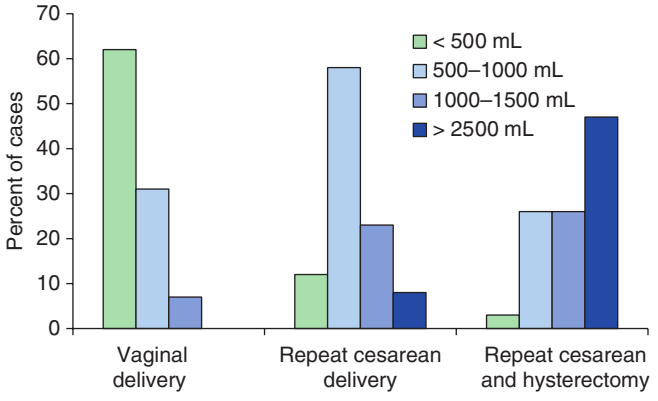

FIGURE 42-1 Measured blood loss with vaginal delivery, repeat cesarean delivery, and repeat cesarean delivery plus hysterectomy.

delivery was 5.3 percent, and it was 10.5 percent for cesarean delivery (Yee, 2019). Importantly, hemorrhage is underreported. From the National Hospital Discharge Summary database, the reported postpartum hemorrhage incidence between 2001 and 2005 was only 2.6 percent (Berg, 2009).

Blood Loss Assessment

At delivery, visual estimation is often used as a *qualitative* measure of blood loss. However, this method is more likely to under estimate the actual blood loss when volumes are high and to over estimate it when volumes are low (Al Kadri, 2011; Natrella, 2018). Thus, estimated blood loss that is considered greater than "average" should alert the provider.

Instead, different methods can be used as *quantitative* measures. First, gravimetric measurement weighs blood-soaked items and subtracts pre-use dry weights. Another evolving tool uses a tablet-device camera and colorimetric analysis to calculate blood loss (Spies, 2020; Venkatesh, 2020). The American College of Obstetricians and Gynecologists (2019b) recognizes the use of quantitative methods to help identify severe hemorrhage.

Intrapartum, quantitative measurement is more accurate than visual estimation, but the effectiveness of these methods on clinical outcomes has not been demonstrated. A Cochrane Review of three trials found no differences between subjective and objective methods when comparing outcomes that included need for transfusion, plasma expanders, or uterotonics (Diaz, 2018).

Postpartum, retrospective estimation also can be informative. The blood volume of a pregnant woman with normal pregnancy-induced hypervolemia usually rises by 50 percent. However, individual increases range from 30 to 60 percent, that is, 1500 to 2000 mL for an average-sized woman (Pritchard, 1965). The equation to calculate blood volume is shown in Table 42-1. It is axiomatic that a normal pregnant woman tolerates, without any decrease in postpartum hematocrit, blood loss at delivery that approaches the volume of blood that was added during pregnancy. Thus, if blood loss is less than the pregnancy-added volume, the hematocrit remains the same acutely and during the first several days postpartum. It then rises as nonpregnant plasma volume levels return during the next week or so. *Whenever the postpartum hematocrit is lower than one obtained on admission for delivery, blood loss can be estimated as the sum of the calculated pregnancy-added volume plus 500 mL for each 3-volume-percent decline of the hematocrit.*

For research and clinical care initiatives, excessive blood loss has been estimated by several methods (Coviello, 2019; Saoud, 2019). Tita and colleagues (2012) used a 6-volume-percent drop in the postpartum hematocrit to define clinically significant blood loss with vaginal delivery. This decline easily signifies a >1000-mL blood loss in the average-sized woman. They documented this amount in a fourth of women.

Another marker used to estimate hemorrhage incidence is the transfusion rate. In the study by Tita just cited, more than 6 percent of women who delivered vaginally underwent blood transfusion. In a study of more than 66,000 women delivered at Parkland Hospital, 2.3 percent overall were given

TABLE 42-1. Calculation of Maternal Total Blood Volume

Nonpregnant blood volume[a]:

$$\frac{[\text{Height (inches)} \times 50] + [\text{Weight (pounds)} \times 25]}{2} = \text{Blood volume (mL)}$$

Pregnancy blood volume:
Average increase is 30 to 60 percent of calculated nonpregnant volume
Increases across gestational age and plateaus at approximately 34 weeks' gestation
Usually larger with low-normal-range hematocrit (~30) and smaller with high-normal-range hematocrit (~40)
Average increase is 40 to 80 percent with multifetal gestation
Average increase is less with preeclampsia – volumes vary inversely with severity

Postpartum blood volume with serious hemorrhage:
Assume acute return to nonpregnant total volume after volume resuscitation
Pregnancy hypervolemia cannot be restored postpartum

[a]Formula arrived at by measuring blood volume and blood loss in more than 100 women using ^{51}Cr-labeled erythrocytes.
Data from Hernandez, 2012; Pritchard, 1962.

blood transfusions for hypovolemia (Hernandez, 2012). Half of these women had undergone cesarean delivery. Importantly, for those transfused, these investigators calculated blood loss to average approximately 3500 mL!

The need for blood transfusion is now followed as a *severe maternal morbidity (SMM)* indicator. The heightened awareness of SMM is outlined in Chapter 1 (p. 5). Transfusions represent more than 80 percent of total SMM rates. The incidence of *massive transfusion* for postpartum hemorrhage has been reported to be from 25 to 65 per 100,000 births (Green, 2016; Ramler, 2019). However, defining healthcare quality using transfusion as an SMM metric is problematic. First, this metric is solely derived from administrative billing codes. Second, transfusion rates may be skewed based on the hospital's case-mix (Bailit, 2013). This can distort values for regional referral centers that care for women at high risk for hemorrhage, such as those with placenta accreta spectrum.

Risk Factors

Hemorrhage can manifest at any time during pregnancy, delivery, or the puerperium. Contributions to maternal death from some of these causes of are shown in Figure 42-2. The Joint Commission (2019) requires accredited delivery services to employ tools that evaluate maternal hemorrhage risk on admission to labor and delivery and postpartum. Several methods are available, and the American College of Obstetricians and Gynecologists' (2019b) scoring tool stratifies risk using several obstetrical factors listed in Table 42-2. Unfortunately, these scoring systems only modestly predict hemorrhage (Chu, 2020). Kawakita and colleagues (2019) examined three commonly referenced tools and found moderate performance in identifying women at risk during cesarean delivery. In contrast, the Association of Women's Health, Obstetric and Neonatal Nurses (AWHONN) risk assessment tool was predictive of those at high risk (Colalillo, 2021).

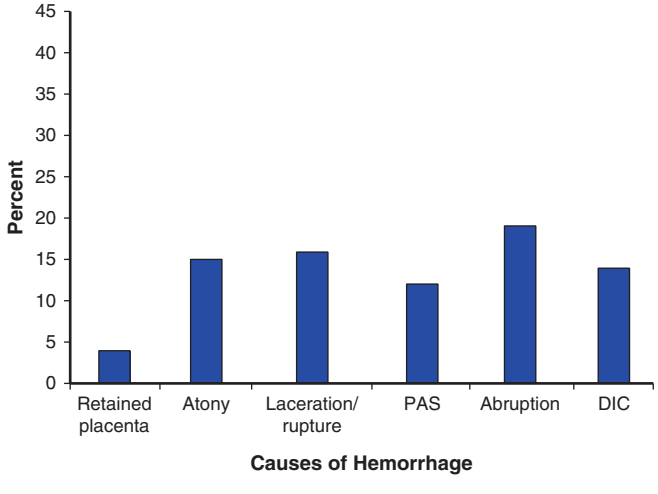

FIGURE 42-2 Contributions to maternal death from various causes of obstetrical hemorrhage. Percentages are approximations because of different classification schemata used. DIC = disseminated intravascular coagulopathy; PAS = placenta accreta spectrum. (Data from Al-Zirqi, 2008; Berg, 2010; Creanga, 2015; Zwart, 2008.)

TABLE 42-2. Obstetrical Hemorrhage: Causes, Predisposing Factors, and Vulnerable Patients

Abnormal Placentation
- Placenta previa
- Placental abruption
- Placenta accreta spectrum
- Ectopic pregnancy
- Hydatidiform mole

Injuries to the Birth Canal
- Episiotomy and lacerations
- Forceps or vacuum delivery
- Cesarean delivery or hysterectomy
- Uterine rupture
  - Previously scarred uterus
  - High parity
  - Tachysystole
  - Obstructed labor
  - Intrauterine manipulation
  - Midforceps rotation
  - Breech extraction

Obstetrical Factors
- Obesity
- Previous postpartum hemorrhage
- Early preterm pregnancy
- Sepsis
- Preeclampsia/eclampsia

Vulnerable Patients
- Chronic renal insufficiency
- Constitutionally small size

Uterine Atony
- Uterine overdistention
  - Large fetus
  - Multiple fetuses
  - Hydramnios
  - Retained clots
- Labor induction
- Anesthesia or analgesia
  - Halogenated agents
  - Regional analgesia with hypotension
- Labor abnormalities
  - Rapid labor
  - Prolonged labor
  - Augmented labor
  - Chorioamnionitis
- Previous uterine atony
- Parity: primiparity, high parity

Coagulation Defects—Intensify Other Causes
- Massive transfusions
- Placental abruption
- Sepsis
- HELLP syndrome
- Acute fatty liver
- Anticoagulant treatment
- Congenital coagulopathies
- Amnionic fluid embolism
- Prolonged retention of dead fetus
- Saline-induced abortion

HELLP = hemolysis, elevated liver enzyme levels, low platelet count.

Timing of Hemorrhage

Obstetrical hemorrhage is traditionally classified as *antepartum*—such as with placenta previa or placental abruption, or as *postpartum*—commonly caused by uterine atony or genital tract lacerations. In individual women, however, these terms are nonspecific, and it is reasonable to specify the cause and gestational age as descriptors.

With antepartum hemorrhage, timing may give a clue to its cause. Many aspects of bleeding during the first half of pregnancy from abortion or ectopic pregnancy are covered in Chapters 11 and 12. Discussions that follow concern pregnancies with a viable-size fetus. *In these cases, rapid assessment should always consider the deleterious fetal effects of maternal hemorrhage.*

During active labor, slight vaginal bleeding is common. This "bloody show" is the consequence of cervical effacement and dilation and concurrent tearing of small vessels. However, with uterine bleeding above the cervix, placental abruption, placenta

previa, and vasa previa must be considered. The first two are presented in Chapter 43 and vasa previa is discussed in Chapter 6 (p. 115). In some women, especially those with a placenta previa, cervical varicosities may bleed (O'Brien, 2013).

Near term in many women, the source of uterine bleeding is not identified, bleeding ceases, and no apparent anatomical cause is found at delivery. In most of these cases, bleeding likely originated from a slight marginal placental separation. *Despite this, any pregnancy with antepartum bleeding remains at higher risk for an adverse outcome even though bleeding has stopped and placenta previa has been excluded sonographically.*

Bleeding after midpregnancy is associated with several adverse outcomes. The Canadian Perinatal Network described 806 women with hemorrhage between 22 and 28 weeks' gestation (Sabourin, 2012). Placental abruption (32 percent), previa (21 percent), and cervical bleeding (6.6 percent) were the most frequent causes identified. In a third, no cause was found. Of all women, 44 percent were delivered before 29 weeks' gestation. In more than 68,000 women in Scotland, the incidence of antepartum hemorrhage after the first trimester was 11 percent (Bhandari, 2014). These women were at significantly higher risk for preterm birth, labor induction, and postpartum hemorrhage.

With postpartum hemorrhage, the source in most cases can and should be determined. Frequent causes are uterine atony with placental site bleeding, genital tract trauma, or both. Postpartum hemorrhage is usually obvious. Important exceptions are unrecognized intrauterine and intravaginal blood accumulation and uterine rupture with intraperitoneal or retroperitoneal bleeding. Another consideration is an expanding vulvar or vaginal hematoma (p. 740). Initial evaluation includes attempts to differentiate uterine atony from genital tract lacerations. For this, risk factors are sought, the lower genital tract is examined, and uterine tone is assessed. Atony is identified by a boggy, soft uterus during bimanual examination and by expression of clots and hemorrhage during uterine massage.

Persistent bleeding despite a firm, well-contracted uterus suggests that hemorrhage most likely is from lacerations. Bright red blood further suggests arterial bleeding. *To confirm that lacerations are a source of bleeding, careful inspection of the vagina, cervix, and uterus is essential.* Examination is easier if regional analgesia is employed. Transfer from a labor and delivery room to an operative suite also may be prudent. If there are no lower genital tract lacerations and the uterus is contracted, yet supracervical bleeding persists, manual exploration of the uterus is done to exclude a uterine tear (Kaplanoglu, 2016). This also is completed routinely after internal podalic version or breech extraction. Some perform this after successful vaginal birth after cesarean, and this is our practice. *Late postpartum hemorrhage* describes bleeding after the first 24 hours. Found in up to 1 percent of women, one risk factor is postpartum hemorrhage at the time of delivery (Fein, 2021). Delayed hemorrhage may be serious and is discussed in Chapter 36 (p. 637).

Appreciation of Estimated Blood Loss

As discussed, visual blood loss estimates are often inaccurate, especially with excessive bleeding. Instead of sudden and massive hemorrhage, postpartum bleeding is frequently steady. If bleeding from atony or laceration persists, it may appear to be only moderate at any given instant but may continue until serious hypovolemia develops. In some cases, after placental separation, blood may not escape vaginally but instead may collect within the uterine cavity, which can become distended by 1000 mL or more of blood. Moreover, postpartum uterine massage will be ineffective if applied to a roll of abdominal fat mistaken for the uterus. All of these factors can lead to an underappreciation of the magnitude of hemorrhage over time.

The effects of hemorrhage depend mainly on the maternal nonpregnant blood volume and the corresponding degree of pregnancy-induced hypervolemia. Small women—even those with appropriate pregnancy-induced hypervolemia—do not tolerate more than seemingly average blood loss. Some gravidas may be particularly susceptible to hemorrhage because their blood volume expansion is less than expected. An example is women with severe preeclampsia or eclampsia, who are more vulnerable to hemorrhage because they frequently do not have a normal blood volume accrual. Specifically, Zeeman and associates (2009) documented a mean increase above nonpregnant volume of only 10 percent in eclamptic women (Chap. 40, p. 693). Another example is the moderate to severe curtailing of pregnancy-induced volume expansion in women with chronic renal insufficiency (Chap. 56, p. 1004). *When excessive hemorrhage is suspected in these high-risk women, crystalloid and blood are promptly administered for suspected hypovolemia.*

A treacherous feature of postpartum hemorrhage is the failure of the pulse and blood pressure to undergo more than moderate alterations until large amounts of blood have been lost. The normotensive woman initially may actually become somewhat hypertensive from catecholamine release in response to hemorrhage. Importantly, women with preeclampsia may become "normotensive" despite remarkable hypovolemia. Accordingly, hypovolemia may not be recognized until very late.

UTERINE ATONY

Third-stage Labor Management

The most frequent cause of obstetrical hemorrhage is failure of the uterus after delivery to contract sufficiently and arrest bleeding from vessels at the placental implantation site (Yee, 2019). That said, some bleeding is inevitable during third-stage labor as the placenta begins to separate. Blood from the implantation site may escape into the vagina immediately—the *Duncan mechanism* of placental separation, or it remains concealed behind the placenta and membranes until the placenta is delivered—the *Schultze mechanism.* Placental descent is signified by a slack umbilical cord. After signs of placental separation, the uterus should be massaged if it is not contracted firmly. *Importantly, separation and delivery of the placenta by cord traction, especially when the uterus is atonic, may cause uterine inversion.*

Following placental delivery, the fundus is always palpated to confirm that the uterus is well contracted. If it is not firm,

vigorous fundal massage usually prevents postpartum hemorrhage from atony (Hofmeyr, 2013). Concurrent administration of a uterotonic agent, discussed in the next sections, is another recommended preventive measure.

Risk Factors

In many women with known risks, uterine atony can at least be anticipated. However, as discussed earlier (p. 733), risk-based scoring systems have limited value. In one study, up to half of women with atony after cesarean delivery had no risk factors (Rouse, 2006). The magnitude of risk for atony imposed by each of the factors shown in Table 42-2 varies considerably between reports. *Primiparity* and *high parity* are two factors (Driessen, 2011). In one study, the incidence of postpartum hemorrhage rose from 0.3 percent in women of low parity to 1.9 percent with parity of four or greater. It was 2.7 percent with parity of seven or greater (Babinszki, 1999). The *overdistended uterus* is prone to hypotonia after delivery, and thus women with a large fetus, multiple fetuses, or hydramnios carry greater risk (Blitz, 2019). *Labor abnormalities* predispose to atony and include hyper- or hypotonic labor. Similarly, *labor induction* or *augmentation* with either prostaglandins or oxytocin is more likely to be followed by atony (Driessen, 2011). The frequency of hemorrhage increases with third-stage labor lasting >20 minutes (Frolova, 2016). Last, the woman who has had a *prior postpartum hemorrhage* is at risk for recurrence.

Evaluation and Management

To improve immediate postpartum care, clinical safety bundles provide a standardized response (Fig. 42-3). In principle, all of these programs suggest notifying unit personnel, activating resources, and standardizing management. With immediate postpartum hemorrhage, careful inspection aims to exclude birth canal laceration. In some cases, bleeding is caused by retained placental fragments, and placental inspection after delivery should be routine. If a defect is seen, the uterus should be manually explored and the fragment removed. Occasionally, retention of a *succenturiate lobe* may cause postpartum hemorrhage (Chap. 6, p. 108). During examination for lacerations and causes of atony, the uterus is massaged and uterotonic agents are administered.

Manual Removal of the Placenta

If heavy bleeding persists after delivery of the newborn but while the placenta remains partially or totally attached, then manual placental removal is indicated (Cummings, 2016; Frolova, 2016). For this, adequate analgesia is mandatory, and aseptic surgical technique is used. As illustrated in Figure 27-8 (p. 508), the fingertips of one hand, with fingers approximated, are insinuated between the uterine wall and placenta. A sweeping forward motion in this plane will peel the placenta off its uterine attachment. After its removal, trailing membranes are carefully teased free from the decidua using ring forceps as needed. Another method to clear membranes is to wipe out the uterine cavity with a gauze-wrapped hand. Bierer forceps guided by ultrasound to remove retained placenta also has been described (Siegel, 2020).

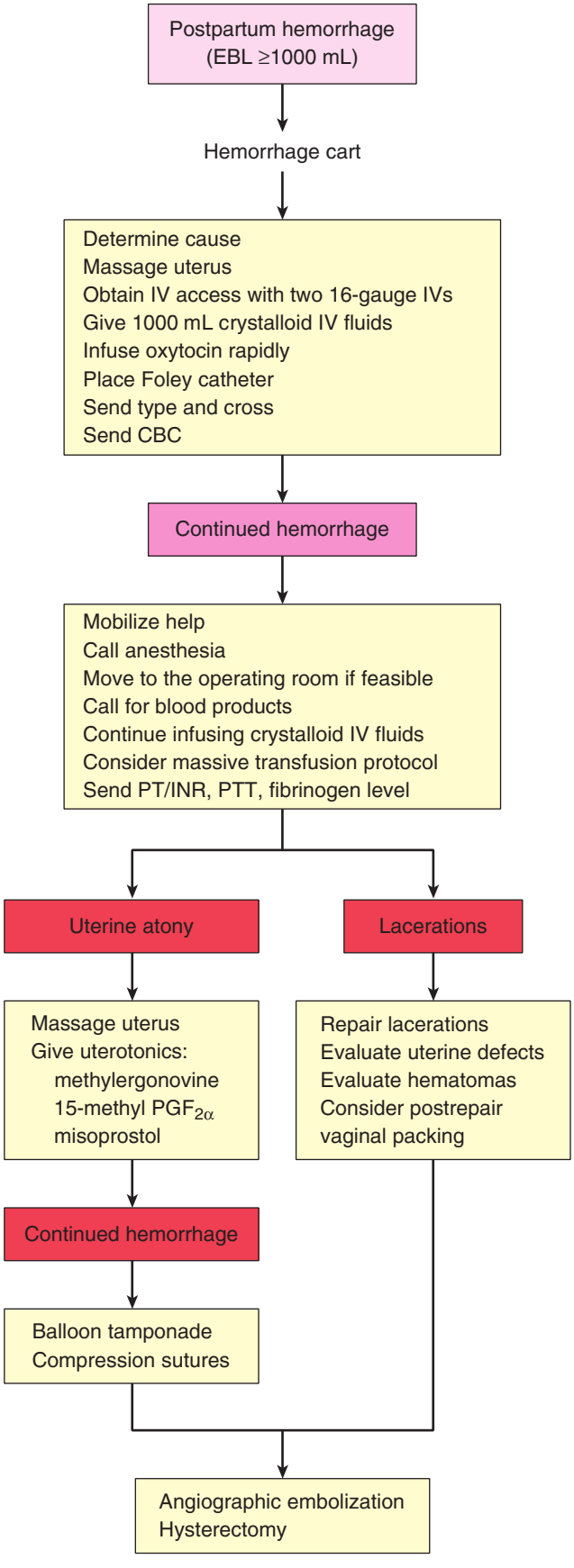

FIGURE 42-3 Parkland Hospital algorithm for management of postpartum hemorrhage. CBC = complete blood count; EBL = estimated blood loss; INR = international normalized ratio; IV = intravenous; PT = prothrombin time; PTT = partial thromboplastin time.

Some administer a single dose of intravenous antibiotics after manual uterine exploration, however, one systematic review of observational studies found no benefits (Chibueze, 2015). The American College of Obstetricians and Gynecologists (2020b) concluded that data neither support nor refute this practice. The World Health Organization (WHO) (2015) recommends ampicillin or cefazolin antimicrobial prophylaxis after manual placenta removal. At Parkland Hospital, we routinely provide a single dose of cefazolin after manual exploration.

Uterotonic Agents

Several compounds can be used to prompt the postpartum uterus to contract. One of these is routinely selected and given to *prevent* postpartum bleeding. Choices for prophylaxis include oxytocin (Pitocin); the ergots, namely ergonovine (Ergotrate) and methylergonovine (Methergine); or misoprostol (Cytotec) (Chap. 27, p. 507). The WHO (2018) recommends oxytocin for first-line use for prophylaxis. For administration, 20 units of oxytocin in 1000 mL of crystalloid solution is effective and given intravenously (IV) at 10 mL/min for a dose of 200 mU/min. Higher concentrations are minimally more efficient (Tita, 2012). A summary of oxytocin administration regimens is found in the Practice Brief of the Association of Women's Health Objective and Neonatal Nurses—AWHONN (2014). In those without IV access, oxytocin may be given intramuscularly (IM). Adnan and colleagues (2018) found the IV route to more effectively prevent severe hemorrhage compared with IM administration. *Oxytocin is never given as an undiluted bolus dose because serious hypotension or cardiac arrhythmias can develop.*

Most agents for prevention of atony are also used to *treat* it. For atony, IV oxytocin is continued or may be initiated if not selected initially. It is considered first-line treatment by the WHO (2012). If bleeding and atony are refractory, an agent from a different group can be added (American College of Obstetricians and Gynecologists, 2019a).

Ergot alkaloids have been used for centuries to treat uterine atony. If atony persists despite oxytocin and other preventive measures, ergot derivatives can be used for second-line treatment. Given parenterally, these drugs rapidly stimulate tetanic uterine contractions and act for approximately 45 minutes (Schimmer, 2011). A common regimen is 0.2 mg of either drug given IM. Methergine can be repeated at 2- to 4-hour intervals as needed. *A caveat is that ergot agents, especially given IV, may cause dangerous hypertension, especially in women with preeclampsia.* Severe hypertension is also seen with concomitant use of protease inhibitors given for human immunodeficiency viral (HIV) infection. These adverse effects notwithstanding, it is speculative whether ergot derivatives offer superior therapeutic effects compared with oxytocin.

Other second-line agents for atony have included the E- and F-series prostaglandins. Carboprost tromethamine (Hemabate) is the 15-methyl derivative of prostaglandin $F_{2\alpha}$. It is approved for uterine atony treatment in a dose of 250 μg (0.25 mg) given IM. This dose can be repeated if necessary, at 15- to 90-minute intervals up to a maximum of eight doses. Observational data indicate an 88-percent success rate (Oleen, 1990).

Carboprost causes side effects in approximately 20 percent of women. These include, in descending order of frequency, diarrhea, hypertension, vomiting, fever, flushing, and tachycardia. Another pharmacological effect is pulmonary airway and vascular constriction. Thus, carboprost should not be used for asthmatic women or those with pulmonary hypertension, including women those with suspected amnionic fluid embolism (p. 745). It has also been reported to cause arterial oxygen desaturation that averaged 10 percent (Hankins, 1988). We have occasionally encountered severe hypertension with carboprost given to women with preeclampsia. Other relative contraindications to carboprost include renal, liver, and cardiac disease (American College of Obstetricians and Gynecologists, 2019a).

Misoprostol is a synthetic prostaglandin E_1 analogue. In a Cochrane review, Mousa and associates (2014) reported no added benefits for misoprostol use for treatment compared with oxytocin or ergonovine. If misoprostol is used to treat atony, the American College of Obstetricians and Gynecologists (2019a) recommends a dose of 600 to 1000 μg rectally, orally, or sublingually.

Dinoprostone (*Cervidil, Prepidil*) is prostaglandin E_2. It may also be used off label for atony treatment and is given as a 20-mg suppository per rectum or per vagina every 2 hours. It typically causes diarrhea, which is problematic for the rectal route, whereas vigorous vaginal bleeding may preclude its use per vagina. Hypotension, which is commonly encountered with hemorrhage, is considered a contraindication by some. For this reason, this agent is not deployed for hemorrhage management at Parkland Hospital. IV prostaglandin E_2—*sulprostone*—is used in Europe, but it is not available in the United States.

Tranexamic Acid

This antifibrinolytic agent has been evaluated to treat postpartum hemorrhage. In the randomized WOMAN trial of gravidas with hemorrhage following vaginal birth or during cesarean delivery, mortality rates from obstetrical hemorrhage were 1.2 percent in those given a 1-g IV tranexamic acid dose plus traditional care for bleeding. This rate was significantly lower than the 1.7-percent death rate in women given traditional care alone (WOMAN Trial Collaborators, 2017). Another study of women with hemorrhage following vaginal birth found that rates of progression to severe PPH, of transfusion, and of peripartum hysterectomy were lower in the TXA group compared with the traditional-care group (Ducloy-Bouthors, 2011). Use of tranexamic acid in hemorrhage is discussed further in Chapter 44 (p. 773).

Bleeding Unresponsive to Uterotonic Agents

If bleeding persists after initial measures for atony, the following management steps are performed immediately and simultaneously:

1. Begin bimanual uterine compression, which is easily done and controls most cases of continuing hemorrhage (Fig. 42-4). This technique is not simply fundal massage. The posterior uterine wall is massaged by one hand on the abdomen, while the other hand is made into a fist and placed into the vagina. This fist kneads the anterior uterine wall through the anterior vaginal wall, and the uterus is compressed between the two hands.
2. Mobilize the emergent-care obstetrical team and call for whole blood or packed red cells.

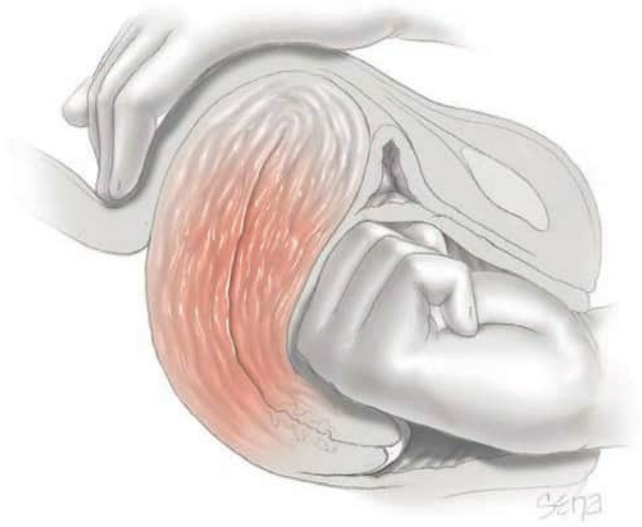

FIGURE 42-4 Bimanual compression for uterine atony. The uterus is positioned with the fist of one hand in the anterior fornix pushing against the anterior wall, which is held in place by the other hand on the abdomen. The abdominal hand is also used for uterine massage.

3. Request urgent help from the anesthesia team.
4. Secure at least two large-bore IV catheters so that crystalloid with oxytocin can be continued simultaneously with blood products. Insert a Foley catheter for continuous urine output monitoring.
5. Begin volume resuscitation with rapid IV crystalloid infusion (p. 734).
6. With sedation, analgesia, or anesthesia established and now with optimal exposure, once again manually explore the uterine cavity for retained placental fragments and for uterine abnormalities, including lacerations or rupture.
7. Thoroughly inspect the cervix and vagina again for lacerations that may have escaped attention.
8. Administer blood transfusions if the woman is still unstable or if bleeding persists (Chap. 44, p. 771).

At this juncture, after causes other than atony have been excluded and after hypovolemia is reversed, several other measures are considered if bleeding continues (Merriam, 2020). Their use depends on several factors such as parity, desire for sterilization, and experience with each method.

Balloon Tamponade and Surgical Procedures. For this, the tip of a 24F to 30F Foley catheter with a 30-mL balloon is guided into the uterine cavity and filled with 60 to 80 mL of saline. The open tip permits continuous drainage of blood from the uterus. We have experienced balloon rupture when more than 50 mL was instilled into the balloon, thus a 34F Foley with a 60-ml balloon can be used. If bleeding subsides, the catheter is typically removed after 12 to 24 hours. Similar devices for tamponade include Sengstaken-Blakemore, Rusch, and ebb balloons and condom catheters (Antony, 2017; Kondoh, 2019). Antibiotic prophylaxis using cefazolin, 1 gram every 8 hours until removal, has recently been suggested to reduce risk of postpartum endometritis (Martingano, 2020).

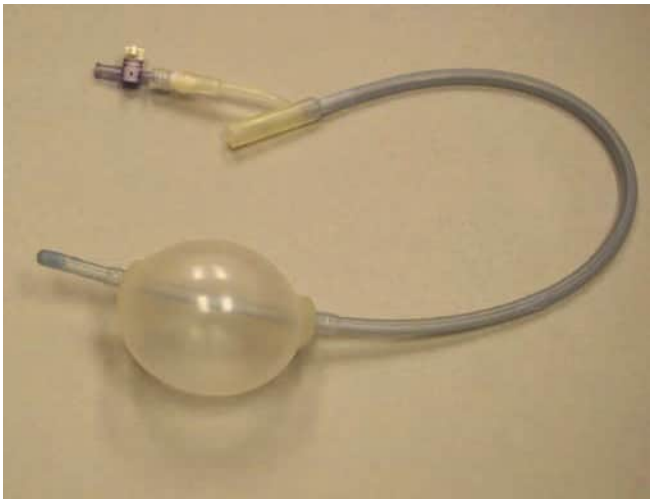

FIGURE 42-5 Intrauterine Bakri balloon for postpartum hemorrhage.

Instead, specially constructed intrauterine balloons are available to treat hemorrhage from uterine atony and other causes. A *Bakri Postpartum Balloon* or *BT-Cath* may be inserted and inflated to tamponade the endometrial cavity and stop bleeding (Fig. 42-5). Insertion requires two or three team members. The first performs abdominal sonography during the procedure. The second places the deflated balloon into the uterus and stabilizes it. The third member instills fluid to inflate the balloon, rapidly infusing at least 150 mL followed by further instillation over a few minutes for a total of 300 to 500 mL to arrest hemorrhage. It is reasonable to remove the balloon after approximately 12 hours (Einerson, 2017).

In small studies evaluating uterine balloons for all causes, the success rate approximated 85 percent (Kaya, 2016; Said Ali, 2021; Vintejoux, 2015). From their review, Suarez and associates (2020) used balloon tamponade in 4729 women and reported a similar success rate. At least one case of uterine rupture with a balloon has been reported (Ngyuen, 2018). Combinations of balloon tamponade and uterine compression sutures also have been described (Diemert, 2012; Yoong, 2012).

Failure of uterotonic agents and tamponade requires more invasive methods. These include uterine compression sutures, major pelvic vessel ligation, angiographic embolization, and hysterectomy. These are discussed in detail in Chapters 44 (p. 778). Peripartum hysterectomy is illustrated in Chapter 30 (p. 560).

UTERINE INVERSION

Puerperal inversion of the uterus is one of the classic hemorrhagic disasters encountered in obstetrics. Unless promptly recognized and managed appropriately, associated bleeding often is massive. Risk factors include alone or in combination: (1) placental implantation at the fundus, (2) uterine atony, (3) cord traction applied *before* placental separation, and (4) abnormally adherent placentation seen with placenta accreta spectrum disorders (Chap. 43, p. 759). Other risk factors are a short cord, uterine wall weakening at the implantation site, uterine tumors, and excessive fundal pressure (Wendel, 2018).

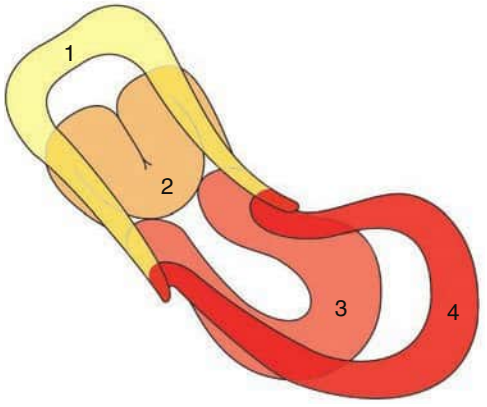

FIGURE 42-6 Progressive degrees of uterine inversion.

Depending on which of these factors are contributory, the incidence and severity of uterine inversion varies and can be progressive (Fig. 42-6). The worst scenario is complete inversion with the uterus protruding from the birth canal (Fig. 42-7).

The incidence of uterine inversion ranges from 1 case in 2000 to 1 in 20,000 vaginal deliveries (Coad, 2017; Witteveen, 2013). Our experiences at Parkland Hospital correspond with the higher 1:2000 incidence. This is despite our policy of discouraging placental delivery by cord traction alone, and before certainty of its separation. It is unknown if *active management of third-stage labor* with cord traction applied ostensibly *after* signs of placental separation raises the likelihood of uterine inversion (Deneux-Tharaux, 2013; Prick, 2013).

Recognition and Management

Immediate recognition of uterine inversion improves the chances of a quick resolution and good outcome. If initially unrecognized, continued hemorrhage likely will prompt closer examination of the birth canal. Although complete inversion is usually evident, the partially inverted uterus can be mistaken for a uterine myoma, and sonography can aid differentiation (Pan, 2015; Smulian, 2013). Many cases are associated with immediate life-threatening hemorrhage, and a fourth require blood replacement (Coad, 2017).

Once any degree of uterine inversion is recognized, several steps must be implemented urgently and simultaneously:

1. Immediate assistance is summoned, including obstetrical and anesthesia personnel.
2. Blood is brought to the delivery suite for potential use.
3. Two large-bore IV infusion systems are secured to begin rapid crystalloid infusion to treat hypovolemia while awaiting arrival of blood products.
4. The woman is evaluated for emergency general anesthesia.
5. If the recently inverted uterus has not contracted and retracted completely and if the placenta has already separated, the uterus may often be replaced simply by pushing up on the inverted fundus with the palm of the hand and fingers in the direction of the long axis of the vagina (Fig. 42-8). Some use two fingers rigidly extended to push the center of the fundus upward. *Care is taken not to apply so much pressure as to perforate the uterus with the fingertips.*
6. If the placenta is still attached, attempts are made to reposition the uterus with the placenta in situ. In theory, the uterus contracts to a lesser degree and placenta-site blood loss is less with an attached placenta. At this time a trial of an intravenously administered tocolytic drug may aid uterine relaxation and repositioning. Of options, a 250-μg subcutaneous dose of terbutaline, a 50- to 100-μg IV dose of nitroglycerin, or a 4-g IV dose of magnesium sulfate are suitable (Catanzarite, 1986; Dufour, 1997). If these fail to provide sufficient relaxation, then a rapid-acting halogenated inhalational

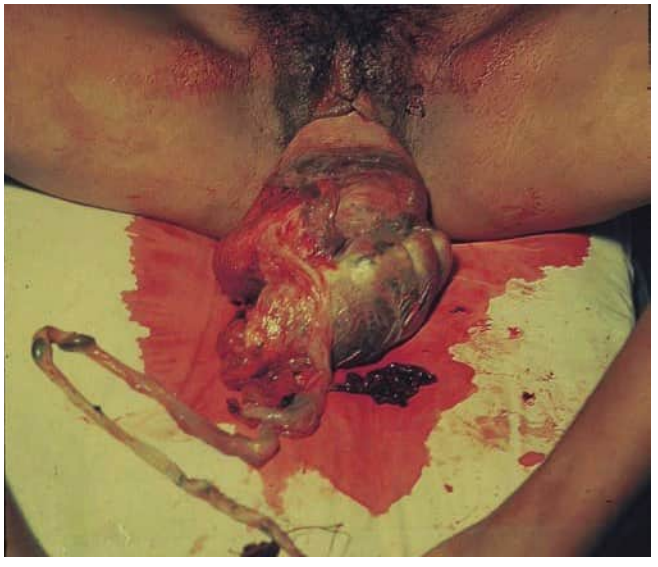

FIGURE 42-7 Maternal death during home delivery caused by exsanguination from uterine inversion, which stemmed from a fundally implanted placenta increta.

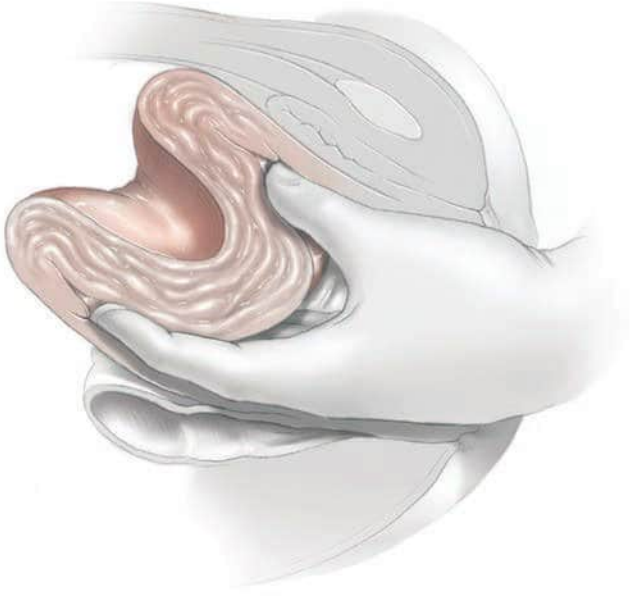

FIGURE 42-8 Incomplete uterine inversion can be repositioned by using the abdominal hand for palpation of the crater-like depression while simultaneously gently pushing the inverted fundus upward.

agent is administered by anesthesia staff. After the uterus is replaced, the placenta is carefully manually removed.

7. If uterine repositioning fails with the placenta attached, it is peeled off, and uterine repositioning is attempted again.
8. Once the uterus is restored to its normal configuration, tocolysis is stopped, oxytocin is then infused, and other uterotonic agents may be given as described for atony (p. 735). Meanwhile, the operator maintains the fundus in its normal anatomical position while applying bimanual compression to control further hemorrhage until the uterus is well contracted (see Fig. 42-4). The operator continues to monitor the uterus transvaginally for evidence of subsequent inversion. A Bakri balloon has been used by some to maintain the repositioned uterus (Haeri, 2015; Ida, 2015).

■ Surgical Intervention

In most cases, the inverted uterus can be restored to its normal position by the just-described techniques. Occasionally, manual replacement fails. One cause is a dense myometrial constriction ring. At this point, laparotomy is imperative. The anatomical configuration found at surgery can be confusing as shown in Figure 42-9. During laparotomy and after tocolysis is given, a combined effort is made to reposition the uterus by concurrently pushing upward from below and pulling upward from above. Application of atraumatic clamps to each round ligament and upward traction may be helpful—the *Huntington procedure*. In some cases, placing a deep traction suture in the inverted fundus or grasping it with tissue forceps may help but can be technically difficult. If a constriction ring still prohibits repositioning, a sagittal surgical cut—*Haultain incision*—is made posteriorly through the muscular ring to release it. The exposed fundus can then be reinverted (Sangwan, 2009).

After uterine replacement, tocolytics are stopped, and oxytocin and other uterotonic agents are given. If the Haultain method is used, the uterine incision is repaired. Risks of separation of this posterior hysterotomy incision during subsequent pregnancy, labor, and delivery are unknown (Wendel, 2018). Further illustration and discussion are found in *Cunningham and Gilstrap's Operative Obstetrics*, 3rd edition (Timofeev, 2017).

In some cases, the uterus will again invert almost immediately after repositioning. With this problem, uterine compression sutures can be used to prevent another inversion (Matsubara, 2009; Mondal, 2012). Occasionally, chronic puerperal uterine inversion may become apparent weeks after delivery.

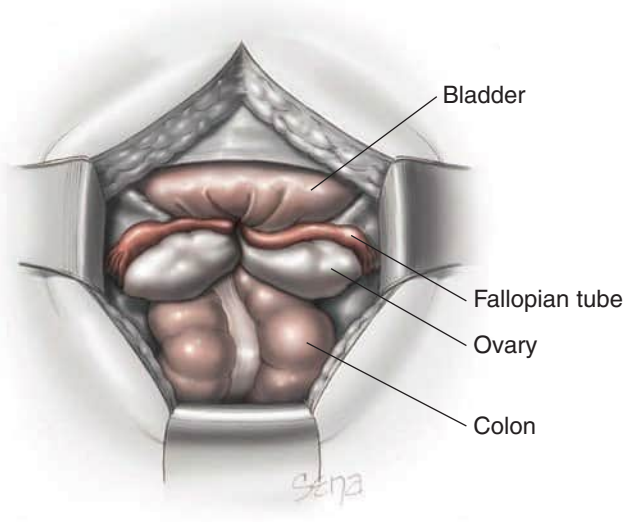

FIGURE 42-9 Surgical anatomy of a completely inverted uterus viewed from above at laparotomy.

BIRTH CANAL INJURIES

■ Vulvovaginal Lacerations

Childbirth is invariably associated with trauma to the uterus and cervix, vagina, and perineum. Injuries range from minor mucosal tears to lacerations that create life-threatening hemorrhage or hematomas. According to the American College of Obstetricians and Gynecologists (2020a), up to 80 percent of women sustain some type of laceration at vaginal birth. These may lie proximally or distally along the lower genital tract.

Small tears of the vaginal wall near the urethra are relatively common. They are often superficial with little to no bleeding but occasionally require fine-gauge absorbable sutures for hemostasis. Those large enough to require extensive repair are typically associated with short-term voiding difficulty, and an indwelling bladder catheter will obviate this.

Deeper perineal lacerations are usually accompanied by varying degrees of injury to the outer third of the vagina. Some extend to involve the anal sphincter or varying depths of the vaginal walls. Repair of these perineal lacerations is detailed in Chapter 27 (p. 510).

Lacerations involving the middle or upper third of the vagina usually are comorbid with injuries of the perineum or cervix. These sometimes are missed unless inspection is thorough. Those that extend upward usually are longitudinal. They may follow spontaneous delivery but frequently result from injuries sustained during operative vaginal delivery. Most involve deeper underlying tissues and thus usually cause significant hemorrhage, which is controlled by suture repair. For this, effective analgesia or anesthesia, clear visualization, capable assistance, and sufficient resuscitation of hypovolemia are mandatory.

Extensive vaginal or cervical tears should prompt a careful search for evidence of retroperitoneal hemorrhage or of peritoneal perforation with hemorrhage. Intrauterine exploration is also considered to exclude uterine tears or rupture (Conrad, 2015). If peritoneal perforation or uterine rupture is strongly suspected, laparotomy is reasonable (Rafi, 2010). As discussed later (p. 742), imaging and potential embolization may be suitable for large retroperitoneal hematomas.

■ Cervical Lacerations

Superficial lacerations of the cervix can be seen on close inspection in more than half of all vaginal deliveries. Most of these measure <0.5 cm and seldom require repair. Deeper lacerations are less frequent, but even these may be unnoticed. Such lacerations are more likely to be associated with vacuum- or

forceps-assisted vaginal delivery (Fong, 2014). Due to ascertainment bias, variable incidences are described. For example, with close inspection, the incidence of cervical lacerations in the Consortium on Safe Labor database was 1 percent in nulliparas and 0.5 percent in multiparas (Landy, 2011). But, the overall incidence in a study of more than 81,000 Israeli women was only 0.16 percent (Melamed, 2009).

Cervical lacerations are not usually problematic unless they cause hemorrhage or extend to the vagina. Rarely, the cervix may be entirely or partially avulsed from the vagina in the anterior, posterior, or lateral fornices, an injury termed *colporrhexis*. Another rare injury is avulsion of the entire vaginal portion of the cervix—*annular* or *circular detachment*. These injuries sometimes follow forceps deliveries performed through an incompletely dilated cervix and with the blades applied against the cervix. In some women, cervical tears reach into the lower uterine segment and involve the uterine artery and its major branches. They occasionally extend into the peritoneal cavity. More severe lacerations usually manifest as external hemorrhage or as a hematoma, however, they may occasionally be unsuspected. In the Israeli study just cited, almost 11 percent of women with a cervical laceration required blood transfusions (Melamed, 2009).

At times, the edematous anterior cervical lip is compressed between the fetal head and maternal symphysis pubis. This usually is of little consequence and resolves spontaneously. Rarely, this causes severe ischemia, and the anterior lip may undergo necrosis and later separate from the rest of the cervix.

As with vulvovaginal lacerations, cervical tears can be more fully appreciated with adequate exposure, which may be best attained with transfer to an operating room. An assistant applies firm downward pressure on the uterus, while the operator exerts gentle traction on the lips of the cervix with ring forceps. A second assistant can provide even better exposure with right-angle vaginal wall retractors or Breisky vaginal retractors. Yankauer or other suction tips also can aid viewing.

In general, cervical lacerations of 1 to 2 cm are not repaired unless they are bleeding. Such tears heal rapidly and ultimately form an irregular, sometimes stellate-appearing, external cervical os (Fig. 36-1, p. 635).

Deep cervical tears usually require surgical repair. When the laceration is limited to the cervix or even when it extends somewhat into the vaginal fornix, satisfactory results are obtained by suturing the cervix after bringing it into view as depicted in Figure 42-10. While cervical lacerations are repaired, any associated vaginal lacerations or an episiotomy may be tamponaded with gauze packs to arrest their bleeding. Because hemorrhage usually comes from the upper angle of the wound, the first suture using 2–0 chromic or polyglactin is placed in tissue above the angle. Subsequently, either interrupted or continuous locking sutures are serially placed outward toward the operator. If the uterus is involved and hemorrhage persists, some of the surgical and angiographic methods described in Chapter 44 (p. 777) may be necessary to obtain hemostasis. Following cervical lacerations, subsequent pregnancy outcomes include excessive recurrent lacerations, cervical incompetence, preterm labor, cesarean delivery, and severe perineal lacerations (Hamou, 2020).

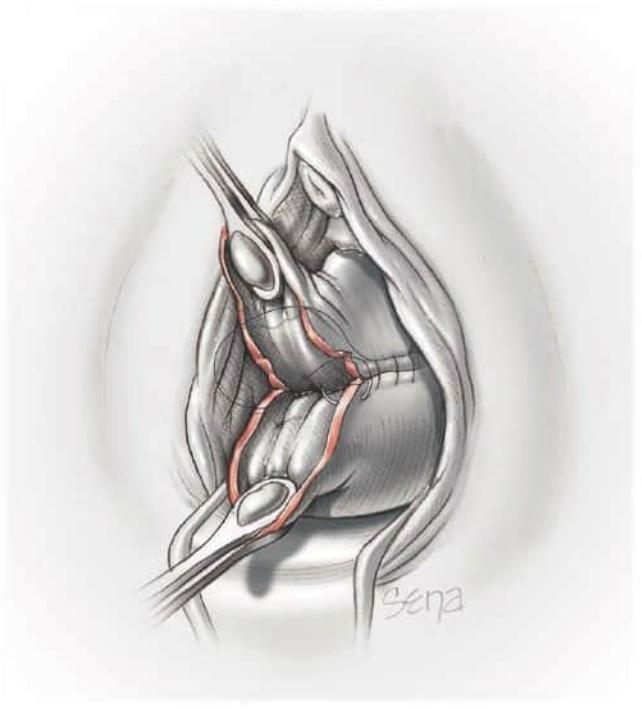

FIGURE 42-10 Repair of cervical laceration with appropriate surgical exposure. Continuous absorbable sutures are placed beginning at the upper angle of the laceration.

Puerperal Hematomas

Pelvic hematomas can have several anatomical manifestations following childbirth. One classification is anatomical and describes vulvar, vulvovaginal, paravaginal, and retroperitoneal hematomas. Vulvar hematomas may involve the vestibular bulb or branches of the pudendal artery, which are the inferior rectal, perineal, and clitoral arteries (Fig. 42-11). Paravaginal hematomas may involve the descending branch of the uterine artery. In some cases, a torn vessel lies above the pelvic fascia, and a *supralevator hematoma* develops. These can extend into the upper portion of the vaginal canal and may almost occlude its lumen. Continued bleeding may dissect retroperitoneally to form a mass palpable above the inguinal ligament. In some cases, it may even dissect up behind the ascending colon to the hepatic flexure (Rafi, 2010).

Risks for puerperal hematomas include vaginal or perineal laceration, episiotomy, or operative vaginal delivery (Iskender, 2016). Any hematoma can also develop following stretch and rupture of a blood vessel without an associated laceration (Alturki, 2018; Lee, 2020). This may be especially true with forceps delivery. Occasionally, they are associated with an underlying coagulopathy (Chap. 44, p. 775).

Diagnosis

Perineal, vulvar, and paravaginal hematomas can develop rapidly and frequently cause excruciating pain (Fig. 42-12). A tense, tender swelling of varying size rapidly develops, encroaches on the vaginal lumen, and causes overlying skin or epithelium to become ecchymotic. A paravaginal hematoma may escape detection initially. However, symptoms of pelvic

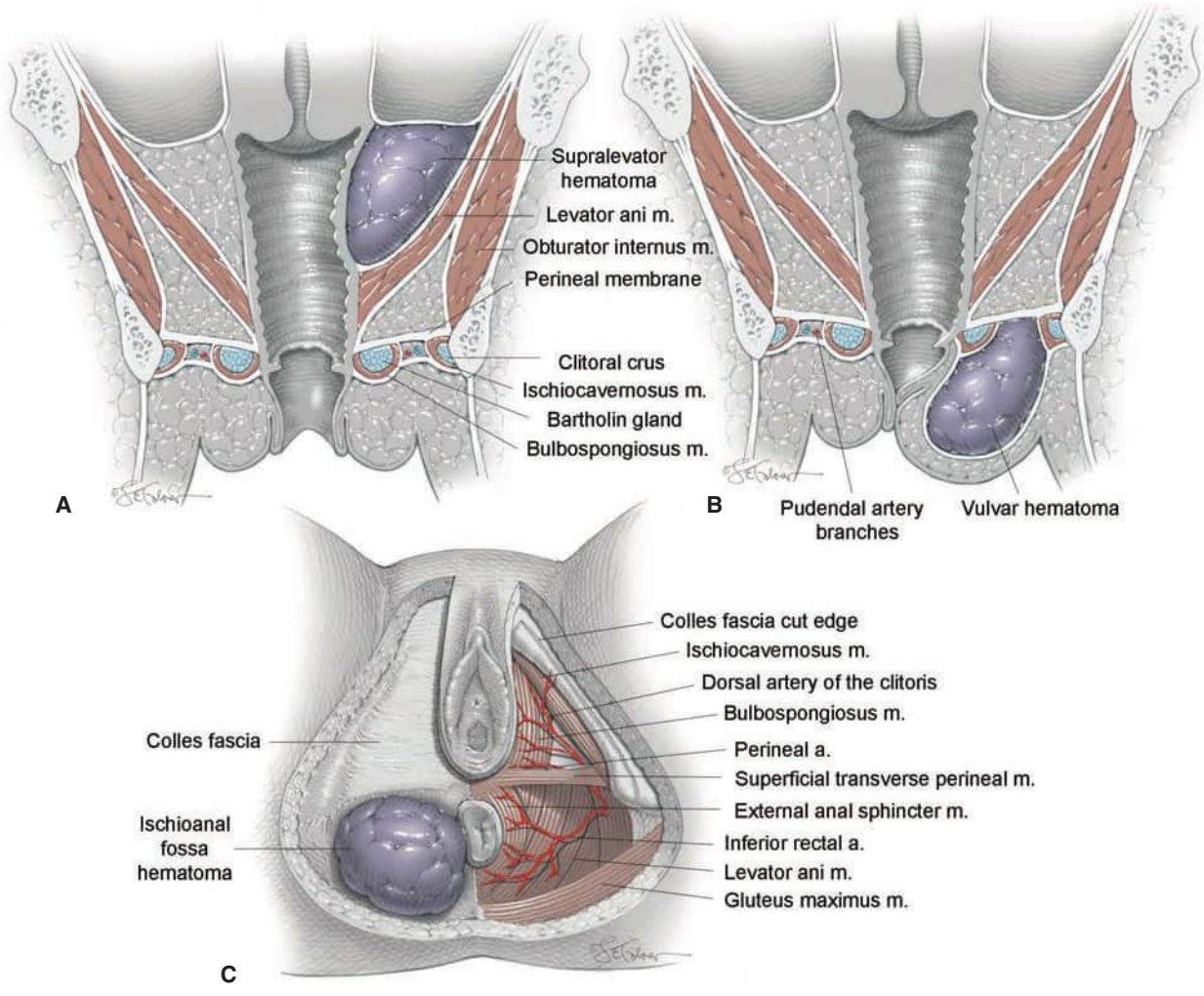

FIGURE 42-11 Schematic drawing showing types of puerperal hematomas. **A.** Coronal view showing a supralevator hematoma. **B.** Coronal view showing a hematoma in the urogenital triangle. **C.** Perineal view showing anal triangle anatomy and an ischioanal fossa hematoma. (Reproduced with permission from Cunningham FG: Genital tract lacerations and hematomas. In Yeomans ER, Hoffman BL, Gilstrap LC III, et al (eds): Cunningham and Gilstrap's Operative Obstetrics, 3rd ed. New York, NY: McGraw Hill; 2017a.)

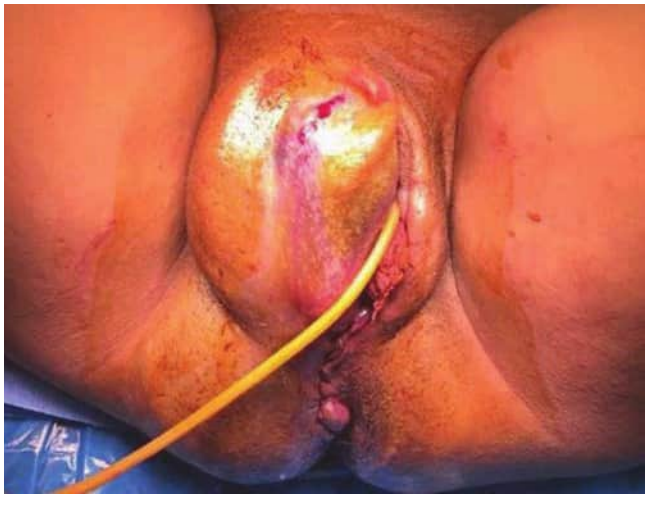

FIGURE 42-12 Right vulvar hematoma that required evacuation. A Foley catheter was placed for bladder drainage. (Reproduced with permission from Dr. Emily H. Adhikari.)

pressure, pain, or inability to void should prompt evaluation. Others may go undetected until other measures of hypovolemia become evident. With a supralevator extension, the hematoma extends upward in the paravaginal space and between the leaves of the broad ligament. The hematoma may escape detection until it can be felt on abdominal palpation or until hypovolemia develops. Imaging with sonography or computed tomographic scanning may be useful (Cichowski, 2017; Kawamura, 2014).

Management

Small hematomas often remain contained and show minimal expansion. In others, the tissues overlying an expanding hematoma may rupture from pressure necrosis. In some, profuse hemorrhage may follow, but in other cases, the hematoma drains in the form of large clots and old blood. In those that involve the paravaginal space and extend above the levator sling, retroperitoneal bleeding may be massive and occasionally fatal. In rare instances, we encountered hematomas that rebled up to 2 weeks postpartum (Cunningham, 2017).

Vulvovaginal hematomas are managed according to their size, location, duration since delivery, and expansion. If bleeding ceases, then small- to moderate-sized hematomas may be treated expectantly until absorbed. Cool packs and analgesics are supportive care, and an inability to void merits catheter drainage. But, if pain is severe or if the hematoma continues to enlarge, surgical exploration is preferable. *Blood loss with large puerperal hematomas is nearly always considerably more than the clinical estimate.* Hypovolemia is common, and transfusions are frequently required when surgical repair is necessary.

For repair, an incision is made at the point of maximal distention, blood and clots are evacuated, and bleeding points ligated. Often, no distinct bleeding vessels are identified. The cavity may then be obliterated in layers with absorbable sutures. With this, layered tissue closure acts to tamponade low-pressure bleeding. With vaginal hematomas, the vagina is packed with 1 to 2 gauze roll(s) for 12 to 24 hours, and the number of rolls is recorded. Supralevator hematomas are more difficult to treat. Although some can be evacuated by vulvar or vaginal incisions, laparotomy or angiographic embolization are considerations if bleeding continues.

Embolization has become popular for management of some puerperal hematomas. This is especially true for supralevator or retroperitoneal hematomas. Embolization can be used primarily, or more likely secondarily, if surgical attempts at hemostasis have failed or if the hematoma is difficult to access surgically (Distefano, 2013; Lee, 2012; Poujade, 2012). The use of a Bakri balloon for a paracervical hematoma also has been described (Gizzo, 2013; Grönvall, 2014). Last, ultrasound-guided drainage of a recurrent supralevator hematoma has been reported (Mukhopadhyay, 2015).

UTERINE RUPTURE

Predisposing Factors

Uterine rupture is another event that may lead to potentially catastrophic hemorrhage. Rupture may be *primary*, defined as occurring in a previously intact or unscarred uterus. More often, rupture is *secondary* and associated with a preexisting incision, anomaly, or injury of the myometrium (Table 42-3).

The contribution of each of these underlying causes has evolved during the past 50 years. Before 1960, when cesarean delivery was infrequent and women of great parity were numerous, primary uterine rupture predominated. As the incidence of cesarean delivery rose, and especially as a subsequent trial of labor in these women became prevalent through the 1990s, uterine rupture through the cesarean hysterotomy scar became the preeminent cause (Chang, 2020; Gibbins, 2015; Mone, 2016).

Concurrent with the diminished enthusiasm for a trial of labor after cesarean delivery (TOLAC), incidence trends for the two types of rupture have again changed. In a study of 3942 cases of uterine rupture in more than 15 million women, only approximately half were in women with a prior cesarean delivery (Yao, 2017). The International Network of Obstetric Survey Systems (INOSS) identified 864 complete uterine ruptures in more than 2.6 million deliveries (Vanderberghe, 2019). The overall prevalence was 3 cases per 10,000 births. In women without a prior cesarean delivery, the prevalence was 0.6 per 10,000 births, and it was 22 per 10,000 in those with a prior cesarean delivery. This is similar to the recent overall rate of 5 cases per 10,000 births at Parkland Hospital. During this time, there were 40 cases of uterine rupture, and despite a very conservative TOLAC policy, 25 of the 40 events were in women with a prior hysterotomy.

TABLE 42-3. Some Causes of Uterine Rupture

Preexisting Uterine Injury or Anomaly	Uterine Injury or Abnormality Incurred in Current Pregnancy
Surgery involving the myometrium:	**Before delivery:**
Cesarean delivery or hysterotomy	Persistent, intense, spontaneous contractions
Previously repaired uterine rupture	Labor stimulation: oxytocin or prostaglandins
Myomectomy incision through or to the endometrium	Intraamnionic instillation: saline or prostaglandins
Deep cornual resection of interstitial fallopian tube	Perforation by internal uterine pressure catheter
Operative hysteroscopy	External trauma: sharp or blunt
Metroplasty	External version
Sharp or blunt trauma—assaults, vehicular accidents, bullets, knives	Uterine overdistention: hydramnios, multifetal pregnancy
Silent rupture in previous pregnancy	**During delivery:**
Congenital:	Internal version of second twin
Pregnancy in rudimentary uterine horn	Difficult forceps delivery
Defective connective tissue—Marfan or Ehlers-Danlos syndrome	Breech extraction
	Fetal anomaly distending the lower segment
	Vigorous uterine pressure during delivery
	Difficult manual removal of placenta
	Acquired:
	Placental accreta spectrum
	Gestational trophoblastic neoplasia
	Adenomyosis
	Sacculation of entrapped retroverted uterus

The current lower incidence of women of great parity also has lowered the primary-rupture rate. In this regard, advancing maternal age may be a greater risk factor (Hochler, 2020). Another risk is excessive or inappropriate uterine stimulation with oxytocin. This previously frequent cause has mostly disappeared. In an analysis of three trials comparing contemporaneous high- and low-dose oxytocin regimens for labor induction in those with an unscarred uterus, the rate of uterine rupture did not differ between groups (Budden, 2014). The rate of rupture, however, is increased with sequential induction of labor with prostaglandins and oxytocin in those both with and without prior cesarean delivery (Al-Zirqi, 2017).

Other operations that traumatize the myometrium include uterine curettage or perforation, endometrial ablation, myomectomy, operative hysteroscopy, or prior uterine rupture (Frank, 2018; Zhao, 2019). Uterine rupture is also linked with disorders associated with connective tissue weakness (Cauldwell, 2019a,b; Noh, 2013). Another report described rupture in a woman with prior childhood pelvic radiotherapy (Huarte Cignada, 2020).

Blunt abdominal trauma also can rupture a substantially gravid uterus (Miller, 1996). Thus, pregnant women in the later second- and third trimesters who sustain such trauma are ideally monitored for signs of uterine rupture. Specific monitoring protocols are outlined in Chapter 50 (p. 896).

Uncommon causes today are those due to internal podalic version and extraction, difficult forceps delivery, breech extraction, and unusual fetal enlargement such as with hydrocephalus. In one unusual case, fundal rupture followed spontaneous labor in a woman with an abdominal cerclage (Dandapani, 2019). Rupture associated with multifetal pregnancy or uterine anomalies also is rare (Bankada, 2015; Tarney, 2013; Tola, 2014). Although rare, rudimentary uterine horns are especially susceptible and described in Chapter 3 (p. 43). Discussed in Chapter 43 (p. 760), placenta percreta may cause focal myometrial weakness and rupture (Sun, 2016).

Pathogenesis

Rupture of the previously intact uterus during labor most often involves the thinned-out lower uterine segment. When the rent is in the immediate vicinity of the cervix, it frequently extends transversely or obliquely. When the rent forms in the portion of the uterus adjacent to the broad ligament, the tear is usually longitudinal (Fig. 42-13). Although these tears develop primarily in the lower uterine segment, they can extend upward into the active segment or downward through the cervix and into the vagina. In some cases, the bladder also may be lacerated.

If the rupture is of sufficient size, the uterine contents will usually escape into the peritoneal cavity. If the presenting fetal part is firmly engaged, however, then only a portion of the fetus may be extruded from the uterus. Fetal prognosis is largely dependent on the size of the rent, the degree of placental separation, the magnitude of maternal hypovolemia, and the rapidity of diagnosis and response (Al-Zirqi, 2018; Rottenstreich, 2021). In some cases, the overlying peritoneum remains intact, and this usually is accompanied by hemorrhage that extends into the broad ligament to cause a large retroperitoneal hematoma.

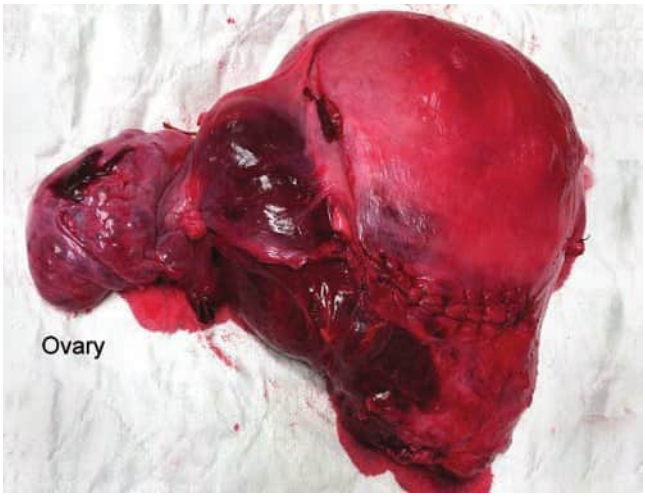

FIGURE 42-13 Peripartum hysterectomy specimen. A right broad ligament hematoma is seen lateral to the closed hysterotomy incision and medial to the ovary. (Reproduced with permission from Dr. Emily H. Adhikari.)

Following vaginal delivery in an unscarred uterus, we and others have occasionally encountered cases of an incomplete tear on the inside of the uterus that extends vertically into the active segment to cause profuse hemorrhage (Conrad, 2015). These tears are usually not visible from below but are found at the time of hysterectomy for intractable bleeding despite a contracted uterus. Hemorrhage with this type of tear can be torrential, and bleeding is usually not slowed until the uterine artery pedicles are clamped bilaterally.

Management and Outcomes

The varied clinical presentations of uterine rupture and its management are discussed in detail in Chapter 31 (p. 579). In the most recent national maternal mortality statistics, uterine rupture accounted for nearly 10 percent of hemorrhage-associated deaths (Creanga, 2015, 2017). Maternal morbidity includes hysterectomy that may be necessary to control hemorrhage. Rates of perinatal mortality and morbidity, which may include severe neurological impairment, also are high (Al-Zirqi, 2018; Rottenstreich, 2021). Table 42-4 lists some perinatal outcomes in 72 women with uterine rupture. Last, maternal obesity comorbid with uterine rupture is associated with increased rates of adverse neonatal outcomes (Yao, 2017). With prior rupture and a subsequent pregnancy, Fox (2020) recommends cesarean delivery prior to labor or at the onset of preterm labor.

AMNIONIC FLUID EMBOLISM

Pathophysiology

This syndrome usually is caused by intravenous embolization of meconium-laden amnionic fluid. It results in rapid cardiorespiratory collapse and profound consumptive coagulopathy. The understanding of the mechanism of injury for amnionic fluid embolism (AFE) has evolved. Early theories proposed that amnionic fluid and debris entered the maternal circulation and obstructed pulmonary artery flow, which led to hypoxia, right

TABLE 42-4. Some Maternal and Perinatal Outcomes in 72 Women with Uterine Rupture

Outcomes	Parkland Hospital[a]	Australia-New Zealand[b]
Number	40	32
Maternal		
Blood loss	2500 mL[c]	2580 mL[d]
Transfusions	55%	63%
Hysterectomy	27%	10%
ICU admission	17%	NS
Perinatal		
Cord artery pH	7.07[c]	NS
Cord pH <7.0	35%	NS
5-min Apgar <7	25%	NS
NNICU	47%	13%
HIE	15%	NS
Death	5%	16%

[a]Date from Yule, 2019.
[b]Data from Chang, 2020.
[c]Median.
[d]Mean.
HIE = hypoxic ischemic encephalopathy; ICU = intensive care unit; NNICU = neonatal intensive care unit; NS = not stated.

heart failure, and death. However, during normal delivery, amnionic fluid commonly enters maternal circulation through venous channels at the placental implantation site or small lacerations. Accordingly, squames, fetal cells, and trophoblasts can often be identified in maternal peripheral blood at delivery (Clark, 1986; Lee, 1986). And, at least in experimental animals, infused clear amnionic fluid is generally innocuous, even in large amounts (Adamsons, 1971; Stolte, 1967).

Instead, meconium-laden amnionic fluid is likely a potent cause of symptomatic AFE (Hankins, 1993). Disruption of the maternal-fetal interface allows material from the fetal compartment to enter maternal circulation. This dyad leads to abnormal activation of proinflammatory mediator systems, similar to the systemic inflammatory response syndrome (SIRS), and causes initial, transient pulmonary vasoconstriction and hypertension (Bernstein, 2019). Pulmonary hypertension causes acute right ventricular failure, which is followed by hemodynamic collapse from right ventricular infarction, interventricular septum displacement, and decreased left-sided cardiac output (Pacheco, 2020). This right and then left ventricular dysfunction leads to cardiogenic pulmonary edema and systemic hypotension. Acute respiratory failure with severe hypoxemia from shunting develops. Notably, the resulting multiorgan dysfunction is an interrelated process, with both the cardiac and pulmonary systems affecting each other.

Women who survive beyond these first phases invariably develop the third component of the classic triad—a consumptive coagulopathy. Material from the fetal compartment that contains tissue factor then activates factor VII. This leads to the development of disseminated intravascular coagulation. The rapidity of the coagulopathy is amazing (Fig. 42-14).

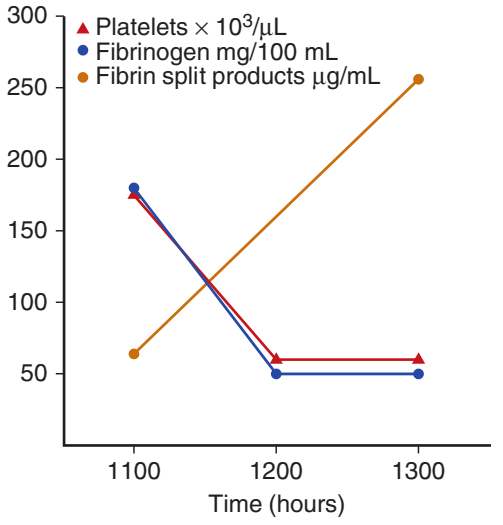

FIGURE 42-14 Fatal amnionic fluid embolism. Results of some coagulation studies show an abrupt drop in plasma fibrinogen levels and platelet count but an extremely elevated serum fibrin split product level.

To those who succumb, postmortem histopathological findings may be obvious. However, detection of squames and keratin may require special stains, and even then, debris may not be seen. In one study, fetal elements were detected in 75 percent of autopsies and in 50 percent of specimens prepared from concentrated buffy coat aspirates taken antepartum from a pulmonary artery catheter (Clark, 1995).

Incidence and Risk Factors

Most reports describe an AFE frequency of 1 to 2 cases per 100,000 births (Clark, 2014; Fitzpatrick, 2019; Knight, 2010). The case-fatality rate in all of these studies ranges from 11 to 43 percent. From another perspective, AFE caused 5 to 15 percent of all pregnancy-related deaths in the United States, Canada, and France (Bonnet, 2018; Kramer, 2012; Petersen, 2019).

Predisposing conditions are rapid labor, meconium-stained amnionic fluid, and tears into uterine and other large pelvic veins that permit an exchange of fluids between the maternal and fetal compartment (Society of Maternal-Fetal Medicine, 2016). Other commonly cited risks include older maternal age; postterm pregnancy; labor induction or augmentation; eclampsia; cesarean, forceps, or vacuum delivery; placental abruption or previa; and hydramnios (Indraccolo, 2018; Knight, 2012; Kramer, 2012). The associations of uterine hypertonus appears to be the *effect* rather than the *cause* because uterine blood flow ceases when intrauterine pressures exceed 35 to 40 mm Hg. Thus, a hypertonic contraction would be the *least* likely circumstance for amnionic fluid and other debris to enter uterine veins (Clark, 1985). For this reason, hypertonus from oxytocin does not seem implicated.

Diagnosis

The classic triad of abrupt hemodynamic and respiratory compromise along with consumptive coagulopathy underpins its diagnosis (Pacheco, 2020). Proposed criteria for AFE diagnosis

TABLE 42-5. Diagnostic Criteria for Amnionic Fluid Embolism

Clinical onset during labor or within 30 minutes of placental delivery
Abrupt onset of cardiorespiratory arrest, or both hypotension and respiratory compromise
Overt disseminated intravascular coagulopathy
No fever ≥38°C

Adapted from Clark, 2016; Pacheco, 2020.

are shown in Table 42-5. In a French study, only 60 percent of women with autopsy-confirmed AFE had all four criteria (Bonnet, 2018). The classic example is dramatic, and a woman in the late stages of labor or immediately postpartum begins gasping for air. Seizures or cardiorespiratory arrest rapidly follow and are accompanied by massive hemorrhage from consumptive coagulopathy (Bernstein, 2019; Tanaka, 2017). Clinical manifestations vary, and we and others have managed several women in whom otherwise uncomplicated vaginal or cesarean delivery was followed by severe acute consumptive coagulopathy without overt cardiorespiratory difficulties. In these women, consumptive coagulopathy appears to be the *forme fruste* of AFE (Kramer, 2012; Porter, 1996).

In such cases, other sources of acute cardiac or respiratory failure should be considered. These include myocardial infarction, pulmonary or air embolism, high spinal blockage, eclampsia, and anaphylactic shock (Bernstein, 2019). In some cases, the temporal relationship of events aids diagnosis. *Unfortunately, no specific diagnostic laboratory test confirms or refutes the diagnosis of AFE, and it remains a clinical diagnosis*. Importantly, women suffering from excessive blood loss and resulting coagulopathy may be misdiagnosed with AFE, when the true culprit is unrecognized or underappreciated hemorrhage (Clark, 2016). In either event, a woman with cardiopulmonary compromise should receive immediate resuscitation (Society for Maternal-Fetal Medicine, 2016).

Management

The initial period of systemic and pulmonary hypertension with AFE is transient. Thus, immediate high-quality cardiopulmonary resuscitation and advanced cardiac life support must be initiated without delay (Pacheco, 2020; Society for Maternal-Fetal Medicine, 2016). These are discussed in detail in Chapter 50 (p. 897). Coagulopathy is managed as described in Chapter 44 (p. 777).

If resuscitation is successful, hemodynamic instability is common in survivors. Both fever and hyperoxia will worsen ischemia-reperfusion injury to the brain. A suitable goal for temperature is 36°C and for mean arterial pressure is 65 mm Hg (Society for Maternal-Fetal Medicine, 2016). Additional supportive care measures such as intubation are usually necessary. During the phase of right ventricular failure, inotropic agents such as dobutamine may improve right heart output, and later systemic hypotension should be treated with vasopressors such as norepinephrine. Excess fluid administration is discouraged because it can worsen dilation of an already engorged right ventricle, which may cause right-sided myocardial infarction and interventricular septum displacement.

Extracorporeal membrane oxygenation (ECMO) has been described in the treatment of AFE (Bernstein, 2019; Webster, 2020). Further discussed in Chapter 50 (p. 886), venovenous ECMO is used for severe hypoxemic respiratory failure, without right or left ventricular failure. Venoarterial ECMO is less readily available and used for impending cardiac arrest and ventricular failure. One recent review of outcomes in 20 women with AFE managed with ECMO reported a maternal mortality rate of only 15 percent. The authors concluded that publication biases may have overestimated the favorable outcomes (Viau-Lapointe, 2019).

Either immediately after cardiopulmonary collapse or during the ensuing phases of injury, a coagulopathy develops in most cases from activation of factor VII and X. This may be exacerbated by ongoing hemorrhage, and a common source is uterine atony. Thus, immediate evaluation of coagulation parameters is indicated with concurrent management of bleeding.

Clinical Outcomes

Most reports describe significant maternal and perinatal mortality with AFE. This is likely influenced by underdiagnosis and reporting biases that favor the most severe cases with the highest mortality rates. From a California database of 1.1 million deliveries, the mortality rate with AFE was 60 percent (Gilbert, 1999). In the INOSS database, maternal mortality rates ranged from 30 to 41 percent (Fitzpatrick, 2019). Death can be rapid, and in one study, 12 of the 34 women died within 30 minutes (Weiwen, 2000). The mortality rate is highest in women who present with cardiac arrest—89 percent (Fitzpatrick, 2019).

Survivors commonly have profound neurological impairment. Clark (1995) observed that only 8 percent of women who lived despite cardiac arrest survived without neurological injury. In a report of 20 cases, the maternal mortality rate was 15 percent, and 40 percent of survivors had neurological disability (Skolnik, 2019). Overall, the prognosis appears to be more associated with disease severity and the attendant cardiac arrest than with any specific treatment modality (Clark, 2014; Fitzpatrick, 2019).

As perhaps expected, perinatal outcomes also are poor and are inversely related to the maternal cardiac arrest-to-delivery interval. Even so, the neonatal survival rate is 70 percent, but unfortunately, up to half of survivors suffer residual neurological impairment. In a Canadian study, 28 percent of neonates were considered to be asphyxiated at birth (Kramer, 2012).

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CHAPTER 43

Hemorrhagic Placental Disorders

Hemorrhage following partial or complete separation of the placenta can be torrential. Recall that the amount of blood flowing through the intervillous space at term exceeds 600 mL/min (Pates, 2010). In the second half of pregnancy, three placental disorders contribute substantially to maternal mortality rates. These include placental abruption, placenta previa, and placenta accreta spectrum.

The contributions of hemorrhagic placental disorders to maternal mortality are discussed in Chapter 1 (p. 7) and Chapter 42 (p. 733). The management and clinical experience with these disorders span more than a generation. Placental abruption, for example, has been emphasized in this text for more than 50 years beginning with the work of Dr. Jack Pritchard. Now more common than years past, placenta accreta spectrum is another substantial threat to maternal well-being.

PLACENTAL ABRUPTION

Etiopathogenesis

Separation of the placenta—either partially or totally—from its implantation site before delivery is called *placental abruption* or *abruptio placentae*. From Latin, the latter translates as "rending asunder of the placenta," which denotes a sudden accident, which is characteristic of most cases. In the purest sense, the cumbersome—and thus seldom used—term *premature separation of the normally implanted placenta* is most descriptive because it excludes separation of a placenta previa.

Abruption likely begins with rupture of a decidual spiral artery and hemorrhage into the decidual basalis. The subsequent expanding retroplacental hematoma splits the decidua and leaves a thin layer adherent to the myometrium. The decidual hematoma grows to lift away and compress the adjacent placenta. In some cases that are associated with preeclampsia, impaired trophoblastic invasion with subsequent atherosis is one underlying predisposition (Brosens, 2011). Inflammation or infection also may be contributory (Mhatre, 2016). However, histological findings cannot be used to determine the timing of the abruption (Chen, 2017).

In the early stages of placental abruption, clinical symptoms may be absent. Even with continued bleeding and placental separation, placental abruption can still be either total or partial (Fig. 43-1). With either, bleeding typically insinuates itself between the membranes and uterine wall, ultimately escaping through the cervix to cause *external hemorrhage*. Less often, the blood is retained, leading to *concealed hemorrhage* and delayed diagnosis. The delay translates into greater maternal and fetal hazards. With concealed hemorrhage, the likelihood of consumptive coagulopathy is also increased. This is because increased pressure within the intervillous space, caused by the expanding retroplacental clot, forces more placental thromboplastin into the maternal circulation (Chap. 44, p. 775).

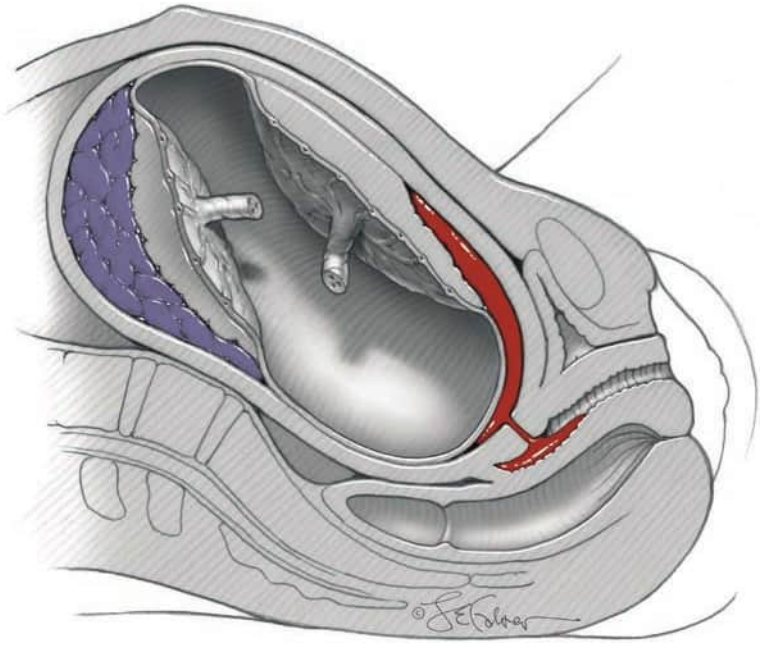


FIGURE 43-1 Schematic of placental abruption. Shown to the left is total placental abruption with concealed hemorrhage. To the right is a partial abruption with blood and clots that dissect between membranes and decidua to reach the internal cervical os and then the vagina.

Traumatic Abruption

External trauma—usually from motor vehicle crashes or aggravated assault—can cause placental separation. The frequency of abruption originating from trauma varies. Importantly, abruption can stem from relatively minor trauma (Huls, 2018). The clinical presentation and consequences of these abruptions differ somewhat from spontaneous cases. For example, associated fetomaternal hemorrhage, while seldom clinically significant with most spontaneous abruptions, is more common with trauma because of concomitant placental tears or "fractures" (Fig. 50-10, p. 895). In eight women with traumatic placental abruption cared for at Parkland Hospital, we found fetal-to-maternal hemorrhage of 80 to 100 mL in three (Stettler, 1992). Importantly, in some cases of trauma, a nonreassuring fetal heart rate tracing may not be accompanied by other evidence of placental separation. A sinusoidal tracing is one example. Following blunt abdominal trauma, uterine contractions are the single most important predictor of placental abruption (Greco, 2019). Traumatic abruption is considered in more detail in Chapter 50 (p. 894).

Most blood in the retroplacental hematoma in a nontraumatic placental abruption is maternal. This is because hemorrhage derives from separation within the maternal decidua, and placental villi are usually initially intact. In 78 women at Parkland Hospital with a nontraumatic placental abruption, fetal-to-maternal hemorrhage was documented in only 20 percent. All of these had <10 mL fetal blood loss (Stettler, 1992). In another series of 68 women with a placental abruption, fetal cells were found in peripheral blood in only 4 percent (Atkinson, 2015).

Placental abruption can create a visible circumscribed depression on the maternal surface of a freshly delivered placenta. These depressions usually measure a few centimeters in diameter and are covered by dark, clotted blood. Because several minutes are required for these anatomical changes to materialize, a very recently separated placenta may appear totally normal at delivery. Our experiences are like those of Benirschke and associates (2012) in that the "age" of the retroplacental clot cannot be determined exactly. In the example shown in Figure 43-2, a large dark clot is well formed. It has depressed the placental bulk and likely is at least several hours old.

Defining placental abruption severity is problematic. We consider placental abruption severe when the fetus dies. However, maternal and fetal complications are frequently serious even with a liveborn fetus. Ananth and coworkers (2016) have defined severe placental abruption as displaying one or more of the following: (1) maternal sequelae that include disseminated intravascular coagulation (DIC), shock, transfusion, hysterectomy, renal failure, or death; (2) fetal complications such as nonreassuring fetal status, growth restriction, or death; or (3) neonatal outcomes that include death, preterm delivery, or growth restriction.

Chronic Abruption

When placental separation is not followed by delivery, the placental abruption is termed chronic. Some of these cases begin early in pregnancy. Dugoff and coworkers (2004) observed an association between some abnormally elevated maternal serum aneuploidy markers and subsequent abruption. Others have correlated first- and second-trimester bleeding with third-trimester placental abruption (Ananth, 2006; Weiss, 2004). In some cases, chronic abruption and oligohydramnios develop and are called the *chronic abruption–oligohydramnios sequence* (CAOS) (Elliott, 1998). Even later in pregnancy, hemorrhage with retroplacental hematoma formation is occasionally arrested completely without delivery. These women may have

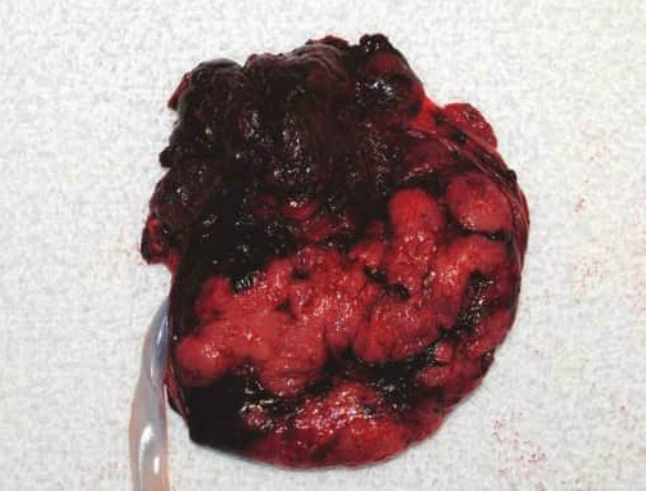


FIGURE 43-2 Partial placental abruption with a dark adherent clot.

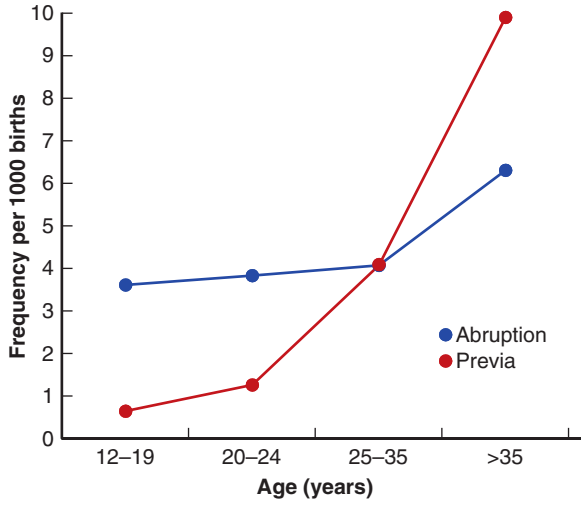


FIGURE 43-3 Frequency of placental abruption and placenta previa by maternal age at Parkland Hospital from 2000 through 2015.

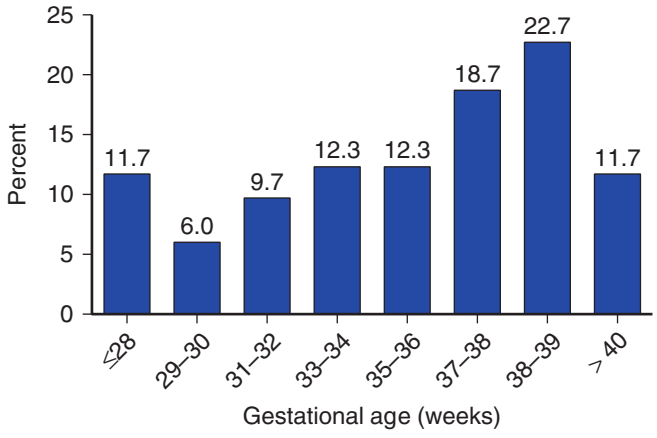


FIGURE 43-4 Frequency of placental abruption by gestational age at Parkland Hospital.

abnormally elevated levels of maternal serum alpha-fetoprotein (MSAFP) or placenta-specific RNAs as markers of the event (Miura, 2017; Ngai, 2012).

Frequency

The reported incidence of placental abruption varies because of differing criteria used for diagnosis. Its frequency averages 0.5 percent or 1 case in 200 deliveries. From one database of more than 125 million births from 1979 through 2010, the incidence of placental abruption was nearly 1 percent (Hill, 2020). In more than 250,000 deliveries at Parkland Hospital from 2000 through 2015, the incidence of placental abruption averaged 1 case in 290 births (Fig. 43-3).

The frequency of placental abruption has risen in this country, and most of this increase is in black women (Ananth, 2005, 2016). This disproportion may be explained in part by the conservative management of early-onset preeclampsia in some institutions (Chap. 41, p. 714). At Parkland Hospital, however, the frequency of severe placental abruption has declined. Specifically, with placental abruption so extensive as to kill the fetus, the incidence was 0.24 percent or 1 case in 420 births from 1956 through 1967 (Pritchard, 1967). Through 2020, this same frequency dropped to 0.05 percent or 1 case in 2060 births. This likely reflects a concurrent decline in the number of high-parity women giving birth and rise in the availability of prenatal care and emergency transportation.

Perinatal Morbidity and Mortality

Overall, perinatal outcomes are influenced by gestational age, and the frequency of placental abruption rises across the third trimester. As seen in Figure 43-4, more than half of the placental abruptions at Parkland Hospital developed at gestational ages ≥37 weeks' gestation. Perinatal mortality and morbidity, however, are more common with earlier abruptions and with concomitant preeclampsia (Furukawa, 2015; Han, 2019). Of other related factors, major fetal congenital anomalies have greater association with placental abruption (Riihimäki, 2013).

Although the rates of fetal death have declined, the contribution of abruption as a cause of stillbirth remains prominent because other causes also have decreased. For example, since the early 1990s, 10 to 12 percent of all third-trimester stillbirths at Parkland Hospital have been the consequence of placental abruption. In a review of more than 15 million singleton births between 1995 and 1998 in the United States, the perinatal mortality rate associated with placental abruption was 119 death per 1000 births. This was higher than the rate of 8 deaths per 1000 births in the general obstetrical population (Salihu, 2005).

Neonatal deaths also are common following placental abruption. At Parkland Hospital, 15 percent of liveborn neonates die. Perinatal morbidity also is common in this group (Downes, 2017). Moreover, associated childhood mortality mainly stems from birth-related asphyxia and prematurity (Riihimäki, 2018). In one series, 20 percent of 43 liveborn neonates had severe fetal acidemia following placental abruption, and 20 percent of survivors developed cerebral palsy (Matsuda, 2013). In another study of 84 liveborns, 29 (35 percent) had an umbilical artery pH <7.00 (Onishi, 2019). Ananth and coworkers (2017) attribute some of the adverse neurodevelopmental outcomes to preterm delivery.

Predisposing Factors

Demographic Factors

Several predisposing factors raise the placental abruption risk (Table 43-1). *Advancing maternal age* is one risk, although data regarding women of great parity are conflicting (see Fig. 43-3) (Okby, 2017). Race or ethnicity also appears important (Eubanks, 2021). In an earlier study, in almost 366,000 deliveries at Parkland Hospital, abruption severe enough to kill the fetus was most common in black and white women—1 case in 200 births; less so in Asian women—1 in 300; and least common in Latinas—1 in 350 (Pritchard, 1991). A *familial association* was found from one Norwegian population-based registry (Rasmussen, 2009). In this study, if a woman had a severe abruption, the risk for her sister was doubled. Candidate genes involved in mitochondrial biogenesis and oxidative phosphorylation pathways, which confer risk for placental abruption, have been described (Workalemahu, 2018).

TABLE 43-1. Risk Factors for Placental Abruption

Risk Factor	Relative Risk
Prior abruption	10–188
Increased age and parity	1.3–2.3
Preeclampsia	2.1–4.0
Chronic hypertension	1.8–3.0
Chorioamnionitis	3.0
Preterm ruptured membranes	2.4–4.9
Multifetal gestation	2–8
Low birthweight	14.0
Hydramnios	1.9
Cigarette smoking	1.4–1.9
Single umbilical artery	3.4
Cocaine use	—
Uterine leiomyoma	2.6
Subchorionic hematoma	5.7

Data from Aviram, 2015; Downes, 2017; Gutvirtz, 2016; Khazaei, 2019; Kortekaas, 2020; Morgan, 2016; Ruiter, 2015; Tuuli, 2011.

Pregnancy-associated Hypertension

Some form of hypertension is the most frequent condition associated with placental abruption. This includes gestational hypertension, preeclampsia, chronic hypertension, or a combination. The hemolysis, elevated liver enzyme levels, low platelet count (HELLP) syndrome carries an increased risk for placental abruption. Moreover, expectant management of preeclampsia in significantly preterm pregnancies was complicated by placental abruption in 4 percent (Shoopala, 2019). In a report by Pritchard and colleagues (1991) that described 408 women with placental abruption and fetal demise, hypertension was apparent in half once hypovolemia was corrected. Half of these latter women—a fourth of all 408—had chronic hypertension. Examined another way, one Maternal-Fetal Medicine Units (MFMU) Network study found that 1.5 percent of pregnant women with chronic hypertension suffered placental abruption (Sibai, 1998). At Parkland Hospital, the placental abruption frequency in women with treated chronic hypertension and significant proteinuria was almost 1 percent. This incidence compared with the 0.3-percent incidence in women with treated hypertension without substantial proteinuria (Morgan, 2016).

Chronic hypertension with superimposed preeclampsia or with fetal-growth restriction confers an even greater risk (Lueth, 2020). Even so, the severity of hypertension does not necessarily correlate with abruption incidence (Morgan, 2016; Zetterstrom, 2005). However, women with preeclampsia that experience placental abruption have worse maternal, fetal, and neonatal outcomes compared with women experiencing abruption alone (Han, 2019). The long-term effects of these associations are apparent from the significantly elevated cardiovascular mortality risk in women with prior abruption, with or without chronic hypertension (DeRoo, 2016; Pariente, 2013). Observations from the Magpie Trial Collaborative Group suggest that women with preeclampsia, with or without chronic hypertension, given magnesium sulfate may have a reduced risk for abruption (Altman, 2002). Last, Roberge and colleagues (2018), performed a metaanalysis and reported that a 100-mg daily aspirin may decrease the incidence of placental abruption.

Preterm Prelabor Ruptured Membranes

The placental abruption risk substantially rises when placental membranes rupture before term. (Hackney, 2016). Of 756 women with ruptured membranes between 20 and 36 weeks' gestation, 5 percent developed an abruption (Major, 1995). The frequency was 17 percent with previable prelabor ruptured membranes (Kibel, 2016). The risk for abruption with preterm membrane rupture is further elevated with comorbid infection (Ananth, 2004). In one cohort study of pregnancies ≥34 weeks' gestation, the placental abruption rate was eightfold higher if hydramnios was comorbid (Aviram, 2015). From a metaanalysis of 10 studies that included term and preterm gestational ages, hydramnios was associated with a twofold greater rate of placental abruption (Khazaei, 2019). Abrupt uterine decompression during membrane rupture may be an inciting factor.

Prior Abruption

Many of the predisposing factors in women with a history of an abruption are chronic conditions, and in these cases, placental abruption has a high recurrence rate. Women with abruption and fetal death have a recurrence rate of 12 percent, and half of these abruptions caused another fetal death (Pritchard, 1970). Furuhashi and colleagues (2002) reported a 22-percent recurrence rate, and half recurred at a gestational age 1 to 3 weeks earlier than the first abruption. In one longitudinal Dutch study, Ruiter and coworkers (2015) cited a recurrence risk of 5.8 percent. In a population-based study of 767,000 pregnancies, the authors found a sevenfold higher risk for recurrence of a "mild" abruption and twelvefold risk for a "severe" abruption (Rasmussen, 2009). For women who had two severe abruptions, the risk for a third was increased 50-fold.

Management of a pregnancy subsequent to an abruption is difficult because another separation may suddenly occur, even remote from term. In many of these recurrences, evaluation of fetal well-being is almost always reassuring beforehand. Thus, antepartum fetal testing is usually not predictive. Because term abruptions tend to be recurrent, Ruiter and coworkers (2015) recommend labor induction at 37 weeks' gestation. It seems reasonable to induce labor at 38 completed weeks if other complications do not develop beforehand.

Other Associations

Of these listed in Table 43-1, cigarette smoking is linked to an elevated risk for placental abruption (Eubanks, 2021). One metaanalysis of 1.6 million pregnancies in smokers found a twofold risk (Ananth, 1999). This risk was five- to eightfold if smokers had chronic hypertension, severe preeclampsia, or both. Similar findings are reported by others (Hogberg, 2007; Kaminsky, 2007). *Cocaine abuse* is linked, and in one series of 50 women who abused cocaine during pregnancy, eight had a stillbirth caused by placental abruption (Bingol, 1987).

Of potential serum markers, MSAFP, inhibin, and pregnancy-associated plasma protein in abnormal levels carry increased

risk (Ananth, 2017). Indeed, preliminary data shows that MSAFP levels >280 μg/L in the third trimester may be predictive (Ngai, 2012). Subclinical hypothyroidism or high levels of antithyroid antibodies have been associated with a two- to threefold higher risk for placental abruption (Abbassi-Ghanavati, 2010; Maraka, 2016). Lupus anticoagulant is associated with maternal floor infarction of the placenta but is less so with typical abruptions. Women affected by some of the thrombophilias have higher associated rates of thromboembolic events during pregnancy, however, no convincing evidence supports a link between thrombophilias and placental abruption (American College of Obstetricians and Gynecologists, 2019; 2020).

Diagnosis

The signs and symptoms of placental abruption can vary considerably. Classically, affected women have a sudden onset of abdominal pain, vaginal bleeding, and uterine tenderness. In an earlier study, 78 percent had vaginal bleeding, 66 percent had uterine tenderness or back pain, and 60 percent had a nonreassuring fetal status (Hurd, 1983). Other findings included frequent contractions and persistent hypertonus. However, in a fifth, preterm labor was diagnosed, and placental abruption was not suspected until fetal distress or death followed.

In some women, external bleeding can be profuse, yet placental separation may not be so extensive as to compromise the fetus. In others, external bleeding is absent, but the placenta is sufficiently sheared off to kill the fetus—a concealed abruption. In either case, bleeding can be massive and leads to hypovolemic shock. In an earlier report from Parkland Hospital, Pritchard and Brekken (1967) described 141 women with abruption so severe as to kill the fetus. Blood loss in these women often amounted to at least half of their pregnant blood volume.

Consumptive Coagulopathy

With placental abruption, some degree of intravascular coagulation is almost universal. Placental abruption is the most common cause of clinically profound consumptive coagulopathy in obstetrics and probably in all specialties (Cunningham, 2015). A primary consequence of intravascular coagulation is the activation of plasminogen to plasmin, which then lyses fibrin microemboli to maintain microcirculatory patency. With placental abruption severe enough to kill the fetus, pathological levels of fibrinogen–fibrin degradation products and D-dimers are almost always found in maternal serum (Erez, 2015). Their quantification is not clinically useful.

In a third of women with an abruption severe enough to kill the fetus, the plasma fibrinogen level will be <150 mg/dL. These levels are dependent on the maternal preabruption fibrinogen level, and thus higher levels are "protective" (Cunningham, 2015; Wang, 2016). Clinically significant low levels may cause troublesome surgical bleeding, and measurement of levels assists fibrinogen-replacement efforts. Levels of several other coagulation factors also are variably decreased. These are not specifically measured in DIC, but factors are replaced empirically with fresh frozen plasma as a part of massive transfusion protocols (Chap. 44, p. 772). In addition, thrombocytopenia, sometimes profound, may accompany severe hypofibrinogenemia and can be common after repeated blood transfusions. This "dilutional coagulopathy" is additive to DIC (Chap. 44, p. 772).

Consumptive coagulopathy is more likely with a concealed abruption because intrauterine pressure is higher. This forces more thromboplastin into the large veins draining the implantation site. With a partial abruption and a live fetus, severe coagulation defects are less common. Our experience has been that if serious coagulopathy develops, it is usually evident by the time abruption symptoms appear. In one unusual case, a woman cared for at Parkland Hospital presented with a nosebleed. She had no pain or vaginal bleeding, but her fetus was dead. Her blood did not clot, and the plasma fibrinogen level was 25 mg/dL. A total placental abruption was confirmed at delivery.

Couvelaire Uterus

At the time of cesarean delivery, it is not uncommon to find widespread extravasation of blood into the uterine musculature and beneath the serosa (Fig. 43-5). This phenomenon is named after Couvelaire, who in the early 1900s termed it *uteroplacental apoplexy*. These myometrial hemorrhages may incite uterine atony, but are not a sole indication for hysterectomy. Effusions of blood may collect beneath the tubal serosa, between the leaves of the broad ligaments, in the ovaries, or in the peritoneal cavity.

End-organ Injury

Acute kidney injury (AKI) is a general term describing renal dysfunction from many causes (Chap. 56, p. 1006). Delayed or incomplete treatment of hypovolemia is one. However, even with placental abruption complicated by severe DIC, prompt and vigorous treatment with blood and crystalloid solutions usually prevents significant renal dysfunction. The risk for renal injury with placental abruption rises when preeclampsia

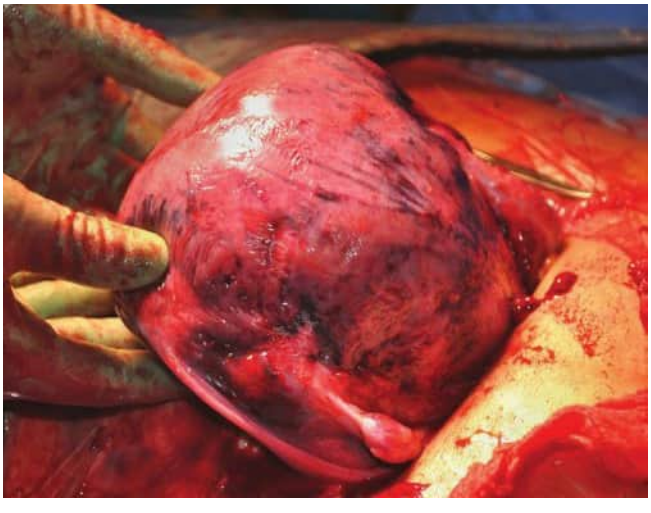


FIGURE 43-5 Couvelaire uterus from total placental abruption after cesarean delivery. Blood markedly infiltrates the myometrium to reach the serosa. (Reproduced with permission from Dr. Steven Blaine Holloway.)

coexists (Alexander, 2015; Drakeley, 2002). Most cases of AKI are reversible, do not require dialysis, and generally have good long-term outcomes (Arazi, 2015). However, irreversible acute cortical necrosis occasionally stems from placental abruption (Gopalakrishnan, 2015).

Rarely, pituitary failure—*Sheehan syndrome*—follows severe intrapartum or early postpartum hemorrhage. Described in Chapter 61 (p. 1104), the exact pathogenesis is not well understood, especially because endocrine abnormalities are infrequent even in women who suffer catastrophic hemorrhage (Matsuwaki, 2014).

Differential Diagnosis

Severe placental abruption usually is obvious. However, less severe forms are not always recognized with certainty, and the diagnosis becomes one of exclusion. Unfortunately, no laboratory tests or other diagnostic methods accurately confirm lesser degrees of placental separation. Sonography has limited use because the placenta and fresh clots may have similar imaging characteristics. In a study of 149 women with a suspected placental abruption, the sensitivity for sonography was only 24 percent (Glantz, 2002). Thus, negative findings with sonographic examination do not exclude placental abruption. Conversely, magnetic resonance (MR) imaging is highly sensitive for placental abruption and should be considered if the diagnostic information would change management (Masselli, 2011). Last, elevated serum levels of D-dimers may be suggestive, but this has not been adequately tested.

Thus, in the woman with vaginal bleeding and a live fetus, placenta previa and other bleeding causes are sought with clinical and sonographic evaluation. It has long been taught—perhaps with some justification—that painful uterine bleeding signifies placental abruption, whereas painless uterine bleeding indicates placenta previa. The differential diagnosis is usually not this straightforward, and labor accompanying previa may cause pain that suggests placental abruption. Conversely, pain from placental abruption may mimic normal labor, or it may be painless, especially with a posterior placenta. At times, the vaginal bleeding source remains obscure even after delivery.

■ Management

Treatment varies depending on maternofetal clinical condition, gestational age, and amount of associated hemorrhage. With a living viable-aged fetus and with vaginal delivery not imminent, emergency cesarean delivery is chosen by most. In some women, fetal compromise will be evident as shown in Figure 43-6. When evaluating fetal status, sonographic confirmation of fetal heart activity may be necessary because sometimes an electrode applied directly to a dead fetus will provide misleading information by recording the maternal heart rate (Chap. 24, p. 447).

If the fetus has died or if it is not considered sufficiently mature to live outside the uterus, vaginal birth is preferable for the mother. In either case, prompt and intensive resuscitation with blood products and crystalloids is begun. These measures are lifesaving for the mother and hopefully for her fetus. If the diagnosis of placental abruption is uncertain and the fetus is alive and without evidence of compromise, close observation may be warranted provided that immediate intervention is available. Colón and coworkers (2016) performed a randomized trial and found no benefits to magnesium sulfate tocolysis given to women with a preterm "nonsevere" abruption at 24 to 34 weeks' gestation.

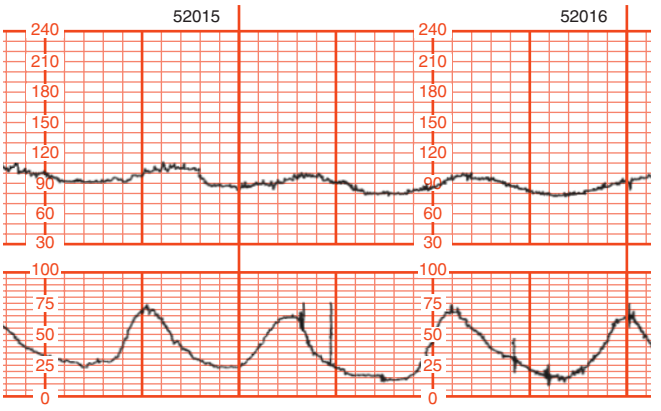


FIGURE 43-6 Placental abruption with fetal compromise. Lower panel: Uterine hypertonus with a baseline pressure of 20 to 25 mm Hg and frequent contractions peaking at approximately 75 mm Hg. Upper panel: The fetal heart rate demonstrates baseline bradycardia with repetitive late decelerations.

Cesarean Delivery

The compromised fetus is usually best served by cesarean delivery, and the speed of response is an important factor in perinatal outcomes. In one study of 33 singleton pregnancies with a clinically overt placental abruption and fetal bradycardia, 15 of the 22 neurologically intact survivors were delivered within a 20-minute decision-to-delivery interval (Kayani, 2003). However, eight of 11 infants who died or developed cerebral palsy were delivered after a 20-minute intervals. Onishi and colleagues (2019) also found a significant negative correlation between these intervals and cord arterial pH. At Parkland Hospital, placental abruption was one of the most powerful antecedents to body-cooling treatment for neonatal encephalopathy (Nelson, 2014).

A major hazard to cesarean delivery is imposed by clinically significant consumptive coagulopathy. Preparations include two large-bore intravenous catheters and plans for blood and component replacement. Measures of hemoglobin, platelet, and fibrinogen levels as well as protime (PT) and partial thromboplastin time (PTT) guide product replacement.

Vaginal Delivery

If the fetus has died, vaginal delivery is usually preferred. As reviewed earlier, hemostasis at the placental implantation site depends primarily on myometrial contraction and not blood coagulability. Thus, after vaginal delivery, uterotonic agents and uterine massage are used to stimulate myometrial contractions. Uterine muscle fibers compress placental site vessels and prompt hemostasis even if coagulation is defective. In some instances, vaginal delivery may not be preferable, even with a dead fetus. One example is brisk hemorrhage that cannot be successfully managed by vigorous blood replacement. Others

are the myriad obstetrical complications that prohibit vaginal delivery in general. In some women with extensive placental abruption, labor tends to be rapid because the uterus is usually persistently hypertonic (see Fig. 43-6). This can magnify fetal compromise. In some cases, baseline intraamnionic pressures reach 50 mm Hg or higher, and with contractions, pressures may attain levels exceeding 100 mm Hg. Overall, however, first- and second-stage labor does not appear to be shorter than usual (Downes, 2017).

Early amniotomy has long been championed in the management of placental abruption. This ostensibly achieves better spiral artery compression to diminish implantation site bleeding and reduce thromboplastin infusion into the maternal vascular system. Although evidence supporting this theory is lacking, membrane rupture may hasten delivery. However, if the fetus is small, the intact sac may be more efficient in promoting cervical dilation. If rhythmic uterine contractions are not superimposed on baseline hypertonus, oxytocin is given in standard doses. No data indicate that oxytocin augments thromboplastin escape into the maternal circulation to worsen coagulopathy. In light of hypertonus associated with placental abruption, misoprostol may be a less favored induction agent due to its association with uterine tachysystole.

In the past, some had set arbitrary time limits to permit vaginal delivery. Instead, experiences illustrate that maternal outcome depends on the diligence with which adequate fluid and blood replacement therapy are pursued rather than on the interval to delivery. Observations from Parkland Hospital described by Pritchard and Brekken (1967) are similar to those from the University of Virginia reported by Brame and associates (1968). Specifically, women with severe abruption who were transfused during 18 hours or more before delivery had similar outcomes to those in whom delivery was accomplished sooner.

Expectant Management

If possible, delaying delivery may benefit an immature fetus. In one series, 43 women with placental abruption before 35 weeks' gestation were expectantly managed, and 31 of them were given tocolytic therapy (Bond, 1989). The mean interval until delivery for all 43 approximated 12 days. Cesarean delivery was performed in 75 percent, and there were no stillbirths. As discussed earlier, women with a very early abruption may develop *chronic abruption–oligohydramnios sequence*. In one report, four women with an abruption at a mean gestational age of 20 weeks subsequently developed oligohydramnios and delivered at an average gestational age of 28 weeks (Elliott, 1998). In another description of 256 women with an abruption at <28 weeks' gestation, a mean of 1.6 weeks was gained (Sabourin, 2012). Of the group, 65 percent were delivered before 29 weeks, and half of all women underwent emergent cesarean delivery.

Unfortunately, even continuous fetal heart rate monitoring does not guarantee universally good outcomes. A normal tracing may precede sudden further separation with instant fetal compromise. In some of these, if the separation is sufficient, the fetus will die before it can be delivered. Tocolysis is advocated by some for suspected abruption if the fetus does not display compromise. Some investigators have observed that tocolysis improved outcomes in a highly selected cohort of women with preterm pregnancies (Bond, 1989; Combs, 1992). In another study, Towers and coworkers (1999) administered magnesium sulfate, terbutaline, or both to 95 of 131 women with abruption diagnosed before 36 weeks' gestation. The perinatal mortality rate was 5 percent in both groups with or without tocolysis. Similar results were reported from a randomized trial (Colón, 2016). A clinical consideration to the use of tocolytic agents, such as terbutaline, is that the drug-induced tachycardia may mask maternal compromise. We are of the opinion that suspected placental abruption contraindicates tocolytic agent use.

PLACENTA PREVIA

Classification

The Latin *previa* means going *before*, and in this sense, the placenta goes before the fetus into the birth canal. *Placenta previa* describes a placenta that is implanted somewhere in the lower uterine segment, either over or very near the internal cervical os. Because these anatomical relationships cannot always be precisely defined and because they frequently change across pregnancy, terminology can sometimes be confusing.

Terminology for placenta previa has evolved, and the National Institutes of Health (NIH)-sponsored Fetal Imaging Workshop (Reddy, 2014) recommends the following classification:

- Placenta previa: the internal os is covered partially or completely by placenta (Figs. 43-7 and 43-8). In the past, these were further classified as either total or partial previa.
- Low-lying placenta: implantation in the lower uterine segment is such that the placental edge does not cover the internal os but lies within a 2-cm wide perimeter around the os. A previously used term, *marginal previa*, described a placenta that was at the edge of the internal os but did not overlie it.

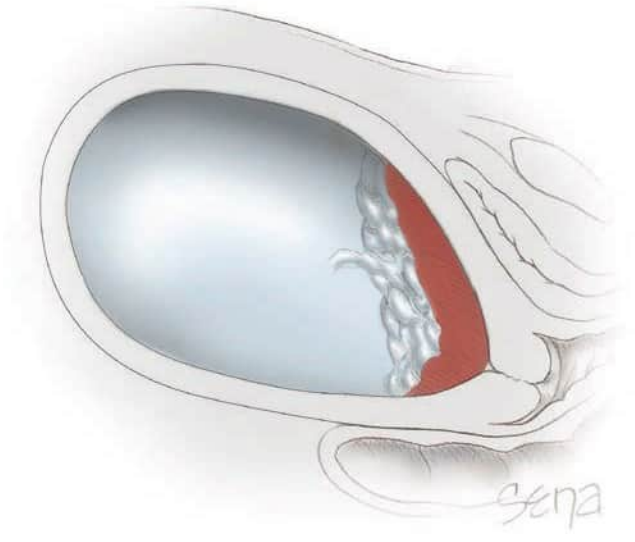


FIGURE 43-7 Placenta previa showing that copious hemorrhage could be anticipated with any cervical dilation.

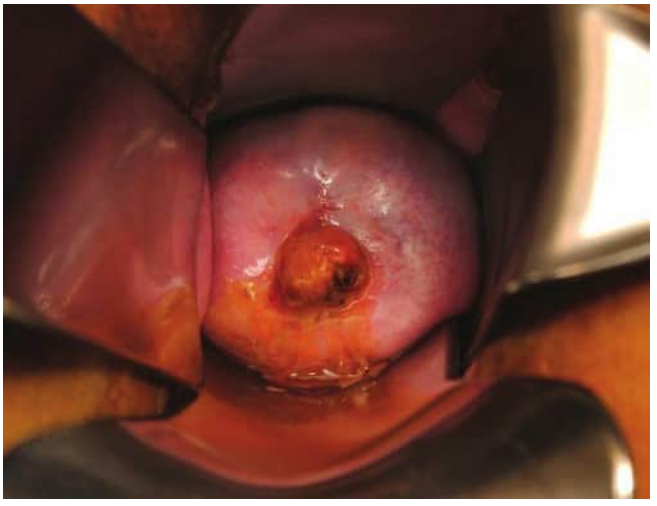


FIGURE 43-8 On speculum examination, placenta is visible protruding through the cervical os. (Reproduced with permission from Dr. Maureen E. Flowers.)

Clearly, the classification of some cases will depend on cervical dilation at the time of assessment. For example, a low-lying placenta at 2-cm dilation may become a partial placenta previa at 4-cm dilation because the cervix has opened to expose the placental edge. Conversely, a placenta previa that appears to be total before cervical dilation may become partial at 4-cm dilation because the cervical opening now extends beyond the edge of the placenta. *Digital palpation in an attempt to ascertain these changing relations between the placental edge and internal os as the cervix dilates usually causes severe hemorrhage!*

With any degree of placenta previa, a certain amount of spontaneous placental separation is inevitable during lower uterine segment remodeling and cervical dilation. Although this frequently causes bleeding and thus technically constitutes a placental abruption, this term is usually not applied in these instances.

Somewhat but not always related is *vasa previa*, in which fetal vessels course through membranes and present at the cervical os. Vasa previa has been reviewed by the Society for Maternal–Fetal Medicine (2015) and is discussed in Chapter 6 (p. 115).

Placental Migration

Beginning with the use of sonography in obstetrics, the term *placental migration* was coined to describe the apparent movement of the placenta away from the internal os (King, 1973). Obviously, the placenta does not actually move, and the mechanism of apparent movement is not completely understood. To begin with, migration is clearly a misnomer, because decidual invasion anchors chorionic villi.

Explanations of placental migration are likely additive. First, apparent movement of the low-lying placenta relative to the internal os is related to the imprecision of two-dimensional sonography. Second, as pregnancy progresses, growth of the lower and upper uterine segments differs. With greater blood flow in the upper uterus, placental growth toward this supply, termed *trophotropism*, is thus more likely directed toward the fundus. Many of those placentas that "migrate" most likely never were circumferentially implanted with true villous invasion that reached the internal cervical os. *Importantly, a low-lying placenta or placenta previa is less likely to "migrate" if there is a prior cesarean delivery scar*.

The frequency of placental migration has been quantified. In one study of 4300 women at midpregnancy, 12 percent had a low-lying placenta (Sanderson, 1991). Of placentas not covering the internal os, previa did not persist, and none subsequently had placental hemorrhage. Conversely, approximately 40 percent of placentas that covered the os at midpregnancy continued to do so until delivery. Thus, placentas that lie close to but not over the internal os until the early third trimester are unlikely to persist as a previa by term (Heller, 2014; Parrott, 2015). The chance that placenta previa persists increases with a hysterotomy scar (Kohari, 2012; Oyelese, 2006).

Incidence and Associated Factors

The incidence of placenta previa has risen during the past 30 years. Reported incidences average about 0.4 percent or 1 case per 250 to 400 deliveries (Hill, 2020). The frequency at Parkland Hospital from 1988 through 2003 for nearly 250,000 births was 2.6 cases per 1000. For the 2004 to 2020 epoch, it rose to 3.8 cases per 1000. Similar frequencies have been reported from Austria, Finland, and Israel (Kollmann, 2016; Räisänen, 2014; Rosenberg, 2011).

Several demographic factors may contribute to this higher rate of placenta previa. First, maternal age increases the frequency (Biro, 2012; Roberts, 2012). In the First- and Second-Trimester Evaluation of Risk (FASTER) trial, which included more than 36,000 women, the frequency of previa was 0.5 percent for women <35 years compared with 1.1 percent in those ≥35 years (Cleary–Goldman, 2005). At Parkland Hospital, the incidence ranged from a rate of approximately 0.65 cases per 1000 births for women ≤19 years to almost 10 cases per 1000 births for women older than 35.

Multiparity also elevates the rate of placenta previa (Räisänen, 2014). Obviously, the effects of advancing maternal age and parity are confounding. Still, Babinszki and colleagues (1999) reported that the 2.2-percent incidence in women with parity of five or greater was significantly higher than that of women with lower parity. The interpregnancy interval does not affect this rate (Fox, 2015).

Cigarette smoking increases the relative risk of placenta previa at least twofold (Usta, 2005). It has been postulated that carbon monoxide hypoxemia causes compensatory placental hypertrophy and greater surface area. Smoking may also be related to decidual vasculopathy.

Several clinical characteristics also raise placenta previa risks. Foremost, women with one or more *prior cesarean deliveries* are at greater risk for subsequent placental disorders that include placenta previa, placental abruption, or placenta accreta spectrum (PAS) (Gibbins, 2018; Klar, 2014). The cumulative risks for placenta previa that accrue with the increasing number of cesarean deliveries are extraordinary. In one MFMU Network study of 30,132 women undergoing cesarean delivery, the incidence was 1.3 percent for those with only one prior cesarean

delivery, but it was 3.4 percent if there were six or more prior cesareans (Silver, 2006). In a retrospective cohort of nearly 400,000 women who were delivered of two consecutive singletons, those with a cesarean delivery for the first pregnancy had a 1.6-fold greater rate for previa in the second pregnancy (Gurol-Urganci, 2011). These same investigators reported a 1.5-fold higher rate from six similar population-based studies. This risk is increased eightfold in women with parity greater than four and who have more than four prior cesarean deliveries (Gilliam, 2002).

Importantly, women with a prior uterine incision and placenta previa have an increased likelihood that cesarean hysterectomy will be necessary because of associated PAS (p. 761). In one study, 6 percent of women with a primary cesarean delivery for placenta previa required a hysterectomy. This rate was 25 percent for women with a placenta previa undergoing repeat cesarean delivery (Frederiksen, 1999).

Multifetal gestation raises placenta previa risk (Ananth, 2003a; Luke, 2017a). Compared with monochorionic twins, dichorionic ones show higher rates, which perhaps stems from having two implantation sites (Weis, 2012).

MSAFP levels, if abnormally elevated for otherwise unexplained reasons during prenatal screening, raise the risk for placenta previa and a host of other abnormalities. Moreover, women with a placenta previa and comorbid MSAFP level >2.0 multiples of the median (MoM) at 16 weeks' gestation were at greater risk for late-pregnancy bleeding and preterm birth (Chap. 17, p. 338).

Assisted reproductive technology (ART) used for conception elevates placenta previa rates. Some of this association may derive from overlapping effects. First, older women constitute a significant portion of patients electing ART (Luke, 2017b). Second, even adjusting for multifetal gestation, ART is still associated with higher previa rates (Karami, 2018). Last, in one systematic review including nearly 256,000 births, uterine leiomyomas were associated with higher placenta previa rates (Jenabi, 2019).

Clinical Features

Painless bleeding is the most characteristic event with placenta previa. Bleeding usually does not develop until near the end of the second trimester or later, but it can begin even before midpregnancy. Undoubtedly, some late abortions are caused by an abnormally located placenta. Initial bleeding from a previa usually begins without warning, and this *sentinel bleed* is rarely so profuse as to prove fatal. Usually it ceases, only to recur. However, in perhaps 10 percent of women, particularly those with a placenta implanted near but not over the cervical os, bleeding is delayed until labor onset. Bleeding at this time varies in degree, and it may mimic placental abruption.

In cases in which the placenta is located over the internal os, a specific sequence of events leads to bleeding. First, the uterine body remodels to form the lower uterine segment. With this, the internal os dilates, and some of the implanted placenta inevitably separates. Bleeding that ensues is augmented by the inherent inability of myometrial fibers in the lower uterine segment to contract and thereby constrict torn vessels. Similarly, bleeding from this lower-segment implantation site also frequently continues after placental delivery. Last, lacerations in the friable cervix and lower segment will bleed. These may be especially problematic following manual removal of a somewhat adhered placenta.

Cervical length may alter the clinical course. Stafford (2010) but not Trudell (2013), both with their associates, found that a placenta previa and a third-trimester cervical length <30 mm increased the risks for hemorrhage, uterine activity, and preterm birth. Similarly, Friszer (2013) but not Trudell (2013), both with their coworkers, showed that women admitted for bleeding had a greater chance of delivery in the subsequent 7 days when the cervical length measured <25 mm sonographically.

Placenta accreta spectrum is a frequent and serious complication associated with placenta previa. This abnormal placental attachment derives in part from poorly developed decidua that lines the lower uterine segment. Biswas and coworkers (1999) performed placental bed biopsies in 50 women with a placenta previa and in 50 control women. Infiltration of spiral arterioles by trophoblastic giant cells, rather than by the expected endovascular trophoblast cells, was found in half of specimens. In contrast, only 20 percent of biopsies from normally implanted placentas had these changes. In another study of 514 cases of placenta previa, abnormal placental attachment was identified in 7 percent (Frederiksen, 1999). As discussed, placenta previa overlying a prior cesarean incision conveys a particularly high risk for PAS.

Coagulopathy rarely complicate placenta previa, even when implantation site separation is extensive (Cunningham, 2015). Placental thromboplastin, which incites the intravascular coagulation seen with placental abruption, is presumed to readily escape through the cervical canal rather than be forced into the maternal circulation. The paucity of large myometrial veins in this area also may be protective.

Diagnosis

For uterine bleeding after midpregnancy, placenta previa and placental abruption are always considered. In one Canadian study, placenta previa accounted for 21 percent of women admitted from 22 to 28 weeks' gestation with vaginal bleeding (Sabourin, 2012). Previa should not be excluded until sonographic evaluation has clearly proved its absence. If sonography is not readily available, diagnosis by digital cervical examination is done in an operating room and with preparations in place for operative delivery. We call these preparations a *double set-up technique*. *Even the gentlest examination can cause torrential hemorrhage.*

Using standard sonographic techniques, quick and accurate placental localization can be accomplished (American Institute of Ultrasound in Medicine, 2018). This is usually done with transabdominal sonography. If the placenta clearly overlies the cervix or if it lies away from the lower uterine segment, the examination has excellent sensitivity and negative predictive value (Olive, 2006; Quant, 2014). Obese women may hinder clear viewing of the lower uterine segment. A full bladder may artificially elongate the cervix and compress the lower uterine

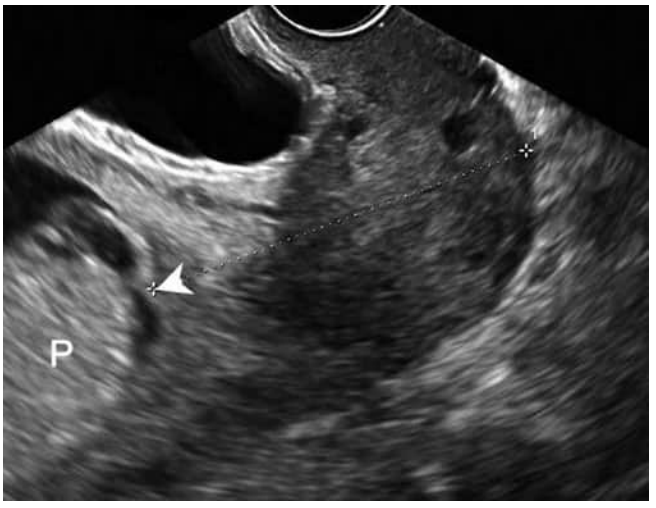


FIGURE 43-9 In this transvaginal image at 21 weeks' gestation, the posterior placenta (*P*) completely covers the internal cervical os (*arrowhead*). The dotted line represents the cervical canal.

segment to give the impression that the placenta overlies the cervix.

If placental location remains unclear, transvaginal sonography is the most accurate sonographic method and is safe even with vaginal bleeding (Fig. 43-9). In a comprehensive study, the internal os was visualized in all cases with transvaginal sonography but in only 30 percent with transabdominal sonography (Farine, 1988). As discussed, if the placental edge lies <2 cm from the internal os, but not covering it, the placenta is considered low lying (Reddy, 2014). In the absence of any other indication, sonography need not be frequently repeated simply to document placental position. At Parkland Hospital, women with placenta previa identified at 18 to 22 weeks' gestation and a prior cesarean delivery are reevaluated sonographically at 28 weeks and again at 32 weeks if it persists. Those with a placenta previa but without prior cesarean delivery undergo reimaging at 32 weeks. Restriction of activity is not necessary unless a previa persists beyond 28 weeks' gestation or if clinical findings such as bleeding or contractions develop before this time. At 32 weeks' gestation, if the placental edge is still <2 cm from the os, transvaginal sonography is repeated at 36 weeks' gestation.

Using MR imaging, several investigators report excellent visualization of placental abnormalities. However, it is unlikely that this modality will replace sonography for routine evaluation anytime soon given availability and cost differences compared with sonography. However, MR imaging is useful for evaluation of PAS (p. 761).

■ Management

Care with placenta previa is individualized, and three prominent factors include fetal maturity, associated labor, and bleeding severity. In one study of 214 women with a placenta previa, 43 percent had an emergency delivery, and half of these were preterm (Ruiter, 2015). Instead, if active bleeding subsides and the fetus is immature, close observation in an obstetrical unit is indicated. Data are sparse regarding tocolytic administration for uterine contractions. Although robust randomized trials are lacking, Bose and colleagues (2011) recommend that if tocolytics are given, they be limited to 48 hours of administration. As noted earlier, the physiological cardiovascular responses to tocolytic agents that include hypotension and tachycardia can mask maternal compromise. We categorically recommend against their use in this setting.

After bleeding has ceased for approximately 2 days and the fetus is judged to be healthy, a woman can usually be discharged home with instructions for "pelvic rest." The Society for Maternal–Fetal Medicine (2018) does not recommend routine cervical length screening in these women. Importantly, the woman and her family must appreciate the possibility of recurrent bleeding and be prepared for immediate transport back to the hospital. In other cases, prolonged hospitalization may be necessary.

The frequency of emergency delivery in women with placenta previa ranges from 25 to 40 percent (Erfani, 2019; Gibbons, 2018). In properly selected patients, however, long-term inpatient care does not appear to add benefits compared with outpatient management (Neilson, 2003). In one randomized study of 53 women who had a bleeding previa at 24 to 36 weeks' gestation, maternal or fetal morbidity rates did not differ between management methods (Wing, 1996). Of all study women, 60 percent had recurrent bleeding, and half eventually required expeditious cesarean delivery.

For women who are near term and who are not bleeding, plans are made for scheduled cesarean delivery. A planned delivery in a controlled setting is optimal, and timing balances fetal immaturity against antepartum hemorrhage. The American College of Obstetricians and Gynecologists and Society for Maternal–Fetal Medicine (2021) recommend delivery for otherwise uncomplicated placenta previa between $36^{0/7}$ and $37^{6/7}$ weeks. At Parkland Hospital, we usually perform elective cesarean delivery at $38^{0/7}$ weeks. Recommendations for delivery of women with PAS are outlined in that section.

■ Delivery

Practically all women with placenta previa undergo cesarean delivery. Some recommend a vertical laparotomy incision to provide rapid entry if bleeding is torrential or if generous operating space is required for hysterectomy. As discussed, cesarean delivery is emergently performed in more than half because of hemorrhage, for which about a fourth require blood transfusion (Sabourin, 2012). Although a low transverse hysterotomy is usually possible, this may cause fetal bleeding if the placenta is implanted anteriorly and the placenta is incised. In such cases, fetal delivery should be expeditious (Silver, 2015a). Thus, a vertical uterine incision may be preferable in some instances. In either case, even when the incision extends through the placenta, maternal or fetal outcomes are rarely compromised.

Following placental removal, the implantation site may bleed uncontrollably due to poorly contracted smooth muscle, which is characteristic of the lower uterine segment. If hemostasis at the placental implantation site cannot be obtained by uterotonic agent administration and pressure, it can be oversewn with no. 0 chromic sutures. Cho and associates (1991) described placing interrupted sutures at 1-cm intervals to form

a circle around the bleeding portion of the lower segment to control hemorrhage. Others have reported success with compression sutures that traverse and compress the anterior and posterior uterine wall (Mohamed, 2019; Sallam, 2019).

Of other methods, Bakri or Foley balloon tamponade used alone or coupled with compression sutures has been described (Albayrak, 2011; Diemert, 2012). Other surgical options are bilateral uterine or internal iliac artery ligation, illustrated in Chapter 44 (p. 779). Pelvic artery embolization also has gained acceptance. Yu and colleagues (2020) performed a randomized trial of perioperative prophylactic internal iliac artery balloon occlusion during cesarean delivery for placenta previa and found that deployment did not reduce postpartum hemorrhage or alter maternal or neonatal morbidity.

If these more conservative methods fail and bleeding is brisk, hysterectomy is necessary. Placenta previa—especially with PAS—currently is a common indication for peripartum hysterectomy at Parkland Hospital and other institutions (Jakobsson, 2015; Wong, 2011). In cases without PAS, the reported incidence of hysterectomy with placenta previa is 2 percent (Gibbins, 2018).

Thus, it is not possible to accurately estimate the effect on the hysterectomy rate from placenta previa alone without considering the associated PAS. *Again, for women whose placenta previa is implanted anteriorly at the site of a prior uterine incision, the likelihood of an associated morbidly adherent placenta and need for hysterectomy is increased.* In a study of 318 peripartum hysterectomies performed in the United Kingdom, 40 percent were done for abnormal placentation (Knight, 2007). At Parkland Hospital, 44 percent of cesarean hysterectomies were done for bleeding placenta previa or for PAS (Wortman, 2015). The technique for peripartum hysterectomy is described in Chapter 30 (p. 560).

■ Maternal and Perinatal Outcomes

Placenta previa and coexistent PAS both contribute substantively to maternal morbidity and mortality rates. The maternal mortality ratio is increased approximately threefold for women with a placenta previa (Gibbins, 2018). In a report of 5367 maternal deaths in the United States from 2006 to 2013, placenta previa alone accounted for nearly 3 percent of deaths from hemorrhage (Creanga, 2014, 2017).

The report from the Consortium on Safe Labor emphasizes the ongoing perinatal morbidity with placenta previa (Lai, 2012). In these cases, preterm delivery continues to be a major cause of perinatal death (Balachandar, 2020; Nørgaard, 2012; Salihu, 2003). Ananth and colleagues (2003b) reported a comparably elevated risk of neonatal death even for fetuses who delivered at term. This is at least partially related to the fetal anomaly rate, which is two- to threefold higher in pregnancies with placenta previa (Crane, 1999; Kancherla, 2015).

The association of fetal-growth restriction with placenta previa is likely minimal after controlling for gestational age. In a population-based cohort of more than 500,000 singleton births, most low-birthweight newborns associated with placenta previa resulted from preterm birth (Ananth, 2001). From their large metaanalysis, Balayla and coworkers (2019) found a slightly increased frequency of fetal-growth restriction. At least two other studies reported an elevated risk (Räisänen, 2014; Weiner, 2016). Apparently, fetal growth effects are similar with placenta previa and PAS (Jauniaux, 2019).

PLACENTA ACCRETA SPECTRUM

The term *placenta accreta spectrum (PAS)* describes aberrant placentation characterized by abnormally implanted, invasive, or adhered placenta. Derivation of accreta comes from the Latin *ac- + crescere*—to adhere or become attached to (Benirschke, 2012). It is also referred to as the morbidly adherent placenta, and in Europe it is referred to as a *pernicious placenta previa with accreta* and *abnormally adherent placenta*.

■ Etiopathogenesis

The major clinical problem is placental failure to separate normally from the myometrium after fetal delivery. This abnormal adherence stems in part from partial or total absence of the decidua basalis and imperfect development of the fibrinoid or Nitabuch layer, described in Chapter 5 (p. 85). If the decidual spongy layer is lacking either partially or totally, the physiological line of cleavage is absent, and some or all cotyledons are densely anchored. Microscopically, placental villi attach to smooth muscle fibers rather than to decidual cells. This decidual deficiency then prevents normal separation after delivery. The surface area involved at the implantation site and the depth of trophoblast ingrowth vary between women, but all affected placentas can potentially cause significant hemorrhage.

Data now suggest that PAS is not solely caused by the decidua's anatomical deficiency. Indeed, the cytotrophoblasts may control decidual invasion through factors such as angiogenesis (Duzyj, 2018; Goh, 2016). Moreover, some tissue specimens show immunologically mediated "hyperinvasiveness" (Harris, 2019). Some genes that code for remodeling and for adherence may be highly expressed (Matsukawa, 2019; Shainker, 2020). Myometrial fibers attached to the basal plate in an antecedent pregnancy are predictive markers for a subsequent PAS (Linn, 2015; Miller, 2016). This implies an antecedent "constitutional endometrial defect" in most cases. The greater risk conveyed by previous surgical uterine trauma may be partially explained by an enhanced vulnerability to trophoblast invasion (Einerson, 2020; Jauniaux, 2018).

This association with prior trauma is reinforced by the close relationship between *cesarean scar pregnancy (CSP)* and later development of PAS in the same pregnancy. Indeed, accruing evidence suggests that CSP and PAS lie on a spectrum and that CSP is a precursor (Happe, 2020; Timor-Tritsch, 2019). Described in Chapter 12 (p. 229), early rupture and hemorrhage with CSP are not uncommon, and women often elect pregnancy-terminating interventions to avoid these (Society for Maternal–Fetal Medicine, 2020; Timor-Tritsch, 2019).

■ Classification

Variants of PAS are classified by the depth of trophoblastic growth (Figs. 43-10 and 43-11). *Placenta accreta* indicates that

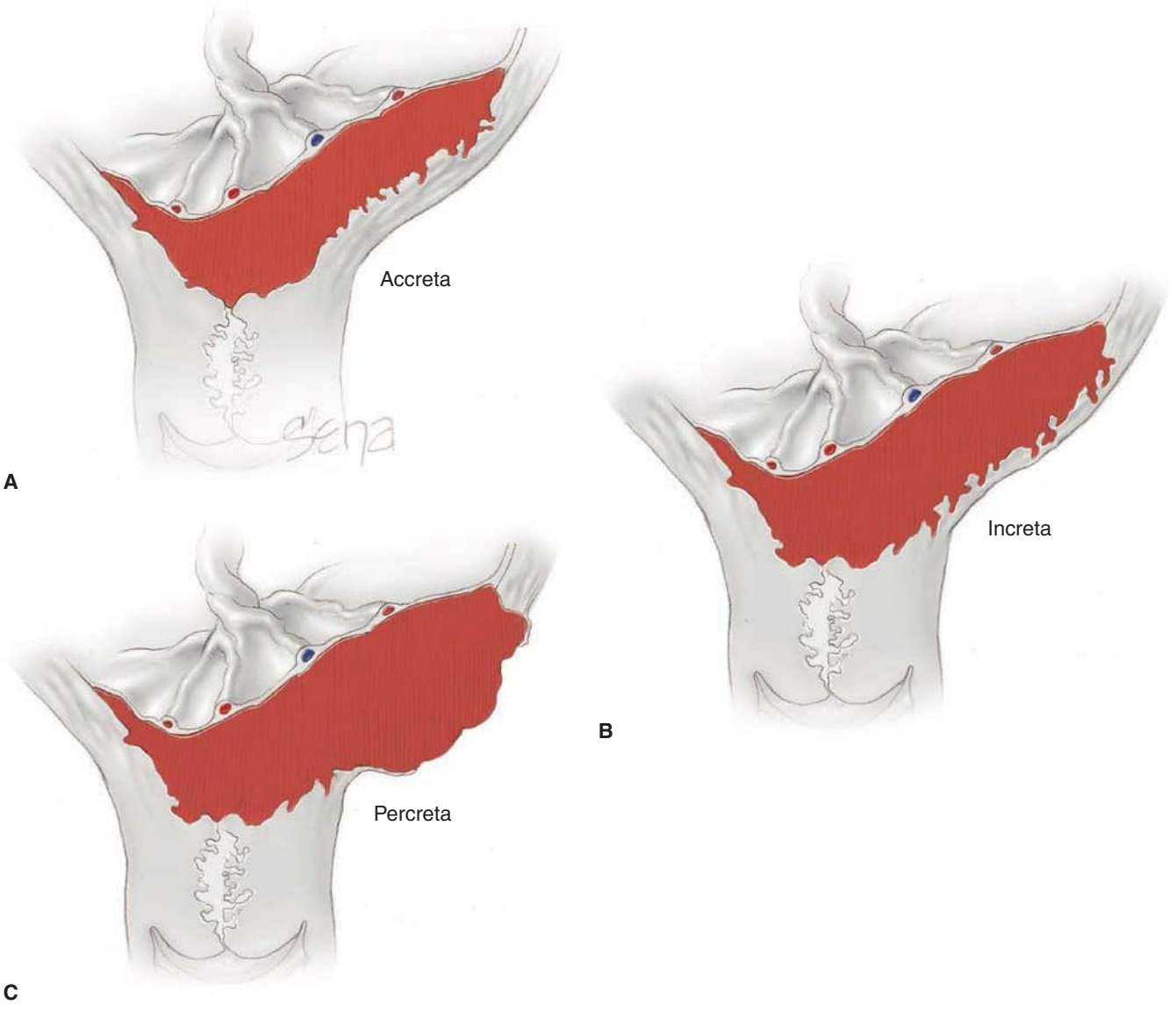


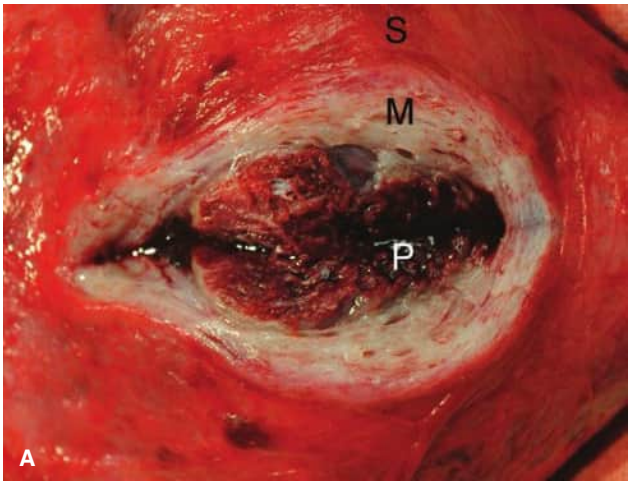
FIGURE 43-10 Placenta accreta spectrum. **A.** Placenta accreta. **B.** Placenta increta. **C.** Placenta percreta.

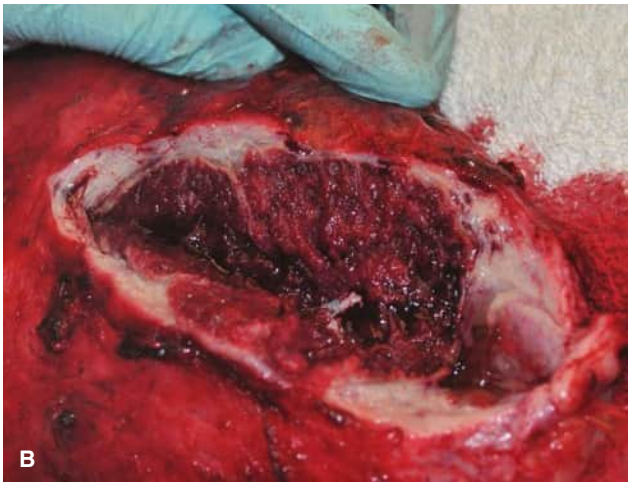
villi are attached to the myometrium. With *placenta increta*, villi actually invade the myometrium, and *placenta percreta* defines villi that penetrate through the myometrium and to or through the serosa (Silver, 2018). In clinical practice, these three variants are encountered in an approximate ratio of 80:15:5, respectively (Wong, 2008). At a referral center, however, the distribution was 22, 24, and 54 percent respectively (Birgani, 2020). In all three varieties, abnormal adherence may involve all lobules—*total placenta accreta*. If all or part of a single lobule is abnormally attached, it is described as *focal placenta accreta*. Histological diagnosis cannot be made from the placenta alone, and myometrial samples are necessary for confirmation (Jauniaux, 2021). Terminology for consistent classification has been lacking because of varying clinical criteria and lack of detailed pathological examinations. To alleviate this, the International Federation of Gynecology and Obstetrics (FIGO) has recently proposed a clinical classification system for PAS (Jauniaux, 2019).

Incidence and Risk Factors

Decades ago, the frequency of PAS was 1 in 20,000 births (McKeogh, 1951). As late as 1971, Hellman and Pritchard in the 14th edition of *Williams Obstetrics* described PAS as the subject of case reports. Since then, the incidence has grown remarkably in direct relationship to the rising cesarean delivery rate. For example, the incidence was 1 case in 2500 births in the 1980s, but it was 1 case per 731 births in a report from the MFMU Network comprising 115,502 women (Bailit, 2015). From the Nationwide Inpatient Sample, the PAS rate was an astounding 1 case in 270 births (Mogos, 2016).

This rising frequency has made PAS one of the most formidable problems in obstetrics. Of 5367 pregnancy-related maternal deaths in the United States from 2006 to 2013, 13 percent were due to hemorrhage caused by PAS (Creanga, 2015, 2017). In addition, PAS is a leading cause of hemorrhage and emergency peripartum hysterectomy (Awan, 2011; Eller, 2011; Rossi, 2010). The American College of Obstetricians and





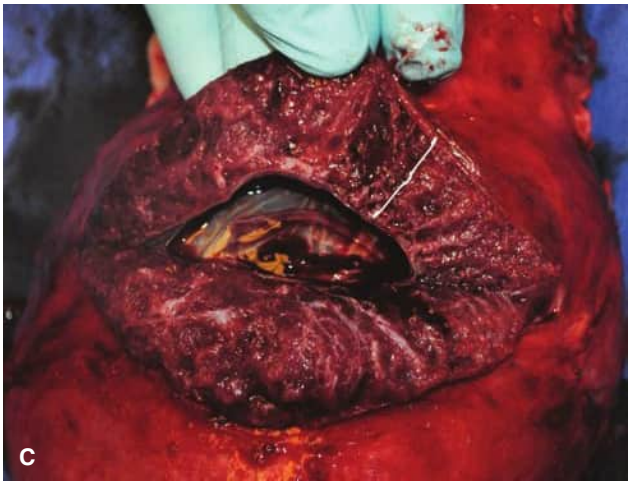


FIGURE 43-11 Varying degrees of myometrial invasion with placenta accreta spectrum disorders. Incisions begin on the serosal surface and extend through to the placenta. **A.** In this case, the myometrium (M) shows minimal invasion by the placenta (*P*). S = uterine serosa. **B.** A greater degree of myometrial invasion is seen here. **C.** In this example, the placenta (brackets) extends to the serosal edge, held by the surgeon's hand. No myometrium remains at this site. (Reproduced with permission from Dr. C. Edward Wells in Cunningham FG: Placenta previa and morbidly adherent placenta. In Yeomans ER, Hoffman BL, Gilstrap LC III, et al (eds): Cunningham and Gilstrap's Operative Obstetrics, 3rd edition. New York, McGraw Hill Education, 2017.)

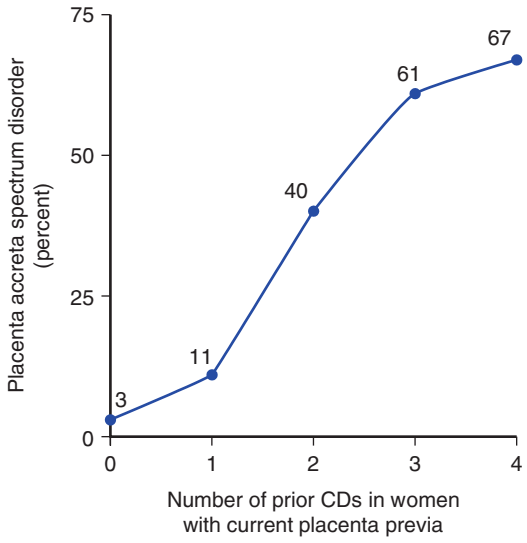


FIGURE 43-12 Frequency of placenta accreta spectrum in women with one to four prior cesarean deliveries (CDs) and now with a placenta previa.

Gynecologists and the Society for Maternal–Fetal Medicine (2018) have outlined optimal management. The International Society for Abnormally Invasive Placenta also has published guidelines (Collins, 2019).

In subsequent pregnancies following PAS, recurrence risks are high. Women in whom hysterectomy is avoided have an estimated 20-percent incidence of recurrence (Cunningham, 2016; Roeca, 2017). Some evidence shows that these women also have greater risks for placenta previa, uterine rupture, manual placental removal, preterm delivery, and hysterectomy (Baldwin, 2020; Eshkoli, 2013).

PAS risk factors are similar to those for placenta previa (p. 756). Shown in Figure 43-12, the two most important elements are an associated placenta previa, a prior cesarean delivery, or more likely both (Klar, 2014; Silver, 2006). A classical hysterotomy incision has a higher risk for subsequent PAS than a lower uterine segment one (Gyamfi-Bannerman, 2012). Of women with a prior cesarean delivery, almost half had myometrial fibers seen microscopically adhered to the placenta (Hardardottir, 1996; Miller, 2016). Dysfunctional decidua may also follow other myometrial trauma such as curettage or endometrial ablation (Baldwin, 2018; Gill, 2015). ART is an independent risk factor for PAS (Salmanian, 2020).

Other risk markers are prenatal MSAFP and human chorionic gonadotropin (hCG) used to screen for neural-tube defects and aneuploidies. In one study of more than 9300 women screened at 14 to 22 weeks' gestation, the risk for PAS was eightfold higher with MSAFP levels >2.5 MoM, and it was increased fourfold with maternal serum free β-hCG levels >2.5 MoM (Hung, 1999).

■ Diagnosis

With first- and second-trimester PAS, hemorrhage usually stems from a coexisting placenta previa. Such bleeding will typically prompt evaluation, and ideally sonography is used (Chantraine, 2013; Jauniaux, 2018).

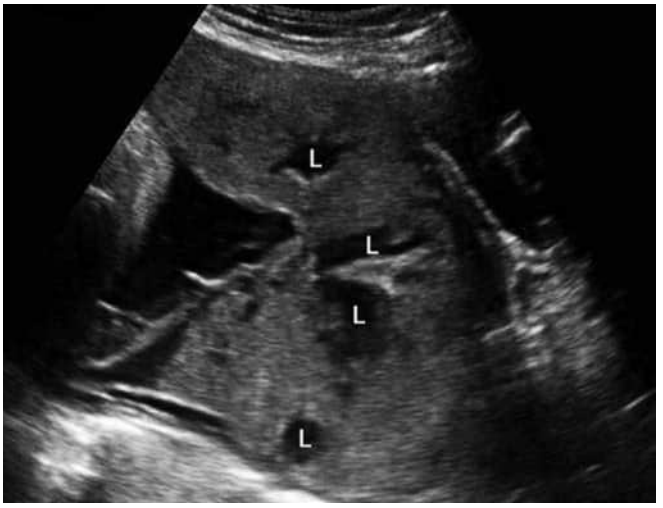


FIGURE 43-13 Transabdominal sonogram of placental percreta shows multiple and massive placental "lakes" or "lacunae" (*L*).

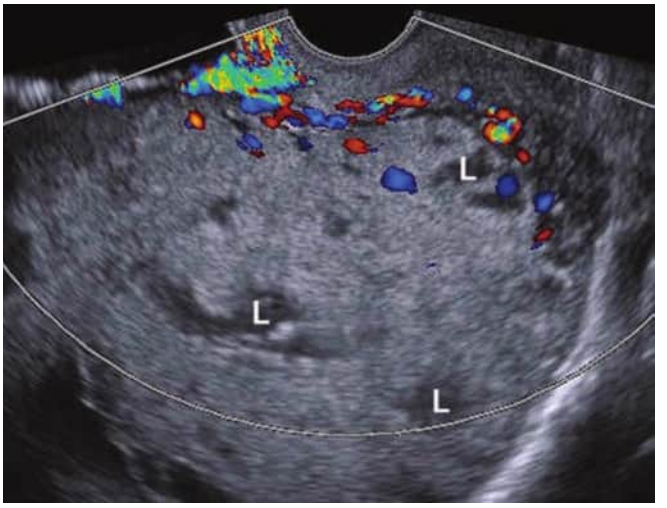


FIGURE 43-14 Transvaginal sonogram of placental invasion with a placenta percreta. Retroplacental vessels (color Doppler) invade the myometrium, and abnormal intraplacental venous lakes (*L*) are commonly seen in this setting.

With lesser degrees of bleeding, first-trimester measurement of the smallest myometrial thickness can help predict the later risk for peripartum hysterectomy with PAS (Happe, 2020). In a screening study of more than 22,000 singleton pregnancies at 11 to 13 weeks' gestation, 6 percent were at high risk for PAS (Panaiotova, 2019). However imaging was less than perfect to identify all of these placentas early. Subsequently, only 14 had a suspected clinical diagnosis, and 13 of these were confirmed at delivery.

Five characteristic sonographic findings suggest PAS: (1) placental lacunae; (2) thinning of the retroplacental myometrium; (3) disruption of the bladder-uterine serosal interface; (4) bridging vessels from the placenta to the bladder-serosal interface; and (5) placental bulge that pushes outward and distorts the contour of the uterus (Fig. 43-13). In a metaanalysis, the sensitivities of these criteria to identify placenta accreta, increta, and percreta were 91, 93, and 89 percent, respectively. Corresponding specificities were 97, 98, and 99 percent, respectively (Pagani, 2018).

These figures may be overestimated because of clinical bias and considerable interobserver variability (Silver, 2018). Some investigators report fewer spectacular results with sonography (Jauniaux, 2016; Primo, 2014). Bowman and colleagues (2014) described the sensitivity of sonography to be 54 percent; specificity, 88 percent; positive predictive value, 82 percent; negative predictive value, 65 percent; and accuracy, 65 percent. Location affects sonographic accuracy. Posterior placental location is associated with delayed diagnosis and increased surgical complications (Morgan, 2019; Tinari, 2021). In one study, the detection rate was 90 percent for anterior placenta accreta compared with 50 percent for posterior ones (Pilloni, 2016). Nageotte (2014) concluded that identification of PAS with sonography should be interpreted with clinical and operative findings.

Better results have been found by some using three-dimensional (3-D) sonography and power Doppler (Collins, 2015). We too have found that the addition of Doppler color flow mapping aids prediction of myometrial invasion (Fig. 43-14). Invasion is suspected if the distance between the uterine serosa–bladder wall interface and the retroplacental vessels measures <1 mm and if large intraplacental lacunae are seen (Rac, 2015a; Twickler, 2000). In another study, hypervascularity of the uterine serosa–bladder wall interface had the highest positive and negative predictive values for placenta percreta (Cali, 2013). Intracervical lakes also have been reported with placenta percreta (di Pasquo, 2020).

Yule and coworkers (2020) reported that the *placenta accreta index* was useful for diagnosis. This index incorporates the number of prior cesarean deliveries, placental location, lacunae, bridging vessels, and smallest myometrial distance. These investigators are also exploring first-trimester color mapping to develop a quantification algorithm (Yule 2021).

To further delineate anatomy, MR imaging can be added. We and others use it to identify invasion of adjacent structures (Chalubinski, 2013; Reddy, 2014). Interobserver variability was reported to be excellent to diagnose PAS and assess invasion depth. There was less agreement in assessing topography of invasion (Finazzo, 2020). Using MR imaging, Mori and colleagues (2020) described a high prevalence of pelvic parasitic arteries with PAS. However, not all investigators have found MR imaging to be beneficial (Einerson, 2018).

Although gadolinium is usually not added during pregnancy, this contrast may enhance images (Millischer, 2017). Lax and coworkers (2007) described three MR imaging findings that suggest PAS: uterine bulging, dark intraplacental bands on T2-weighted imaging, and heterogeneous signal intensity within the placenta indicative of lacunae. Some recommend MR imaging if sonography results are inconclusive or there is a posterior previa (American College of Obstetricians and Gynecologists, 2018; Silver, 2018).

Management

Preoperative assessment ideally begins once a possible PAS is recognized antenatally. *A major decision concerns the timing and the ideal facility for delivery.* Considerations include appropriate

TABLE 43-2. Criteria to Consider for Delivery of Placenta Accreta Spectrum (PAS) in a Center of Excellence

Sonogram findings suspicious for PAS
Placenta previa with abnormal ultrasound appearance
Placenta previa with 2 to 3 prior cesarean deliveries
Prior classical cesarean delivery and anterior placentation
Prior endometrial ablation or pelvic irradiation
Inability to adequately evaluate or exclude PAS
Any other reason to suspect PAS

surgical, anesthesia, intensive care, and blood banking capabilities. An obstetrical surgeon or gynecological oncologist and surgical, urological, and interventional radiological consultants should be available (Collins, 2019; Shamshirsaz, 2018). The American College of Obstetricians and Gynecologists (2018) and the Society for Maternal–Fetal Medicine recommend planned delivery in a tertiary-care facility. In some, specially designed teams have been assembled and are on call (Shamshirsaz, 2018). A metaanalysis described the improved maternal outcomes with such management (Bartels, 2018).

Silver and colleagues (2015b) have provided requisites for accreta centers of excellence and their criteria to consider transfer to a higher level-of-care hospital (Table 43-2). If possible, delivery is best scheduled for peak availability of all resources and team members. Even so, a third of cases require unscheduled delivery, and contingency plans should be ready (Pettit, 2019). Women who refuse blood or its derivatives pose especially difficult management dilemmas (Barth, 2011).

Delivery Timing

In one study, 40 percent of women with PAS had bleeding mandating unplanned delivery prior to 34 weeks' gestation. Timing balances fetal immaturity against adverse maternal consequences of hemorrhage and emergency cesarean delivery (Perlman, 2017; Pettit, 2019). The American College of Obstetricians and Gynecologists (2018; 2021) recommends individualization and suggests delivery between $34^{0/7}$ and $35^{6/7}$ weeks' gestation. They cite a decision-analysis study that justifies elective delivery without fetal lung maturity testing after 34 completed weeks (Robinson, 2010). The Society for Maternal–Fetal Medicine (2018) recommends delivery between 34 and 37 weeks. Two earlier surveys found that most practitioners do not deliver these women until 36 weeks or later (Esakoff, 2012; Wright, 2013). At Parkland Hospital, we generally schedule these procedures after 36 completed weeks but are prepared also to manage them in nonelective situations (Rac, 2015b).

In some cases, PAS is not recognized until laparotomy. If resources are inadequate to surgically manage the percreta and if the woman is stable and not bleeding, the fetus is not delivered. The abdominal incision is closed, and she is transferred to a tertiary-care facility.

Preoperative Prophylactic Catheterization

In cases that may involve the ureters, catheterization may aid their dissection or identification. However, these catheters overall do not lower urinary tract injury rates (Crocetto, 2021). Some, but not all, advocate preoperative ureteral catheterization (American College of Obstetricians and Gynecologists, 2018; Eller, 2011). The role of catheters for ureteral injury repair is outlined in Chapter 30 (p. 564).

With a*rterial catheterization*, balloon-tipped catheters aim to mitigate blood loss and thereby enhance surgical visibility. Catheters are advanced preoperatively into the internal iliac arteries and are inflated after fetal delivery to occlude pelvic blood flow (Ballas, 2012; Desai, 2012; Zhou, 2021). Some prefer an infrarenal aortic balloon occlusion catheter (Mei, 2020). Alternatively, the catheters can be used to deliver occluding emboli to bleeding arterial sites (Mei, 2018). Others have concluded that these procedures offer borderline efficacy and have serious risks (Chen, 2020; Makary, 2019; Mohr-Sasson, 2020). Rare complications have included thrombosis of the common iliac artery (Bishop, 2011). At this time, the American College of Obstetricians and Gynecologists (2018) concludes that a firm recommendation cannot be made for or against intra-arterial catheter use. Similarly, there are no obvious benefits to prophylactic internal iliac artery ligation in this setting (Po, 2012; Yu, 2020).

Cesarean Delivery and Hysterectomy

Before commencing with delivery, the risk of hysterectomy to prevent exsanguination should be estimated. Some of these abnormal placentations, especially if partial, may be amenable to placental delivery with hemostatic suture placement. Confirmation of a percreta or increta almost always mandates hysterectomy. Because the scope of invasion may not be apparent before delivery of the fetus, some complete a number of dissection steps early. This also minimizes blood loss during potentially tedious dissection after hysterotomy and if the placenta bleeds. Thus, an attempt can be made to create a wide bladder flap before making the hysterotomy incision (Cunningham, 2017). The round ligaments are divided, and the lateral edges of the peritoneal reflection are dissected downward. If possible, these incisions are extended to encircle the entire placental implantation site that visibly occupies the prevesical space and posterior bladder wall. Following this, a classical hysterotomy, transverse fundal, or high posterior incision is made to avoid the placenta (Kotsuji, 2013).

After fetal delivery, the extent of placental invasion is assessed without attempts at manual placental removal. In a report from the United Kingdom, attempts at partial or total placental removal prior to hysterectomy were associated with twice as much blood loss (Fitzpatrick, 2014). Generally speaking, with obvious percreta or increta, hysterectomy is usually the best course, and the placenta is left in situ. With more extensive placental ingrowth, bleeding may be minimal until manual placental removal is attempted. Unless there is spontaneous separation with bleeding that mandates emergency hysterectomy, the operation begins after full assessment is made. Cesarean hysterectomy is carried out as described in Chapter 30 (p.560).

With heavy bleeding, successful treatment depends on immediate blood replacement and other measures that can include uterine or internal iliac artery ligation, balloon occlusion, or

TABLE 43-3. Steps in Cesarean Hysterectomy for Management of Placenta Percreta

Midline vertical laparotomy and midline hysterotomy: enter uterus to avoid placenta

Superior devascularization: divide and ligate uteroovarian pedicles and round ligaments

Retroperitoneal dissection: incise down to paravesical space; consider cephalad dissection to expose ureters and bifurcation of common iliac arteries

Bladder dissection: progress lateral to medial and down to vaginal fornices; associated with troublesome venous bleeding

Colpotomy: inferior dissection of extremely vascular paravesical space may cause significant hemorrhage

embolization. In some cases, the operation is made easier by performance of a supracervical hysterectomy (Levin, 2020). Kingdom and colleagues (2020) have described a modified radical hysterectomy for PAS (Table 43-3). This technique is also detailed in *Cunningham and Gilstrap's Operative Obstetrics*, 3rd edition (Cunningham, 2017). Because of a high risk for postoperative venous thromboembolism, consideration is given for thromboprophylaxis (Silver, 2018).

Conservative Management

Occasionally, it may be possible to trim the umbilical cord, repair the hysterotomy incision, leave the placenta in situ, and not pursue hysterectomy (Sentilhes, 2021). This option may be used for women in whom abnormal placentation was not suspected before cesarean delivery and in whom uterine closure stops bleeding. After this, she can be transferred to a higher level-of-care facility for definitive management. Another consideration is the woman with a strong desire for fertility and who has received extensive counseling. Resection of the adherent placenta and underlying myometrium has been advocated as a uterine-sparing technique (Palacios-Jaraquemada, 2020).

Conservative management was reviewed by Perez-Delboy (2014) and Fox (2015) and their colleagues. In some of these cases, the placenta spontaneously resorbed between 1 and 12 months with a mean of 6 months. Numerous complications can occur and include sepsis, coagulopathy, pulmonary embolism, and arteriovenous malformation (Fox, 2015; Judy, 2015; Roach, 2015). In other cases, sutures are placed through the outside wall of the uterus overlying the placental bed. Shih and associates (2019) described this using a Nausicaa procedure.

In some of these women, a subsequent hysterectomy—either planned or prompted by bleeding or infection—is performed days to weeks postpartum when blood loss might be less (Al-Khan, 2014; Sentilhes, 2009, 2021; Zuckerwise, 2020). In some studies, 20 percent or fewer of women ultimately required hysterectomy (Bretelle, 2007; Kutuk, 2018). In other reports, however, up to 60 percent eventually required emergency hysterectomy (Clausen, 2013; Pather, 2014). Evidence that treatment with methotrexate aids resorption is lacking. Last, for women in whom the placenta is left in situ, serial serum β-hCG measurements are not informative, and serial sonographic or MR imaging is recommended (Timmermans, 2007; Worley, 2008).

At this time, we agree with the American College of Obstetricians and Gynecologists (2018) that leaving the placenta in situ should be considered investigational. Exceptions permit transfer to a higher level of care. Guidelines from the International Society for Abnormally Invasive Placenta are more permissive (Collins, 2019).

TABLE 43-4. Selected Maternal Outcomes in Women with Placenta Accreta Spectrum Identified Prenatally and Delivered in Tertiary-Care Units

Outcome[a]	San Diego[b] n = 62	Utah[c] n = 60	Houston[d] n = 189	Adelaide[e] n = 67	Montreal[f] n = 42
Gestational age (wk)	33.0 ± 1.1	34 (17–41)	34 (32, 35)	35 (32, 36)	NS
Operating time (min)	194 ± 1.6	NS	NS	NS	112 ± 49
Transfusions	~75%	70%	NS	43%	34%
RBC (units)	4.7 ± 2.2	≥4 (30%)	2 (0–5)	4 (3, 6)	4
Bladder injury	23%	37%	3.7%	6%	13%
ICU admission	72%	30%	100%	NS	9%
LOS (days)	7.4 ± 1.8	3–13	NS	7.9	5.2

[a]Outcomes shown as mean ± 1 SD; median (range).
[b]Data from Warshak, 2010.
[c]Data from Eller, 2011.
[d]Data from Erfani, 2019.
[e]Data from Yasin, 2019.
[f]Data from Mitric, 2019.
ICU = intensive care unit; LOS = length of stay; NS = not stated; RBC = red blood cells.

Pregnancy Outcomes

In sum, PAS can have disastrous outcomes for both mother and fetus. Although the depth of placental invasion does not correspond with perinatal outcome, it is of paramount maternal significance. Table 43-4 displays outcomes of women at tertiary-care hospitals and in whom the PAS diagnosis was usually made preoperatively. Despite these advantages, complications included hemorrhage, urinary tract injury, intensive care unit admission, secondary surgical procedures, and maternal death. Some of these same reports chronicle outcomes in a second cohort of women in whom care was not given at a tertiary-care facility or in whom the diagnosis of percreta was not made until delivery, or both. In these cohorts, morbidity and mortality rates were higher (Erfani, 2019).

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CHAPTER 44

Management of Obstetrical Hemorrhage

Recognition of obstetrical hemorrhage severity is crucial to its management. However, visual estimates, especially when blood losses are excessive, are notoriously inaccurate. In many cases, true volume losses are often two to three times the clinical estimate. Moreover, in obstetrics, part and sometimes even all of the lost blood may be concealed. Estimation is further complicated in that peripartum hemorrhage also includes the pregnancy-augmented blood volume. After pregnancy hypervolemia is lost at delivery, blood loss can be estimated by calculating 500 mL loss for each 3 volume percent drop in hematocrit. Its nadir depends on the speed of resuscitation with intravenous crystalloids and blood products. *With ongoing blood loss, the real-time hematocrit is at its maximum whenever measured in the delivery, operating, or recovery room.*

Prudently, if blood loss is considered more than average, the hematocrit is determined, and plans are made for close observation for potential physiological deterioration. Blood loss determination as recommended by the American College of Obstetricians and Gynecologists (2019b) is discussed in detail in Chapter 42. Urine output measured hourly is one of the most important "vital signs." *Unless diuretic agents are given—and these are seldom indicated with active bleeding—accurately measured urine flow reflects renal perfusion. This in turn reflects perfusion of other vital organs.* The volume of urine output should be ≥30 mL/hr and preferably ≥50 mL/hr.

Another important factor to consider with management of hemorrhage is whether there are adequate procoagulants to achieve clot formation and stability. Many cases of severe obstetrical hemorrhage are further complicated by disseminated intravascular coagulation (DIC), in which blood has dysfunctional coagulation (p. 775).

MANAGEMENT OF HEMORRHAGE

Hypovolemic Shock

Shock from hemorrhage evolves through several stages (Cannon, 2018). Early, the mean arterial pressure, stroke volume, cardiac output, central venous pressure, and pulmonary capillary wedge pressure decline. Greater differences in arteriovenous oxygen content values reflect enhanced tissue oxygen extraction, although overall oxygen consumption falls.

Blood flow to capillary beds is controlled by arterioles, which are resistance vessels and partially controlled by the central nervous system (CNS). However, approximately 70 percent of total blood volume is contained in venules, which are passive resistance vessels controlled by humoral factors. Thus, the catecholamine release during hemorrhage prompts greater venular tone, and this provides an autotransfusion from this capacitance reservoir. This volume boost is accompanied by compensatory rises in heart rate, systemic and pulmonary vascular resistance, and myocardial contractility. At the same time, selective, CNS-mediated arteriolar constriction or relaxation, termed autoregulation, preferentially redistributes cardiac output and blood volume. Thus, more blood flow is diverted to the heart, brain, and adrenal glands, whereas perfusion to the kidneys, splanchnic beds, muscles, skin, and uterus is relatively diminished.

When the blood volume deficit exceeds approximately 25 percent, compensatory mechanisms usually are inadequate to maintain cardiac output and blood pressure. Importantly, additional small losses of blood will now cause rapid clinical

deterioration. Following an initial augmented total oxygen extraction by maternal tissue, maldistribution of blood flow results in local tissue hypoxia and metabolic acidosis. This creates a vicious cycle of vasoconstriction, organ ischemia, and cellular death.

Hemorrhage also activates lymphocytes and monocytes, which in turn prompts endothelial cell activation and platelet aggregation (Cannon, 2018). This endotheliopathy promotes release of vasoactive mediators that occlude small vessels and further impair microcirculatory perfusion. Comorbid preeclampsia or sepsis also leads to loss of capillary endothelial integrity, additional loss of intravascular volume into the extracellular space, and platelet aggregation. These then can incite DIC.

The pathophysiological events just described create important but often overlooked extracellular fluid and electrolyte shifts involved in both the genesis and successful treatment of hypovolemic shock. These include changes in the cellular transport of various ions such as sodium and water into skeletal muscle as well as potassium loss. Replacement of extracellular fluid and intravascular volume are both necessary. Patient survival rates are enhanced in acute hemorrhagic shock if blood plus crystalloid solution are given compared with blood transfusions alone.

Fluid Resuscitation

Whenever excessive blood loss is suspected, steps are simultaneously taken to identify the bleeding source and to begin resuscitation. Refer to the algorithm for hemorrhage management (Fig. 42-3, p. 735). If the woman is undelivered, restoration of blood volume benefits both mother and fetus. It also prepares for emergent delivery. If she is postpartum, immediately identifying uterine atony, retained placental fragments, or genital tract lacerations is essential. One or two large-bore intravenous infusion systems are ideally established promptly, crystalloid solutions are rapidly infused, and blood products are ordered. An operating room is readied, and a surgical and anesthesia team are quickly assembled. Specific management of hemorrhage is further dependent on its etiology. A neonatal resuscitation team is included if imminent delivery is planned.

Serious hemorrhage demands prompt and adequate refilling of the intravascular compartment with crystalloid solutions. These rapidly equilibrate into the extravascular space, and only 20 percent of crystalloid remains intravascular in critically ill patients after 1 hour (Zuckerbraun, 2010). *Because of this, initial fluid is infused in a volume two to three times the estimated blood loss.*

Crystalloid Versus Colloid Solutions

Resuscitation of hypovolemic shock with colloid versus crystalloid solutions has been debated. In a Cochrane review of resuscitation of nonpregnant critically ill patients, Lewis and coworkers (2018) found selection of colloids versus crystalloids probably makes little or no difference to mortality rates. Similar results were found in the Saline versus Albumin Fluid Evaluation (SAFE) randomized trial of almost 7000 nonpregnant patients (Finfer, 2004). At Parkland Hospital, acute volume resuscitation is preferably done with crystalloid solutions and blood.

Either a saline-based or a balanced crystalloid solution may be infused. The latter includes Ringer lactate and Plasma-Lyte solutions, which have electrolyte compositions similar to plasma. In some studies, but not in all, balanced crystalloid solutions were found to be superior to saline-based ones (Semler, 2018; Yule, 2020). Excessive saline-based crystalloid solution can theoretically lead to hyperchloremic acidosis. In comparisons, the difficulty lies in separating the effects of the underlying pathophysiology driving the acidosis.

Blood Replacement

Type and Screen Versus Crossmatch

A blood type and antibody screen should be performed for any woman at significant risk for hemorrhage. Because prediction of women at risk for postpartum hemorrhage is poor, we perform type and screen in all women upon admission to labor and delivery. Screening involves mixing maternal serum with standard reagent red cells that carry antigens to which most of the common clinically significant antibodies react. Instead, crossmatching involves the use of actual donor erythrocytes rather than the standardized red cells. This process is efficient, and only 0.03 to 0.07 percent of patients identified as having no antibodies are subsequently found to them (Boral, 1979). *Importantly, administration of screened blood rarely results in adverse clinical sequelae.*

Transfusion Thresholds

The hematocrit level or hemoglobin concentration threshold that mandates blood transfusion is controversial (Bienstock, 2021). Cardiac output does not substantively drop until the hemoglobin concentration falls to approximately 7 g/dL or when the hematocrit approximates 20 volume percent. Military combat trauma units have used a target hematocrit of 21 volume percent, and at this level, most experts recommend consideration of red cell transfusion (Carson, 2017; Kogutt, 2019). In general, with ongoing obstetrical hemorrhage, we recommend rapid blood infusion when the hematocrit is <25 volume percent. Other decision-modifying factors are whether the fetus is undelivered; surgery is imminent or ongoing operative blood loss is expected; or maternal hypoxia, vascular collapse, or other factors are present.

Limited data address these issues. In a study from the Canadian Critical Care Trials Group, nonpregnant patients were randomly assigned to restrictive red cell transfusions to maintain hemoglobin concentration >7 g/dL or to liberal transfusions to maintain the hemoglobin level at 10 to 12 g/dL. The 30-day mortality rate was similar—19 versus 23 percent—in the restrictive versus liberal groups, respectively (Hébert, 1999). Transfusion therapy in nonpregnant patients with septic shock had similar mortality rates when 7 g/dL was compared with 9 g/dL as targets for transfusions (Holst, 2014). *The number of units transfused in a given woman to reach a target hematocrit depends on her body mass and on the expectations of additional blood loss.*

Blood Component Products

The content and effects of transfusion of various blood components are shown in Table 44-1. Because whole blood is rarely available, most women with obstetrical hemorrhage and ongoing

TABLE 44-1. Blood Products Commonly Transfused in Obstetrical Hemorrhage

Product	Volume per Unit	Contents per Unit	Effect on Hemorrhage
Whole blood	About 50 mL: Hct ~40 percent	RBCs, plasma, 600–700 mg fibrinogen, no platelets	Restores blood volume and fibrinogen, increases Hct 3–4 volume percent per unit
Packed RBCs	250–300 mL: Hct ~55–80 percent	RBCs, minimal fibrinogen, no platelets	Increases Hct 3–4 volume percent per unit
FFP	About 250 mL; 30-minute thaw	Colloid, 600–700 mg fibrinogen, no platelets	Restores circulating volume and fibrinogen
Cryoprecipitate	About 15 mL, frozen	One unit has 200 mg fibrinogen, other clotting factors, no platelets	15–20 units or 3–4 g will increase baseline fibrinogen ~150 mg/dL
Platelets	About 50 mL, stored at room temperature	One unit raises platelet count ~5000/μL; single-donor apheresis bag preferable	6–10 units transfused; single-donor bag preferable to raise platelets ~50,000 μ/L

FFP = fresh-frozen plasma; Hct = hematocrit; RBCs = red blood cells.

massive blood loss are given packed red cells, crystalloid solutions, and blood components. As subsequently discussed, many institutions use *massive transfusion protocols (MTPs)* designed to anticipate all facets of massive obstetrical hemorrhage. These protocols commonly contain plasma, cryoprecipitate, and platelets in various ratios (Cunningham, 2015; Shields, 2011).

Several studies have assessed plasma:red cell ratios with MTPs used in civilian trauma units and military combat hospitals (Hardin, 2014; Rahouma, 2018). Patients receiving a massive transfusion—defined as 10 or more units of blood—had much higher survival rates as the ratio of plasma to red cell units neared 1:1.4, that is, one unit of plasma given for each 1.4 units of packed red cells. By way of contrast, the highest mortality group had a ratio of 1:8.

From the foregoing, when red cell replacement exceeds five units or so, evaluation of platelet count, clotting studies, and plasma fibrinogen concentration is reasonable (Bienstock, 2021; Pacheco, 2019). In the woman with obstetrical hemorrhage, the platelet count should be maintained >50,000/μL by the infusion of platelet concentrates. A fibrinogen level <150 mg/dL or a sufficiently prolonged PT or PTT in a woman with surgical bleeding is an indication for replacement. Fresh-frozen plasma is administered in doses of 10 to 15 mL/kg, or alternatively, cryoprecipitate is infused (see Table 44-1).

At Parkland Hospital, we use a standardized response to active hemorrhage. If whole blood is not available, the following escalation of blood products is applied: 2 units packed red blood cells, and if continued bleeding, 2 units packed red blood cells and 2 units fresh-frozen plasma are automatically ordered. Beyond this, MTP is initiated.

Whole Blood and Packed Red Blood Cells

Compatible whole blood is ideal for management of severe obstetrical hemorrhage. It has a shelf life of 40 days, and 70 percent of the transfused red cells function for at least 24 hours following transfusion. One unit raises the hematocrit by 3 to 4 volume percent. Important for obstetrical hemorrhage, whole blood replaces many coagulation factors needed in obstetrics—especially fibrinogen—and its plasma treats hypovolemia. A collateral derivative is that women with severe hemorrhage are resuscitated with fewer blood donor exposures than with packed red cells and components.

Experience at Parkland Hospital supports the preferable use of whole blood for massive hemorrhage (Alexander, 2009; Hernandez, 2012). Of more than 66,000 deliveries, women with obstetrical hemorrhage treated with whole blood had significantly lower incidences of severe maternal morbidity that included renal failure, acute respiratory distress syndrome, pulmonary edema, hypofibrinogenemia, intensive care unit admissions, or maternal death compared with those given packed red cells and component therapy. One unit of packed erythrocytes is derived from one unit of whole blood to have a hematocrit of 55 to 80 volume percent. One unit will increase the hematocrit by 3 to 4 volume percent depending on the size of the woman.

Dilutional Coagulopathy

A major drawback of massive hemorrhage treatment with crystalloid solutions and packed red blood cells is depletion of platelets and clotting factors. Discussed later, this can lead to a dilutional coagulopathy that is clinically indistinguishable from DIC (Cunningham, 2015; Hossain, 2013). Thrombocytopenia is the most frequent coagulation defect found with blood loss and multiple transfusions. In addition, packed red cells have only very small amounts of soluble clotting factors, and stored whole blood is deficient in platelets and in factors V, VIII, and XI. Thus, *hypofibrinogenemia* and prolongation of the prothrombin (PT) and partial thromboplastin times (PTT) are other sequelae. Because many causes of obstetrical hemorrhage also cause DIC, the distinction between dilutional and consumptive coagulopathy can be confusing. Fortunately, treatment for both is similar.

Platelets

Platelet transfusions are considered with ongoing obstetrical hemorrhage if the platelet count falls below 50,000/μL (Kenny,

2015). In the nonsurgical patient, bleeding is rarely encountered if the platelet count is 10,000/μL or higher (Murphy, 2010). The preferable source of platelets is one "bag" obtained by single-donor apheresis. This contains the equivalent of one unit each from six individual donors. Depending on maternal size, each single-donor-apheresis, six-unit bag raises the platelet count by approximately 20,000/μL. If these bags are not available, then individual-donor platelet units are used, and six to eight such units are generally transfused.

Importantly, the donor plasma in platelet units must be compatible with recipient erythrocytes. Further, because some red blood cells are invariably transfused along with the platelets, only units from D-negative donors should be given to D-negative recipients.

Fresh-frozen Plasma

This component is prepared by separating plasma from whole blood and then freezing it. Approximately 30 minutes are required for frozen plasma to thaw. It is a source of all stable and labile clotting factors, including fibrinogen. Thus, it is often used for treatment of women with consumptive or dilutional coagulopathy. *Plasma is not a suitable volume expander in the absence of specific clotting factor deficiencies.* It is considered in a bleeding woman with a fibrinogen level <150 mg/dL or with an abnormal PT or PTT.

An alternative to frozen plasma is *liquid plasma (LQP)*. This never-frozen plasma is stored at 1 to 6^0 C for up to 40 days, and its use compares favorably with fresh-frozen plasma (Backholder, 2017). Liquid plasma is not universally available in many centers.

Cryoprecipitate and Fibrinogen Concentrate

Each unit of cryoprecipitate is prepared from one unit of fresh-frozen plasma. Each 10- to 15-mL unit contains at least 200 mg of fibrinogen along with factor VIII:C, factor VIII:von Willebrand factor, factor XIII, and fibronectin (American Association of Blood Banks, 2017). It is usually given as a "pool" or "bag" using an aliquot of fibrinogen concentrate taken from 8 to 120 donors. Cryoprecipitate is an ideal source of fibrinogen when levels are dangerously low and surgical incisions show oozing. Because of transit time, the return of cryoprecipitate to transfusion services is often not feasible and is considered wastage if not deployed. Nearly 17 percent of ordered cryoprecipitate has been reported to be wasted in labor and delivery units, and this is the most commonly wasted product (Yee, 2019). Another alternative is virus-inactivated fibrinogen concentrate (Ng, 2020). These pooled fibrinogen products are marketed as *RiaSTAP* and *Fibryna*. Each gram of concentrate raises the plasma fibrinogen level approximately 40 mg/dL. These concentrates are used to treat congenital hypofibrinogenemia syndromes.

Recombinant Activated Factor VII

This synthetic vitamin K–dependent protein is available as *NovoSeven*. Recombinant activated factor VII (rFVIIa) binds to exposed tissue factor at the injury site to generate thrombin that activates platelets and the coagulation cascade. Since its introduction, rFVIIa has been used to help control hemorrhage from surgery, trauma, and obstetrical causes (Goodnough, 2016; Murakami, 2015). Many Level I trauma centers include it in MTPs. Importantly, rFVIIa will not be effective if the plasma fibrinogen level is <50 mg/dL or the platelet count is <30,000/μL.

One concern with rFVIIa is associated arterial—and to a lesser degree—venous thrombosis. In a review of 35 randomized trials, arterial thromboembolism developed in 55 percent (Levi, 2010). A second concern is that it has been found to have only marginal efficacy (Pacheco, 2019).

Tranexamic Acid

Normally, plasminogen binds with tissue plasminogen activator (tPA) to form plasmin. This binding degrades fibrin into fibrinogen–fibrin degradation products and leads to clot lysis. Instead, tranexamic acid (TXA) reversibly binds to plasminogen, and thereby blocks plasmin binding to fibrin. Fibrin strands are not broken, and a clot persists to slow down bleeding.

Ahmadzia and coworkers (2021) recently reported the pharmacodynamics of TXA at cesarean delivery using rotational thromboelastometry. TXA inhibited tPA-induced clot lysis in a dose-dependent manner. In the randomized WOMAN trial of gravidas with hemorrhage following vaginal birth or during cesarean delivery, mortality rates from obstetrical hemorrhage were 1.2 percent in those given a 1-g intravenous TXA dose plus traditional care for bleeding. This rate was statistically lower than the 1.7-percent death rate in women given traditional care alone (WOMAN Trial Collaborators, 2017). The trial was carried out in developing nations and because of the results, the drug is recommended by the World Health Organization (2017). In a large randomized trial of tranexamic acid given for *prophylaxis*, the drug did not decrease the rate of postpartum hemorrhage following vaginal delivery (Sentilhes, 2018). In the Tranexamic Acid for Preventing Postpartum Hemorrhage Following a Cesarean Delivery—TRAAP2 trial—women undergoing cesarean delivery who were given tranexamic acid prophylaxis had a lower incidence of red-cell transfusions (Sentilhes, 2021).

Gayet-Ageron and coworkers (2018) conducted a metaanalysis with more than 1000 patients with postpartum hemorrhage treated with TXA. They also analyzed data from two randomized trials that included more than 40,000 women treated with TXA. They concluded that treatment must be given soon after bleeding onset to reduce maternal mortality rates. Shakur and colleagues (2018) performed a Cochrane database review and also concluded that early TXA administration decreases maternal deaths.

Most of these studies were conducted in impoverished countries, and the American College of Obstetricians and Gynecologists (2019a) does not recommend TXA for either prophylaxis or first-line treatment of obstetrical hemorrhage. If used, administration within 3 hours of delivery is recommended.

Massive Transfusion Protocols

As noted, these protocols are initiated once four to five units of packed red cells have been given within 2 hours or so. These protocols speed blood product delivery to provide early resuscitation and help avoid dilutional coagulopathy. Once activated, packed red cells, plasma, platelets, and fibrinogen are given set ratios (Table 44-2). Some protocols include rFVIIa, TXA, or prothrombin complex concentrates (Jackson, 2018).

The data supporting the superiority of MTPs compared with traditional component replacement to improve survival

TABLE 44-2. Parkland Hospital Obstetrical Massive Transfusion Protocol

Round No.	PRBC 5 Units	FFP 3 Units	Plts 6-Pack	Cryo 1 Unit
1	X	X	—	—
2	X	X	X	—
3	X	X	—	X
4	X	X	X	—
5	X	X	—	—
6	X	X	X	X
7	X	X	—	—
8	X	X	X	—

Cryo = cryoprecipitate; FFP = fresh-frozen plasma; Plts = platelets; PRBC = packed red blood cells.

rates in obstetrical studies are limited. Most reports describe nonpregnant trauma victims, but some observational studies address obstetrical hemorrhage (Green, 2016; Pacheco, 2016).

Viscoelastic Assays

Thromboelastography (TEG) and *rotational thromboelastometry (ROTEM)* are point-of-care tests that assess coagulation in whole blood during massive transfusions. These tests work by analyzing both clot formation and breakdown in a whole blood sample from a given patient. Testing produces a profile of coagulation dynamics, and displayed values indicate the speed and quality of clot formation (Fig. 44-1). These assays provide information regarding time to clot formation, clot strength, and fibrinolysis (Arnolds, 2020). Currently, they guide blood product replacement in trauma, liver transplant, and cardiac surgery patients. Studies of TEG and ROTEM techniques in pregnant women have confirmed the hypercoagulable state of pregnancy and provide reference ranges for use in this population (Lee, 2021; McNamara, 2019; Pacheco, 2019).

Although promising, they also have several limitations. For example, they are less informative in a woman with torrential hemorrhage in whom clotting function would need to be measured minute-by-minute. They cannot be used to detect disorders of primary hemostasis (Solomon, 2012). A major drawback is the risk of misinterpretation when tests are used by inadequately trained personnel. Although use is gaining favor, we and others recommend further study before these tests are widely applied for obstetrical hemorrhage treatment (Amgalan, 2020). We have found this testing modality to be more applicable after initial management of hemorrhage and with intensive care recovery than during acute hemorrhage.

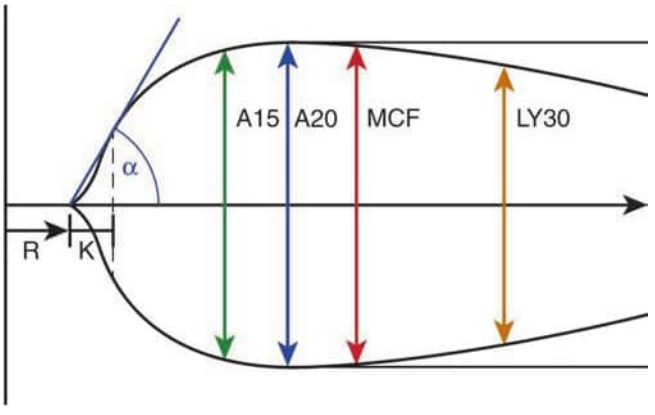

FIGURE 44-1 Normal thromboelastograph (TEG). R (reaction time: start of test to clot forming. K (clotting time): from start to 20 mm amplitude. Alpha (α) angle: speed of fibrin formation. A15, A20: amplitude at 15 and 20 minutes. MCF: maximum clot firmness. LY30: amount of clot lysed at 30 minutes.

Cell Salvage and Autologous Transfusion

Preoperative patient phlebotomy and *autologous blood storage* for transfusion in obstetrics has been disappointing. Exceptions are women with a rare blood type or with unusual antibodies (Pacheco, 2013; Sullivan, 2019).

Intraoperative blood salvage with reinfusion is considered a safe intervention in obstetrical patients. This practice may aid women declining transfusion (Chap. 30, p. 549). Prior concern centered on amnionic fluid contamination and embolism (Dhariwal, 2014; Goucher, 2015). To evaluate benefits, one trial randomly assigned 3028 women at risk for hemorrhage and undergoing cesarean delivery either to routine care or to cell salvage. The rate of nonautologous donor blood transfusion was not significantly reduced in the cell salvage group—2.5 versus 3.5 percent (Khan, 2017). In another study, Sullivan and colleagues (2019) routinely set up most cesarean deliveries for autologous transfusions and reported a lower rate of nonautologous donor transfusion. Similar to prior reports, no cases of amnionic fluid embolism were reported in these two studies.

■ Transfusion Complications

Of serious known risks, *transfusion of an incompatible blood component* may result in acute hemolysis. If severe, this can cause DIC, acute kidney injury, and death. Preventable errors responsible for most of these reactions frequently include mislabeling of a specimen or incorrectly transfusing a patient not slated for those products.

The rate of such errors in the United States is estimated to be 1 case in 14,000 units, but these events are likely underreported (Lerner, 2010). A transfusion reaction is characterized by fever, hypotension, tachycardia, dyspnea, chest or back pain, flushing, severe anxiety, and hemoglobinuria. Immediate supportive measures include stopping the transfusion, treating hypotension and hyperkalemia, provoking diuresis, and alkalinizing the urine.

Transfusion-related acute lung injury (TRALI) and *transfusion-associated circulatory overload (TACO)* are the most common causes of transfusion-related mortality (Semple, 2019). Affected women characteristically have severe dyspnea, hypoxia, and pulmonary edema that develop within 6 hours of transfusion (Peters, 2015). Of the two, TACO is more common, and its incidence nears 1 percent. TRALI is estimated to complicate at least 1 in 12,000 transfusions (Carson, 2017). Although their pathogenesis is incompletely understood, injury to the pulmonary capillaries may arise from human leukocyte antigen (HLA) antibodies and human neutrophil antibodies (HNA) in donor plasma (McCullough, 2016). Management is supportive and may include mechanical ventilation (Chap. 50, p. 885).

Bacterial infection from transfusion of a contaminated blood component is unusual because organism growth is discouraged by refrigeration. The most often implicated contaminants of red cells include *Yersinia*, *Pseudomonas*, *Serratia*, *Acinetobacter*, and *Escherichia* species. The more important risk is from bacterial contamination of platelets, which are stored at room temperature. Current estimates are that 1 in 1000 to 2000 platelet units are contaminated. Death from transfusion-related sepsis is 1 case in 17,000 transfused single-donor platelets and 1 case in 61,000 transfused apheresis-donor packs (Lerner, 2010).

Viral infection risks from transfusion have been curtailed. The estimated risk of human immunodeficiency virus (HIV) or of hepatitis C virus infection in screened blood is 1 case in 1 to 2 million transfused units (Carson, 2017). The estimated hepatitis B transmission rate is <1 case in 100,000 transfused units (Jackson, 2003). Because of the high prevalence of the virus, cytomegalovirus-infected leukocytes are often transfused.

Risks for transmitting West Nile virus, parvovirus B19, human T-lymphotropic virus type 1, and toxoplasmosis are slight (American Association of Blood Banks, 2013; Foroutan-Rad, 2016). Although rare, Zika virus has emerged as another relevant transfusion-transmitted infection (Motta, 2016). Collection of all whole blood components now includes testing for Zika virus (Centers for Disease Control and Prevention, 2018). At this time, transmission of SARS-CoV-2 virus from a COVID-positive donor is hypothetical (Leblanc, 2020).

OBSTETRICAL COAGULOPATHIES

The terms *consumptive coagulopathy*, *defibrination syndrome*, and *disseminated intravascular coagulation (DIC)* are often used interchangeably, but distinctions are important. Actual consumption of procoagulants within the intravascular tree results in a consumptive coagulopathy. In contrast, massive loss of procoagulants from hemorrhage results in a dilutional coagulopathy. Semantics aside, consumptive coagulopathy culminates in a systemic intravascular activation that completely disrupts natural hemostasis. As a result, an ineffective balance of natural anticoagulant mechanisms leads to widespread fibrin deposition that can cause multiorgan failure (Levi, 2016).

Pregnancy-induced Coagulation Changes

During normal pregnancy, the balance between coagulation and fibrinolysis changes to create a procoagulant state. Changes that promote coagulation include appreciable elevation in the plasma concentrations of factors I (fibrinogen), VII, VII, IX, and X. A partial list of these normal values is found in the Appendix (p. 1228). Concurrently, levels of plasminogen, which lyses fibrin, rise considerably. However, plasminogen activator inhibitor 1 and 2 (PAI-1 and PAI-2) levels also increase. Thus, plasmin activity usually declines until after delivery (Hale, 2012; Hui, 2012). As shown in Figure 4-7, (p. 62), mean platelet count drops by 10 percent during pregnancy, and platelet activation is enhanced (Kenny, 2015; Reese, 2018).

The net results of these changes include greater levels of fibrinopeptide A, β-thromboglobulin, platelet factor 4, and fibrinogen–fibrin degradation products, which includes D-dimers. In addition to lower concentrations of the anticoagulant protein S, pregnancy-related hypercoagulability, and decreased fibrinolysis, there is augmented—yet compensated—intravascular coagulation that may function to maintain the uteroplacental interface.

Disseminated Intravascular Coagulation

Because of the many definitions and variable severity, the incidence of consumptive coagulopathy in gravidas varies and ranges from 0.03 to 0.35 percent (Erez, 2014; Rattray, 2012). For example, some degree of significant coagulopathy is found in virtually all cases of placental abruption and amnionic fluid embolism. Other instances in which frequently occurring but less recognized degrees of coagulation activation can be found include sepsis; thrombotic microangiopathies; acute kidney injury; acute fatty liver; severe preeclampsia; and hemolysis, elevated liver enzyme levels, low platelet count (HELLP) syndrome (Cunningham, 2015).

When consumptive coagulopathy is severe, the likelihood of maternal and perinatal morbidity and mortality rises. In one study of 49 cases, antecedent causes included those listed above, and 59 percent received blood transfusions, 18 percent underwent hysterectomy, 6 percent required renal dialysis, and three mothers died (Rattray, 2012). In this series, the perinatal mortality rate was 30 percent. From 2010 to 2011, DIC was the second most common severe maternal morbidity indicator (Creanga, 2014). DIC was associated with nearly a fourth of maternal deaths during this study period. Despite these statistics, consumptive coagulopathy as the sole cause of maternal death is uncommon and accounts for only 0.2 percent of pregnancy-related deaths in the United States (Creanga, 2015).

Activation of Normal Coagulation

Instead of the "waterfall" sequential activation of the clotting cascade, a current theory proposes that *tissue factor*—an integral membrane glycoprotein—serves as the principal initiator of coagulation (Levi, 2016). Coagulation then moves forward but incorporates a feedback loop. To begin, tissue factor forms complexes with factor VII/VIIa to activate factors IX and X. Tissue factor is found in highly vascularized organs such as the brain, lungs, and placenta; in amnionic fluid; and in certain other cells (Kuczyfiski, 2002; Østerud, 2006; Uszyfiski, 2001).

Tissue factor–factor VIIa complexes ultimately generate activated factor X (Xa) to initiate clotting. Subsequently, the previously labeled "intrinsic" pathway amplifies this process. Specifically, the initial thrombin produced directly activates factor XI by providing a feedback amplification loop (Fig. 44-2). The end result of this amplified coagulation process is fibrin formation. This is then counterbalanced by the fibrinolytic system, in which plasminogen is activated. Even this process is tied initially to tissue factor. The final product is fibrin degradation products, sometimes called fibrin split products, which include D-dimers.

Activation of Pathological Coagulation

With DIC, pathological entities prompt tissue factor release from subendothelial tissue and stimulated monocytes, which in

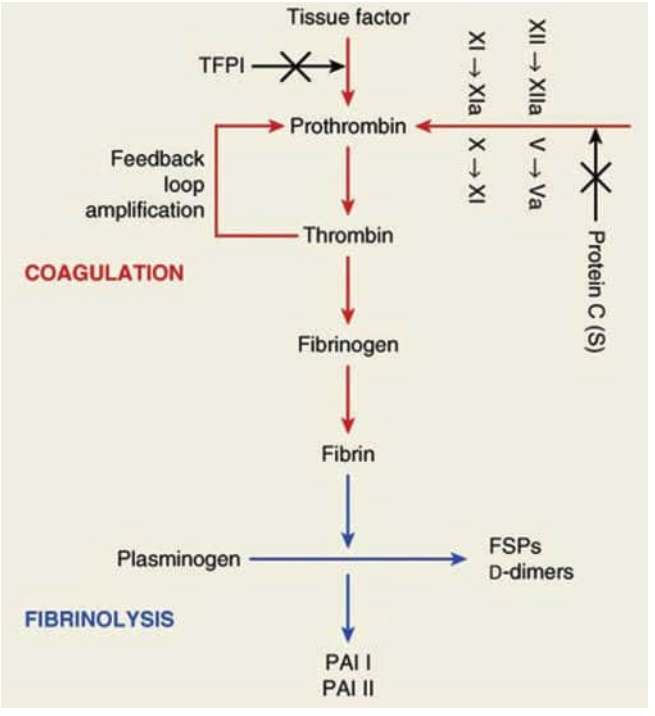

FIGURE 44-2 Coagulation pathway schematic. FSP = fibrin split products; PAI = plasminogen activator inhibitor; TFPI = tissue factor pathway inhibitor.

turn provoke cytokine release from the endothelium. With generalized endothelial activation, diffuse activation of coagulation follows. This pathological cycle of coagulation and fibrinolysis becomes clinically important when coagulation factors and platelets are sufficiently depleted to create consumptive coagulopathy.

Purpura fulminans is a severe—often lethal—form of consumptive coagulopathy. It is caused by microthrombi in small blood vessels leading to skin necrosis and sometimes vasculitis. Debridement of large areas of skin over the extremities and buttocks frequently requires treatment in a burn unit. Rarely, four-extremity amputation is required (Bhatti, 2019). Purpura fulminans usually complicates sepsis in women with heterozygous protein C deficiencies and low protein C serum levels (Bhatti, 2019; Levi, 2016). Importantly, homozygous protein C or S deficiency results in neonatal purpura fulminans, which is fatal (Chap. 55, p. 976).

Inciting Conditions

Several obstetrical syndromes can trigger consumptive coagulopathy. Of these, *placental abruption* is the most common cause of severe consumptive coagulopathy in obstetrics and is discussed more fully in Chapter 43 (p. 749). With *preeclampsia*, *eclampsia*, and *HELLP syndrome*, endothelial activation is a hallmark. Perhaps 10 percent of HELLP cases have some disseminated coagulation (Haram, 2017). In general, the clinical severity of preeclampsia is directly correlated with thrombocytopenia and fibrin degradation products (Gedik 2017; Kenny, 2015). That said, intravascular coagulation is seldom severe enough to be clinically worrisome (Pritchard, 1976). Acute fatty liver of pregnancy also causes intravascular coagulation in addition to decreased procoagulant synthesis (Chap. 58, p. 1034).

Amnionic fluid embolism is usually caused by intravenous embolization of meconium-laden amnionic fluid. It results in rapid cardiorespiratory collapse and profound consumptive coagulopathy. The Society for Maternal-Fetal Medicine (2021) has developed a checklist for the initial management of amnionic fluid embolism. It is discussed in Chapter 42 (p. 745).

Sepsis stemming from various infections can be accompanied by endo-or exotoxin release. Although a feature of sepsis syndrome includes activation of coagulation, seldom does sepsis alone cause massive procoagulant consumption. *Escherichia coli* bacteremia is frequently seen with antepartum pyelonephritis and puerperal infections, however, accompanying consumptive coagulopathy is usually not severe. Some notable exceptions are septicemia caused by exotoxins released from group A *Streptococcus pyogenes*, *Staphylococcus aureus*, or *Clostridium perfringens*, *C sordellii*, or *C novyi* (Herrera, 2016; Pritchard, 1971). Treatment of sepsis and septic shock is discussed in Chapter 50 (p. 889). *Septic abortion*—especially associated with these organisms—can incite coagulation and worsen hemorrhage.

Second-trimester induced abortions can stimulate intravascular coagulation even in the absence of sepsis. Ben-Ami and associates (2012) described a 1.6-percent incidence in 1249 late-second-trimester pregnancies terminated by dilation and evacuation. Two thirds were done for fetal demise, which may have contributed to coagulopathy (Kerns, 2019). Another source of intense coagulation is instillation of hypertonic solutions to effect midtrimester abortions. These are not commonly used currently for pregnancy terminations. The mechanism is thought to initiate coagulation by thromboplastin release into maternal circulation from the placenta, fetus, and decidua by the necrobiotic effect of hypertonic solutions.

Prolonged retention of a dead fetus is an unusual cause of consumptive coagulopathy today. Namely, fetal death can be easily confirmed, and highly effective methods for labor induction are available. Moreover, if the dead fetus is undelivered, most women enter spontaneous labor within 2 weeks and gross disruption of maternal coagulation rarely develops before 4 weeks (Pritchard, 1959, 1973). After 1 month, however, almost a fourth will develop consumptive coagulopathy.

Diagnosis

Bioassay is an excellent method to detect or suspect clinically significant coagulopathy. Excessive bleeding at sites of modest trauma characterizes defective hemostasis. Examples include persistent bleeding from venipuncture sites, nicks from preoperative shaving, trauma from bladder catheterization, and spontaneous bleeding from the gums, nose, or gastrointestinal tract. Purpura or petechiae at pressure sites such as sphygmomanometer cuffs or tourniquets suggest significant thrombocytopenia. Any surgical procedure provides the ultimate bioassay and elicits generalized oozing from abdominal wall layers, the retroperitoneal space, the episiotomy, or incisions and dissections for cesarean delivery or hysterectomy.

Of laboratory tests, fibrinogen and D-dimer levels can be informative. In late pregnancy, plasma fibrinogen levels typically have risen to 300 to 600 mg/dL. Thus, even with severe consumptive coagulopathy, levels may sometimes be

sufficiently high to protect against clinically harmful hypofibrinogenemia. For example, defibrination caused by a placental abruption might lower an initial fibrinogen level of 600 mg/dL to 250 mg/dL. Although this would indicate massive fibrinogen consumption, levels are still adequate to promote clinical coagulation. The clinically impactful threshold usually approximates 150 mg/dL. The effects of serious hypofibrinogenemia—less than 50 mg/dL—can be illustrated with clinical *thrombin clot test*. With low fibrinogen levels, the clot formed from whole blood in a glass phlebotomy tube will initially be soft and cannot retract in volume. Instead, during the next half hour, *platelet-induced* clot retraction ensues, and this causes a tighter clot to form.

As depicted in Figure 44-2, fibrinolysis cleaves fibrin into various fibrin degradation products, and one of the smaller ones is the D-dimer. Several sensitive assays contain monoclonal antibodies specific for D-dimers (Johnson, 2019). Assay values are almost always abnormally high with clinically significant consumptive coagulopathy. At least in obstetrical disorders, quantification does not correlate with outcomes. Examples of the magnitude of fibrin split product elevations in various obstetrical coagulopathies are shown in Figure 44-3.

Thrombocytopenia is likely if petechiae are abundant or if clotted blood fails to retract within an hour or so. Confirmation is provided by a low platelet count. If severe preeclampsia syndrome is comorbid, qualitative platelet dysfunction may coexist (Chap. 40, p. 696).

Prothrombin time (PT) and *partial thromboplastin time (PTT)* are standard coagulation tests. Prolongation may stem from very low fibrinogen concentrations, from appreciably reduced levels of the procoagulants needed to generate thrombin, or from large amounts of circulating fibrinogen–fibrin degradation products.

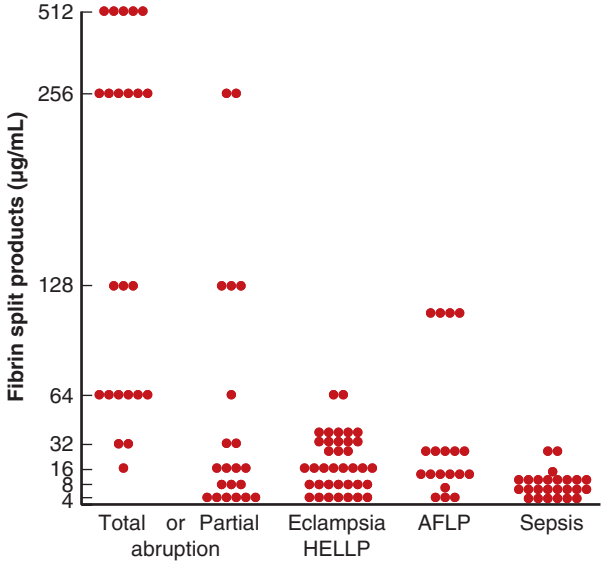

FIGURE 44-3 Quantification of fibrin split products in various obstetrical syndromes that cause disseminated intravascular coagulation. AFLP = acute fatty liver of pregnancy; HELLP = hemolysis, elevated liver enzyme levels, low platelet count. (Reproduced with permission from Cunningham FG, Nelson DB: Disseminated intravascular coagulation syndromes in obstetrics. Obstet Gynecol. 2015 Nov;126(5):999–1011)

Thromboelastometry and *thromboelastography* are point-of-care tests used as adjuncts to conventional laboratory studies (McNamara, 2019; Pacheco, 2019). Their current role may serve to guide blood product replacements as discussed earlier (p. 774). Using many of these tests, several organizations have attempted to establish a more uniform definition of DIC. One is the International Society on Thrombosis and Haemostasis (ISTH) scoring system. The score is used only after a condition known to cause intravascular coagulation is identified and is calculated using a combination of laboratory tests. Composite ISTH-DIC scores <5 suggest nonovert DIC, whereas scores ≥5 are compatible with overt DIC. A scoring system for nonovert DIC has been developed by Alhousseini and coworkers (2020). These scoring systems have not been applied widely in obstetrics (Hizkiyahu, 2019; Jonard, 2016; Nelson, 2014).

General Management

To halt ongoing defibrination, identifying and removing the inciting source is a priority. With incisions or extensive lacerations accompanied by severe hemorrhage, rapid replacement of procoagulants is usually indicated. Vigorous restoration and maintenance of the circulation to treat hypovolemia cannot be overemphasized. Adequate perfusion restores hepatic and endothelial synthesis of procoagulants and permits prompt removal of activated coagulation factors, fibrin, and fibrin degradation products by the reticuloendothelial system.

Aside from these fundamental steps, few other agents have proved soundly effective. Although its use is seemingly counterintuitive, unfractionated heparin has now been abandoned. Other agents not recommended for first-line use include tranexamic acid or epsilon-aminocaproic acid, both antifibrinolytic agents (American College of Obstetricians and Gynecologists, 2019a; Pacheco, 2017). This is because the fibrinolytic system is necessary for dissolution of widespread fibrin thromboses caused by generalized intravascular coagulation (Levi, 2016). Discussed earlier (p. 773), recombinant factor VIIa (rFVIIa) can be used to help control severe obstetrical hemorrhage from other causes. However, current clinical evidence is insufficient to make firm recommendations on its administration for obstetrical coagulopathies.

SURGICAL MANAGEMENT OF HEMORRHAGE

Several invasive procedures can help to arrest severe postpartum hemorrhage. A report from the Agency for Healthcare Research and Quality concluded that most studies addressing these methods are of poor quality (Likis, 2015). In one study of 6660 women with postpartum hemorrhage, 4 percent underwent an invasive procedure, and 1 percent had a hysterectomy (Kayem, 2016). The failure rate of conservative surgical and embolization procedures was 15 percent.

Of specific methods, use of uterine balloon tamponade for treatment of atony has doubled in the past decade (Merriam, 2020; Suarez, 2020). It is described in Chapter 42 (p. 737).

For low-pressure bleeding, topical hemostatic agents can be used to control persistent surgical oozing. These were

reviewed by Stachowicz and colleagues (2020). Other than for cesarean hysterectomy, these are seldom used in obstetrical hemorrhage.

Uterine Compression Sutures

This surgical technique uses a no. 2 chromic suture to compress the anterior and posterior uterine walls together (B-Lynch, 1997). Because they give the appearance of suspenders, they are also called braces (Fig. 44-4). Several modifications of the B-Lynch technique have been described (Gilmandyar, 2019; Matsubara, 2013; Nelson, 2007).

B-Lynch sutures are mainly used to treat atony. These may help diminish DIC-associated bleeding, while coagulation is corrected by transfusion. Success rates vary by indication. For example, B-Lynch (2005) cited 948 cases with only 7 failures. Conversely, in other series, overall failure rates were 20 to 25 percent (Kaya, 2016; Kayem, 2011).

Some unique complications can rarely follow compression sutures (Matsubara, 2013). Most involve variations of

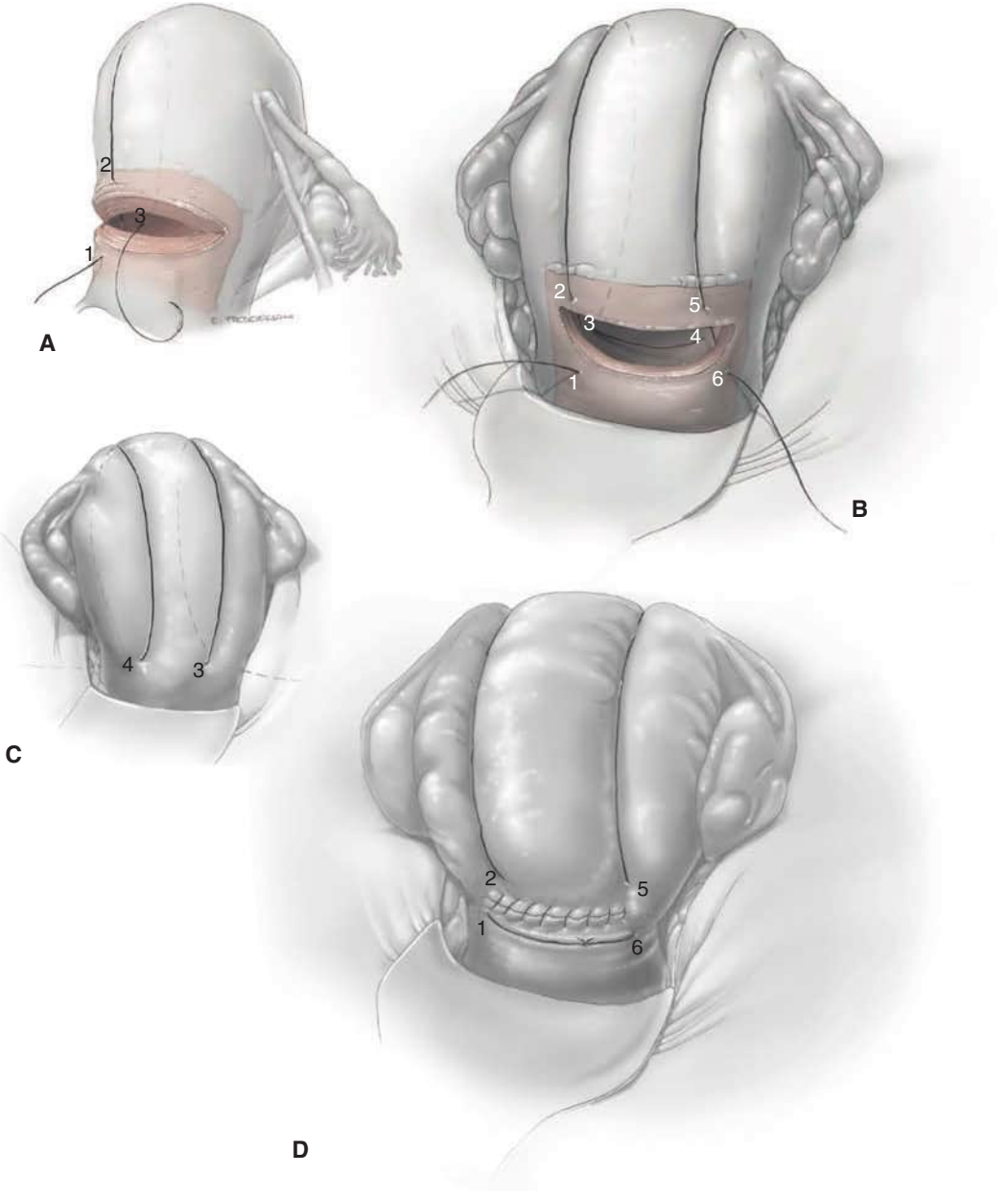

FIGURE 44-4 Uterine compression suture or "brace." The B-Lynch suture technique is illustrated from an anterior view of the uterus in Figures **A**, **B**, and **D** and a posterior view in Figure **C**. The numbers denote the sequential path of the suture and are shown in more than one figure. **Step 1.** Beginning below the incision, the needle pierces the lower uterine segment to enter the uterine cavity. **Step 2.** The needle exits the cavity above the incision. The suture then loops up and around the fundus to the posterior uterine surface. **Step 3.** The needle pierces the posterior uterine wall to reenter the uterine cavity. The suture then traverses to the opposite side within the cavity. **Step 4.** The needle exits the uterine cavity through the posterior uterine wall. From the back of the uterus, the suture loops up and around the fundus to the front of the uterus. **Step 5.** The needle pierces the myometrium above the incision to reenter the uterine cavity. **Step 6.** The needle exits below the incision, and the sutures at points 1 and 6 are tied below the incision. The hysterotomy incision is then closed in the usual fashion.

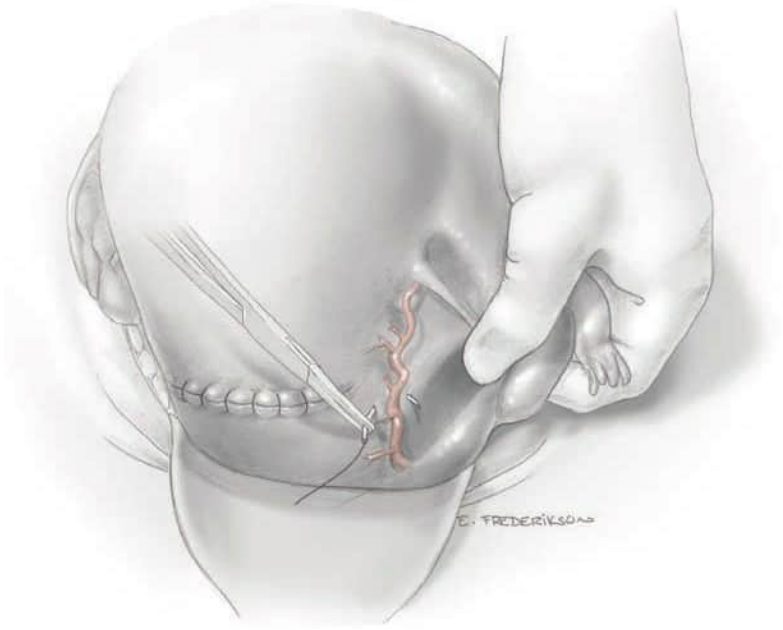

FIGURE 44-5 Uterine artery ligation. The suture goes through the lateral uterine wall anteriorly, curves posteriorly, and then re-enters anteriorly. When tied, it encompasses the uterine artery.

uterine ischemic necrosis with peritonitis (Gottlieb, 2008; Joshi, 2004; Treloar, 2006). In most cases, subsequent pregnancies are uneventful if compression sutures are used (An, 2013). A few women with B-Lynch sutures, however, developed uterine wall defects or uterine cavity synechiae (Akoury, 2008; Alouini, 2011; Ibrahim, 2013).

Artery Ligation

Ligation of arterial blood flow to the uterus can halt or diminish obstetrical hemorrhage. Common indications include uterine hysterotomy incision laceration, uterine atony, and abnormal placentation.

Uterine artery ligation may be unilateral or bilateral and is used mainly for lacerations at the lateral part of a hysterotomy incision (Fig. 44-5). In our experiences, this procedure is less helpful for other hemorrhage etiologies. In rare cases with torrential hemorrhage from placenta accreta syndrome, a tourniquet wrapped around the lower uterine segment may slow bleeding sufficiently while resuscitation ensues and dissection for hysterectomy is performed.

Internal iliac artery ligation may also be unilateral or bilateral. For years, ligation has been used to reduce pelvic hemorrhage. However, the procedure may be technically difficult and is successful in only half of cases (American College of Obstetricians and Gynecologists, 2019a; Bienstock, 2021). Wei and colleagues (2019) reported it to be successful for improved hemostasis with placenta previa. It is not particularly helpful for abating hemorrhage with postpartum atony (Clark, 1985).

For internal iliac ligation, adequate exposure is obtained by opening the peritoneum over the common iliac artery and dissecting down to the bifurcation of the external and internal iliac arteries (Fig. 44-6). Branches distal to the external iliac arteries are palpated to verify pulsations at or below the inguinal area. Ligation of the internal iliac artery at a point 5 cm distal to the common iliac bifurcation will usually avoid the internal iliac artery's posterior division branches (Bleich, 2007). The areolar sheath of the artery is incised longitudinally, and a right-angle clamp is carefully passed just beneath the artery from lateral to medial. Care must be taken not to perforate contiguous large veins, especially the internal iliac vein. Suture—usually nonabsorbable—is passed under the artery with a clamp, and the vessel is then securely ligated.

The most important mechanism of action with internal iliac artery ligation is an 85-percent reduction in pulse pressure in those arteries distal to the ligation (Burchell, 1968). This converts an arterial pressure system into one with pressures approaching those in the venous circulation. This creates vessels more amenable to hemostasis via pressure and clot formation.

Even bilateral internal iliac artery ligation does not appear to interfere with subsequent reproduction. Nizard and colleagues (2003) reported subsequent pregnancy in 17 such women. From a total of 21 pregnancies, 13 were normal, 3 ended with miscarriage, 3 were terminated, and 2 were ectopic.

Angiographic Embolization

This modality is now used for many causes of intractable hemorrhage when surgical access is difficult. Its use has increased remarkably in the past decade (Merriam, 2020). In more than

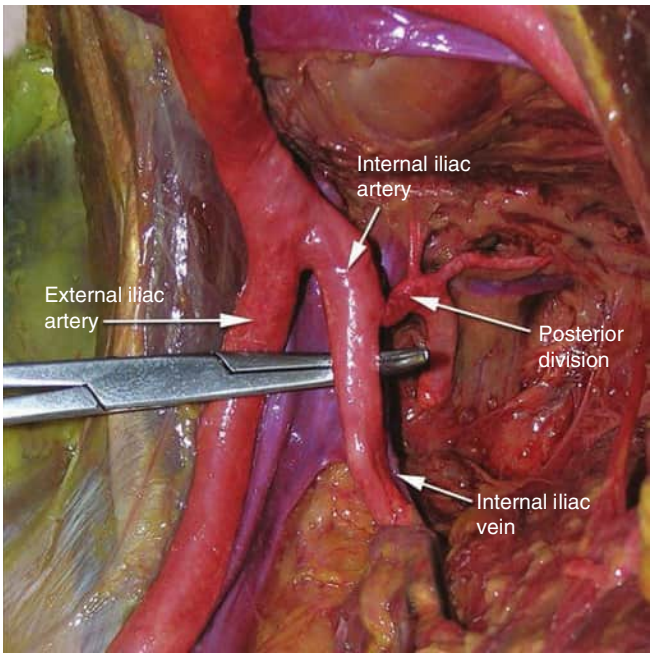

FIGURE 44-6 Ligation of the right internal iliac artery. Unembalmed cadaveric dissection shows the right-angle clamp passing underneath the anterior division of the internal iliac artery just distal to its posterior division. (Reproduced with permission from Dr. Marlene Corton.)

500 pregnancy-related cases, embolization was effective in 90 percent (Grönvall, 2014; Lee, 2012; Poujade, 2011; Zhang, 2015). After his review, Rouse (2013) concluded that embolization can be used to arrest refractory postpartum hemorrhage. Other reports have been less enthusiastic. Fertility is not impaired, and many subsequent successful pregnancies have been reported (Fiori, 2009; Kolomeyevskaya, 2009). *An important caveat for these procedures is that women with hemodynamic instability related to active bleeding should not be removed from the operating room*.

Complications are relatively uncommon but can be severe. Case reports detail instances of iatrogenic iliac artery rupture, uterine ischemic necrosis, and uterine infection (Grönvall, 2014; Katakam, 2009; Nakash, 2012). A rare case of massive buttock necrosis and paraplegia followed bilateral internal iliac artery embolization (Al-Thunyun, 2012). A myometrial defect in subsequent pregnancy also has been reported (Choo, 2019).

In a few instances, massive blood loss and difficult surgical dissection is anticipated. The use of balloon-tipped catheters preoperatively inserted into the iliac or uterine arteries is described in management of placenta accreta spectrum (Chap. 43, p. 759).

Aortic Compression

Prophylactic use of an aortic balloon occlusion device has been reported to reduce blood loss and the need for hysterectomy (Chen, 2019). Also known as *resuscitative endovascular balloon occlusion of the aorta* (*REBOA*), such occlusion lowers the perfusion pressure distally, increases cardiac afterload, and redistributes blood volume to the heart and brain (Cannon, 2018). Prolonged occlusion can result in lower limb ischemia requiring amputation. Whittington and colleagues (2020) described its successful prophylactic use in 11 women with placenta accreta spectrum disorders.

Instead, manual compression of the aorta above the sacral promontory can be used in cases in which pelvic hemorrhage is torrential. If the abdomen is closed, pressure placed above the umbilicus reduces blood pressure distally (Barbieri, 2018).

Pelvic Packing

If hysterectomy fails to curtail hemorrhage, then pelvic packing with gauze and termination of the operation may be considered (Pacheo, 2018; Touhami, 2018). Rolls of gauze are packed to provide constant local pressure. In some cases, this may serve as a temporizing step prior to interventional embolization. In other cases, packing alone may be left for 48 to 72 hours. If the patient is stable and bleeding appears to have stopped, packing is removed. In one review of 104 cases, the success rate was 79 percent. Packing failed in 24 patients, and 13 of these women died, yielding an overall mortality rate of 13 percent (Touhami, 2018).

The *umbrella* or *parachute pack* uses a similar concept (Logothetopulos, 1926). Although seldom used today, it can be lifesaving if all other measures have failed, especially in low-resource areas (Dildy, 2006; Touhami, 2018). The pack is constructed of a sturdy sterile plastic bag that is filled with gauze rolls that are unwound and knotted together. Sufficient rolls are used to provide adequate volume in the bag to fill the pelvis. The pack is introduced transabdominally with the stalk exiting the vagina. Mild traction is applied by tying the stalk to a 1-liter fluid bag, which is hung over the foot of the bed. The umbrella pack is removed vaginally after 24 hours.

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CHAPTER 45

Preterm Birth

Preterm birth is a substantial global health issue with significant consequences to the newborn, family, and society. Preterm delivery affects nearly 15 million births worldwide, is the leading cause of death in children younger than 5 years, and remains a prominent issue in obstetrics (Chawanpaiboon, 2019). Although the burden of preterm birth is clear, defining the biology of human parturition and identifying strategies to reduce preterm birth rates remain elusive.

DEFINITION OF PRETERM BIRTH

Preterm birth is delivery before 37 completed weeks, that is, before $36^{6/7}$ weeks. Subdivisions vary among organizations. According to the American College of Obstetricians and Gynecologists (2021b), births occurring between 34 and 36 completed weeks are considered *late preterm*. The Centers for Disease Control and Prevention recognizes this late preterm definition but also labels births before $33^{6/7}$ weeks as *early preterm* (Martin, 2021). Instead, the World Health Organization (2018) defines births before 28 completed weeks as *extremely preterm*, those from 28 to 32 weeks as *very preterm*, and from 32 to 37 weeks as *moderate to late preterm*.

These definitions lack a functional basis and should be distinguished from the concept of *prematurity*, which represents incomplete development of various organ systems at birth. For example, the lungs are particularly affected and may be susceptible to the respiratory distress syndrome (Chap. 34, p. 615). Similarly, neonates born before term can be small or large for gestational age but are still preterm by definition. *Low birthweight* refers to neonates weighing 1500 to 2500 g; *very low birthweight* describes those between 1000 and 1500 g; and *extremely low birthweight* refers to those <1000 g (World Health Organization, 2019).

PRETERM BIRTH RATE TRENDS

In the United States, the preterm birth rate rose from 10.02 percent in 2018 to 10.23 percent for 2019. When interpreting these data, important factors and trends merit discussion. First, during the past two decades, the percentage of preterm neonates fell from 2007 to 2014 but has since risen (Martin, 2021). Some argue that the rate drop reflected changes in obstetrical dating criteria rather than true declines (Frey, 2016). Specifically, beginning in 2014, the National Center for Health Statistics transitioned to a new standard for estimating newborn gestational age for birth certificate completion (Martin, 2015). The new measure, which is the *obstetrical estimate* of gestational age at delivery, replaced calculations based on the date of the *last menstrual period*. These measures differ and do not provide equivalent absolute numerical comparisons of preterm

birth rates. *Thus, current national data are now not directly comparable to previously reported preterm birth rates.*

Although the percentage of neonates born early preterm rose slightly, the rise in the overall preterm rate from 2018 to 2019 was due primarily to the increase in late-preterm births. Rates of these preterm births have gradually risen since 2013 (Martin, 2021). Notably, national data do not separate spontaneous preterm births from those that may be prompted for medical indication.

One disturbing aspect of preterm birth rate trends in the United States is persistent disparities. Rates of preterm birth among black women are markedly elevated above those for white and Hispanic women (Martin, 2021). Some investigators attribute this to differing socioeconomical circumstances (Collins, 2007; Leveno, 2009). The rates of preterm birth in the United States are also higher compared with those in other industrialized countries (Ananth, 2009; Delnord, 2017). Internationally, preterm birth rates also are rising (Chawanpaiboon, 2019).

Last, births in singleton pregnancies should be analyzed separately from *all* births. Namely, multifetal gestations have a shorter average gestational length and raise preterm birth rates (Martin, 2021).

PRETERM NEWBORN MORBIDITY AND MORTALITY

In 2018 in the United States, 21,498 infants died in their first year of life, and 66 percent of infant deaths were among those born preterm. Gestational age at delivery and the risk of neonatal morbidity and mortality are inversely related. Namely, neonates born in the early-preterm period make up the smallest proportion of births, but these infants experience disproportionately higher rates of prematurity-related complications, including death (Table 45-1) (Ely, 2020). For context, the infant mortality rate in those born at less than 28 weeks' gestation was *186 times higher* than in those born at 37 to 41 weeks in the United States in 2018.

TABLE 45-1. Infant Mortality Rates in the United States in 2018

	Live Births	Infant Deaths
Total infants	3,791,712	21,498
Gestational age (weeks)		
<34	104,031	12,004
34–36	275,746	2263
<37	379,777	14,267
37–38	1,005,405	3135
39–41	2,292,705	3843
≥42	11,318	61

The joint effect of gestational age and infant condition at birth also has been examined. Data from the Swedish Medical Birth Register correlated Apgar scores at 5 and 10 minutes in preterm neonates across gestational ages. The relative risk of death consistently increased with decreased Apgar scores (Cnattingius, 2020). Low Apgar scores in preterm newborns may reflect biological immaturity rather than fetal depression. However, Apgar scores and changes in the score between 5 and 10 minutes were associated with neonatal mortality among preterm newborns.

Preterm neonates who survive are at risk for a range of short- and long-term morbidities, largely due to organ system immaturity (Table 45-2) (Eichenwald, 2008). That said, remarkable strides have been made in neonatal survival for those born preterm. In a study of more than 18,000 newborns weighing between 400 and 1500 g or aged between 22 and

TABLE 45-2. Major Short- and Long-Term Problems in Very-Low-Birthweight Infants

Organ or System	Short-Term Problems	Long-Term Problems
Pulmonary	Respiratory distress syndrome, air leak, bronchopulmonary dysplasia, apnea of prematurity	Bronchopulmonary dysplasia, reactive airway disease, asthma
Gastrointestinal or nutritional	Hyperbilirubinemia, feeding intolerance, necrotizing enterocolitis, growth failure	Failure to thrive, short-bowel syndrome, cholestasis
Immunological	Hospital-acquired infection, immune deficiency, perinatal infection	Respiratory syncytial virus infection, bronchiolitis
Central nervous system	Intraventricular hemorrhage, periventricular leukomalacia, hydrocephalus	Cerebral palsy, hydrocephalus, cerebral atrophy, neurodevelopmental delay, hearing loss
Ophthalmological	Retinopathy of prematurity	Blindness, retinal detachment, myopia, strabismus
Cardiovascular	Hypotension, patent ductus arteriosus, pulmonary hypertension	Pulmonary hypertension, systemic hypertension, hypertension in adulthood
Renal	Water and electrolyte imbalance, acid-base disturbances	Hypertension in adulthood
Hematological	Iatrogenic anemia, need for frequent transfusions, anemia of prematurity	
Endocrinological	Hypoglycemia, transiently low thyroxine levels, cortisol deficiency	Impaired glucose regulation, increased insulin resistance

32 weeks' gestation, survival rates were analyzed as a function of both birthweight *and* gestational age (Fanaroff, 2007). After achieving a birthweight ≥1000 g, a gestational age ≥28 weeks for females, or age ≥30 weeks for males, survival rates reach 95 percent.

Threshold of Viability

Births once considered to be "abortuses" because the fetus weighed <500 g are now classified as live births. In the United States in 2019, 5189 live births weighed <500 g (Martin, 2021). Fortunately, perinatal and neonatal care has advanced tremendously for these births. As a result, the *threshold of viability,* which is the lower limit of fetal maturation compatible with extrauterine survival, has been reassessed. Currently, the threshold of viability lies between $20^{0/7}$ and $25^{6/7}$ weeks' gestation. Neonates born in this *periviable period* are vulnerable because of their immature organ systems. Complications include brain injury and sepsis, both described in Chapter 34, (p. 618). To guide obstetrical decision-making and care of these fetuses, a national perinatal workshop convened in 2013 (Raju, 2014). The executive summary statement from this meeting served as the foundation for an Obstetric Care Consensus document (American College of Obstetricians and Gynecologists, 2019d).

Periviable Neonatal Survival

Delivery before 23 weeks' gestation often results in death, and survival rates approximate 5 to 10 percent (Fig. 45-1). Among survivors, morbidity is significant. Practices regarding active resuscitation vary between institutions and may explain the differing perinatal outcomes among these. Neonatal survival rates also vary among international comparisons, and rates at 24 weeks' gestation range from 35 to 84 percent (Helenius, 2017).

A retrospective analysis of infants born at the University of Iowa from 2006 to 2015 at 22 to 25 weeks' gestation underscores this issue (Watkins, 2020). After excluding anomalous fetuses, death in the delivery room, and parental request for palliation, the neurodevelopmental outcomes were analyzed for 169 of 214 survivors at 18 to 22 months. Active management was defined as antenatal corticosteroids and resuscitation when desired by the parents. The survival rate was lower in neonates born at 22 to 23 weeks' than at 24 to 25 weeks' gestation. However, mild or no neurodevelopmental impairment was reported in 64 percent of the surviving 22- to 23-week infants.

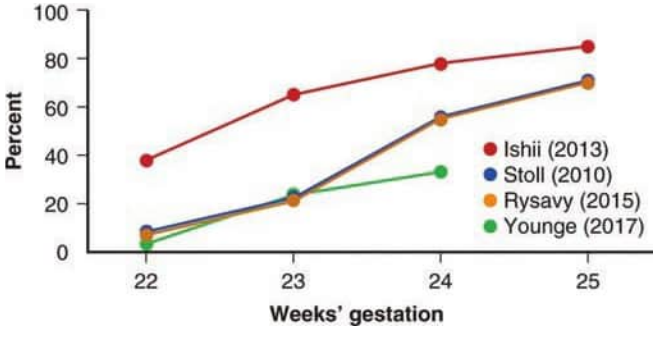

FIGURE 45-1 Neonatal survival rates according to condition at birth and gestational age. Ishii (2013) data curve reflects liveborn survival rates; Stoll (2010) curve reflects liveborn survival rates; Rysavy (2015) curve reflects overall survival rates; Younge (2017) curve reflects survival and neurodevelopmental outcomes.

An important caveat when examining perinatal outcomes, however, is ascertainment bias. For example, the mean survival rate is 45 percent if the denominator is all live births compared with 72 percent if the denominator is only newborns admitted to neonatal intensive care (Guillen, 2011). Another source of bias is use of multicenter datasets with considerable differences in obstetrical and early neonatal interventions (Stoll, 2010).

To evaluate contemporaneous outcomes of neonates born at 22 to 24 weeks, the National Institute of Child Health and Human Development (NICHD) Neonatal Research Network reported both survival and neurodevelopmental outcomes across consecutive birth-year epochs of 2000 to 2003, 2004 to 2007, and 2008 to 2011 in infants aged 18 to 22 months (Younge, 2017). The percentage of infants who survived rose significantly from 30 percent in 2000 to 2003 to 36 percent in 2008 to 2011. The percentage of infants who survived without neurodevelopmental impairment also significantly grew from 16 percent to 20 percent during the same time period. Although rates of survival without neurodevelopmental impairment increased over time for those born at 23 and 24 weeks, only 1 percent of infants born at 22 weeks survived without neurodevelopmental impairment (Younge, 2017).

Somewhat similar results were published from Sweden. This report details a national population-based study of all neonates born at 22 to 26 weeks. Rates of survival to 1 year from 2004 to 2007 were compared with rates from 2014 to 2016. Survival rates at 1 year among live-born neonates at 22 to 26 weeks' gestation significantly improved during the later period (Table 45-3) (Norman, 2019).

Clinical Management

The Periviable Birth Obstetric Care Consensus document also addresses management options based on the clinical characteristics of a given pregnancy. Nonmodifiable factors are fetal gender, weight, and plurality. Potentially modifiable antepartum and intrapartum factors include the location of delivery, intent to intervene by cesarean delivery, and administration of antenatal corticosteroids (Table 45-4). Postnatal management addresses the initiation or withdrawal of intensive care after birth.

Cesarean delivery at the threshold of viability is controversial. If the fetus-neonate is perceived to be too immature for aggressive support, cesarean delivery for common indications such as breech presentation or nonreassuring fetal heart rate patterns might be preempted. Moreover, observational studies have been inconsistent in demonstrating a benefit of cesarean delivery for the sole indication of periviability. Moreover, cesarean delivery may predispose the gravida to adverse intraoperative events and morbidity (Bertholdt, 2018; Blanc, 2019).

In a study of 2906 singletons between $24^{0/7}$ and $31^{6/7}$ weeks eligible for attempted vaginal birth, 84 percent of cephalic presenting fetuses were delivered vaginally (Reddy, 2012). Neonatal mortality rates did not differ compared with those associated with planned cesarean delivery. For *breech*

TABLE 45-3. One-Year Survival Among Infants Delivered at 22–26 Weeks' Gestational Age in Sweden

	22 Weeks' Gestation No./Total (%)		23 Weeks' Gestation No./Total (%)		24 Weeks' Gestation No./Total (%)	
	2004–2007	2014–2016	2004–2007	2014–2016	2004–2007	2014–2016
All Deliveries						
Stillbirths	91/140 (65)	52/148 (35)	82/183 (45)	59/207 (29)	47/191 (25)	68/260 (26)
Live born	49/140 (35)	96/148 (65)	101/183 (55)	148/207 (71)	144/191 (75)	192/260 (74)
1-yr Survival						
NICU admission	5/17 (29)	29/50 (58)	53/81 (65)	91/138 (66)	96/132 (73)	151/191 (79)
Live born[a]	5/49 (10)	29/96 (30)	53/101 (52)	91/148 (61)	96/144 (67)	151/192 (79)
All deliveries[b]	5/140 (3.6)	29/148 (20)	53/183 (29)	91/207 (44)	96/191 (50)	151/260 (58)
1-yr Survival; No Major Morbidity[c]						
NICU admission	1/5 (20)	5/29 (17)	9/53 (17)	25/91 (28)	30/96 (31)	60/151 (40)
Live born[d]	1/49 (2.0)	5/96 (5.2)	9/101 (8.9)	25/148 (17)	30/144 (21)	60/192 (31)

	25 Weeks' Gestation No./Total (%)		26 Weeks' Gestation No./Total (%)		22–26 Gestation (all infants) No./Total (%)	
	2004–2007	2014–2016	2004–2007	2014–2016	2004–2007	2014–2016
All Deliveries						
Stillbirths	45/250 (18)	58/277 (21)	39/245 (16)	36/304 (12)	304/1009 (30)	273/1196 (23)
Live born	205/250 (82)	219/277 (79)	206/245 (84)	268/304 (88)	705/1009 (70)	923/1196 (77)
1-yr Survival						
NICU admission	167/200 (84)	193/219 (88)	176/204 (86)	247/267 (93)	497/634 (78)	711/865 (82)
Live born[a]	167/205 (81)	193/219 (88)	176/206 (85)	247/268 (92)	497/705 (70)	711/923 (77)
All deliveries[b]	167/250 (67)	193/277 (70)	176/245 (72)	247/304 (81)	497/1009(49)	711/1196 (59)
1-y Survival; No Major Morbidity[c]						
NICU admission	75/167 (45)	104/193 (54)	111/176 (63)	161/247 (65)	226/497 (45)	355/711 (50)
Live born[d]	75/205 (37)	104/219 (47)	111/206 (54)	161/268 (60)	226/705 (32)	355/923 (38)

[a]Primary outcome.
[b]Includes stillbirths.
[c]Major neonatal morbidity defined as intraventricular hemorrhage grade 3 or 4; periventricular leukomalacia; necrotizing enterocolitis; retinopathy of prematurity stage 3, 4, or 5; or severe bronchopulmonary dysplasia.
[d]Secondary outcome.
NICU = neonatal intensive care unit.

TABLE 45-4. General Guidance for Threatened Periviable Birth

	Weeks' Gestation			
	<22	$22^{0/7}$– $22^{6/7}$	$23^{0/7}$– $23^{6/7}$	$24^{0/7}$ +
Assess neonate for resuscitation	Not recommended	Consider	Consider	Recommended
Corticosteroid therapy	Not recommended	Not recommended	Consider	Recommended
Tocolysis to allow CS therapy	Not recommended	Not recommended	Consider	Recommended
MS for neuroprotection	Not recommended	Not recommended	Consider	Recommended
Antibiotics for PPROM	Consider	Consider	Consider	Recommended
GBS prophylaxis	Not recommended	Not recommended	Consider	Recommended
CD for fetal indication	Not recommended	Not recommended	Consider	Consider[a]/recommended

[a]CD is considered for fetuses $24^{0/7}$– $24^{6/7}$ but recommend for those $25^{0/7}$ weeks and older.
CD = cesarean delivery; CS = corticosteroid; GBS = Group B streptococcus; MS = magnesium sulfate; PPROM = preterm prelabor rupture of membranes.

presentations, however, relative risk for mortality was threefold higher with attempted vaginal delivery. In another study, Werner and colleagues (2013) analyzed 20,231 newborns delivered at 24 to 34 weeks. Cesarean delivery did not protect against poor outcomes such as neonatal death, intraventricular hemorrhage, seizures, respiratory distress, and subdural hemorrhage.

From these findings, the Obstetric Care Consensus proposes that cesarean delivery be *considered* for fetal indications at $23^{0/7}$ to $24^{6/7}$ weeks. However, before 22 weeks, this route is reserved only for maternal indications. As emphasized by the authors of the Iowa report cited earlier, providing active management—such as antenatal corticosteroids—can be uncoupled from the decision of cesarean in the periviable period (Watkins, 2020). That said, the frequency of cesarean in the 23rd week has increased in the United States following publication of the perinatal workshop executive summary in 2014 (Rossi, 2019).

It is difficult to summarize the current practices of obstetrical care in the management of the periviable pregnancy given its continued rapid evolution. Moreover, it appears that maternal and neonatal interventions are shifting during the 22- to 23-week gestational age period. Data from the National Center for Health Statistics show that rates of at least one maternal or neonatal intervention were 38.9 percent and 78.3 percent for 22 and 23 weeks' gestation, respectively (Hajdu, 2020).

In this uncertain environment, individualized, patient-centered care with a multidisciplinary team remains essential. This is particularly relevant given that nearly 20 percent of women may have serious morbidity with delivery during the periviable period (Rossi, 2018).

For cases with threatened periviable delivery, neonatal and perinatal consultation aids informed decision-making and helps form expectations for the family. For fetuses with a life-limiting condition, such as extreme prematurity, *perinatal palliative care* is a strategy that emphasizes comfort (American College of Obstetricians and Gynecologists, 2019c). Care team members can include obstetric and neonatal professionals, chaplaincy, and mental health specialists.

Late-preterm Birth

As discussed, neonates born between 34 and 36 weeks' gestation account for more than 70 percent of all preterm births (Fig. 45-2) (Martin, 2021). Most of the increase in the total preterm birth rate for the United States 2018 to 2019 was among neonates born at 34 to 36 weeks. To estimate the risks associated with late-preterm births, investigators analyzed neonatal mortality and morbidity rates at 34, 35, and 36 weeks compared with those of births at term at Parkland Hospital (McIntire, 2008). Approximately 3 percent of all births during the study period were between 24 and 32 weeks, and 9 percent were during the late-preterm period. Thus, and similar to the national rates, late-preterm births accounted for three fourths of all preterm births. Approximately 80 percent of these resulted from idiopathic spontaneous preterm labor or prematurely ruptured membranes (Fig. 45-3). Other obstetrical complications were implicated in the remaining 20 percent of cases. Rates of morbidity and mortality were greater in these late-preterm newborns compared with rates in term ones (Table 45-5) (McIntire, 2008). Similarly, Tomashek (2007) reported higher neonatal mortality rates for late-preterm newborns. Rates of adverse neurodevelopment outcomes also are increased in these late-preterm infants (Petrini, 2009). Taken together, these findings suggest that a health-care focus on prematurity should include these late-preterm births.

CAUSES OF PRETERM BIRTH

Four direct causes for preterm births in the United States include (1) spontaneous unexplained preterm labor with intact membranes, (2) idiopathic preterm prelabor rupture of membranes, (3) delivery for maternal or fetal indications, and (4) twins and higher-order multifetal births. Of all preterm births, 30 to 35 percent are indicated, 40 to 45 percent are due to spontaneous preterm labor, and 30 to 35 percent follow preterm membrane rupture (Goldenberg, 2008). More than

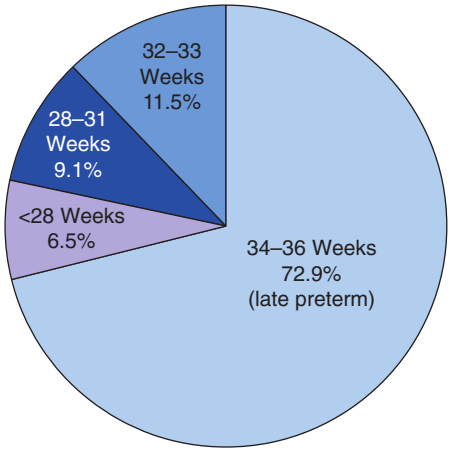

FIGURE 45-2 Distribution of preterm births by gestational age in the United States in 2019.

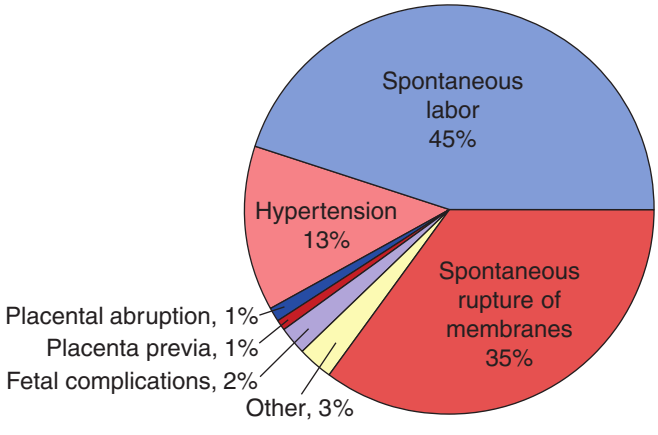

FIGURE 45-3 Obstetrical complications associated with 21,771 late-preterm births at Parkland Hospital.

TABLE 45-5. Neonatal Outcomes in Live Births Delivered Late Preterm Compared with Referent Group at 39 Weeks

	Weeks' Gestation			
	34	35	36	39
Neonatal death rate per 1000 live births (no.)				
	1.1	1.5	0.5	0.2
Morbidity (%)				
Resp. distress				
Ventilator	3.3[a]	1.7[a]	0.8[a]	0.3
TTN	2.4[a]	1.6[a]	1.1[a]	0.4
IVH				
Grades 1, 2	0.5[a]	0.2[a]	0.06[a]	0.01
Grades 3, 4	0	0.02	0.01	0.004
Sepsis				
Work-up	31[a]	22[a]	15[a]	12
Proven	0.5[a]	0.4[a]	0.2[b]	0.1
Phototherapy	6.1[a]	3.5[a]	2.0[a]	1
NEC	0.09[a]	0.02[b]	0.01	0.001
5-min Apgar ≤3	0.1	0.2[a]	0.9	0.06
Intubation	1.4[a]	0.8[b]	0.6	0.6
≥1 of above	34[a]	24[a]	17[a]	14

[a] $p < .001$ compared with the 39 weeks referent.
[b] $p < .05$ compared with the 39 weeks referent.
IVH = intraventricular hemorrhage; NEC = necrotizing enterocolitis; Resp. = respiratory; TTN = transient tachypnea

98 percent of triplets and 60 percent of twins are born preterm (Martin, 2021).

At term, a common parturition pathway is activated physiologically and leads to labor. For preterm labor, several disease processes are thought to activate one or more of the components of this common pathway (Romero, 2014). Put another way, preterm labor is not simply labor that starts too soon. This paradigm is supported by the rationale that causes of preterm birth have multiple, often interacting, antecedents and contributing factors that lead to a heterogenous syndrome (Deindl, 2020; Esplin, 2016). Analogous to other complex disease processes, multiple coexistent genetic alterations, bacterial and viral colonization, and diverse environmental factors may lead to preterm birth (Bayar, 2020; Mekonnen, 2021; Volozonoka, 2020). These multiple factors continue to pose challenges in identifying predictive biomarkers in blood, urine, or cervicovaginal fluid, despite significant technical advances in multiomic approaches (Ghaemi, 2021; Jehan, 2020; Peterson, 2020; Parry, 2020).

■ Spontaneous Preterm Labor

Pregnancies with spontaneous preterm labor yet intact fetal membranes must be distinguished from those complicated by ruptured membranes. Even so, spontaneous preterm labor does not constitute a homogeneous group. Evidence suggests it is a syndrome attributable to multiple pathological processes (Romero, 2014). Among the more common associated findings

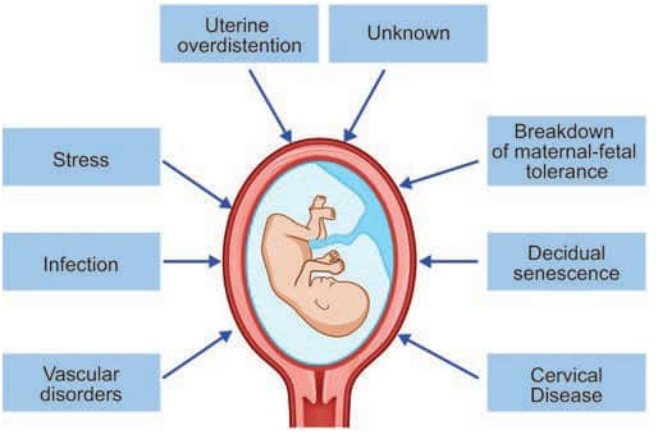

FIGURE 45-4 Proposed mechanisms of disease implicated in spontaneous preterm labor. Genetic and environmental factors are likely contributors to each mechanism.

are multifetal pregnancy, intrauterine infection, bleeding, placental infarction, premature cervical dilation, cervical insufficiency, hydramnios, uterine fundal abnormalities, and fetal anomalies. Severe maternal illness from infections, autoimmune diseases, and gestational hypertension also elevate preterm labor risks.

These processes culminate in a common end point of premature cervical dilation, effacement, and activation of uterine contractions. Importantly, the actual process of preterm labor should be considered a final step stemming from progressive or acute changes that could be initiated days or even weeks before labor onset. Diverse pathways to instigate parturition exist and are dependent on the etiology of preterm birth (Fig. 45-4) (Romero, 2014). Major causes include uterine overdistention, premature cervical changes, infection, and maternal–fetal stress. Genetic and environmental factors likely contribute to each mechanism.

Uterine Overdistention

Multifetal pregnancy and hydramnios are well-recognized risks for preterm birth. With these, *uterine overdistention* imparts greater stress on the myometrium. In nonhuman primates, inflation of intraamnionic balloons can stimulate uterine contractility, preterm labor, and an "inflammatory pulse." Similar inflammatory responses have been observed in the amnion of women with polyhydramnios and twins (Adams Waldorf, 2015).

Early uterine overdistention likely acts to initiate expression of contraction-associated proteins in the myometrium. These genes include those coding for gap-junction proteins, oxytocin receptors, and prostaglandin synthase (Korita, 2002; Lyall, 2002; Sooranna, 2004). Excessive uterine distention also leads to early activation of the placental–fetal endocrine cascade (Chap. 21, p. 407). Taken together, mechanical stress-induced distension and activation of endocrine cascades both lead to premature activation of inflammatory responses that result in uterine contractile activation (Gomez-Lopez, 2014; Stephen, 2015). A possible compensatory response to uterine distention is tissue remodeling and muscle growth (Adams Waldorf, 2015).

Cervical Dysfunction

In most cases, premature cervical remodeling precedes labor onset. In some instances, cervical dysfunction of the epithelia or its stromal extracellular matrix is the underlying cause (Nallasamy, 2017). Importantly, an intact cervical epithelial barrier is critical to prevent ascending infection. For example, loss of hyaluronan in cervical epithelia or colonization of group B streptococcus (GBS) enhances risk of preterm birth (Akgul, 2014; Coleman, 2021). GBS has the unique ability to synthesize the hyaluronan-degrading enzyme hyaluronidase to aid bacterial ascension (Vornhagen, 2017). Second, the mechanical competence of the cervix can be reduced. Genetic mutations in components of collagen and elastic fibers or proteins required for their assembly can be risk factors for cervical insufficiency and preterm birth (Nallasamy, 2017; Volozonoka, 2020).

Infection

Of all the mechanisms listed in Figure 45-4, only intraamnionic infection has been causally linked to spontaneous preterm delivery (Romero, 2014). Bacteria can gain access to intrauterine tissues through (1) transplacental transfer of maternal systemic infection, (2) flow of infection via the fallopian tubes, or (3) ascending infection with bacteria from the vagina and cervix. Because the lower pole of the fetal membrane–decidual junction is contiguous with the cervical canal orifice, this anatomical arrangement provides a passageway for microorganisms. Ascending infection is considered to be the most common entry route where microorganisms colonize the cervix, decidua, and possibly the membranes, and then may enter the amnionic sac.

Colonization with an infectious agent has been detected in 25 to 40 percent of all preterm deliveries (Goldenberg, 2008). In some instances, histological evidence of microbial inflammation is found in the fetal membranes, decidua, or umbilical cord. Other cases are deemed sterile intraamnionic inflammation. Despite the substantial association of infection with preterm birth, the cellular and molecular mechanisms underlying inflammation-driven preterm birth remain undefined (Cappelletti, 2020; Purisch, 2017).

Current data suggest that microbial invasion of the reproductive tract is sufficient to induce infection-mediated preterm birth. The level and kinetics of inflammation can vary between a polymicrobial or single-microbe exposure (Tong, 2021). Affected women are more likely to develop clinical chorioamnionitis and rupture of membranes compared with women whose cultures are sterile. Moreover, their neonates are also more likely to have perinatal complications such as neonatal sepsis (Villamor-Martinez, 2020). Although the clinical course is more severe when intraamnionic infection is obvious, inflammation in the absence of detectable intraamnionic microorganisms—termed *sterile intraamnionic inflammation*—is also a risk factor for an inflammatory response (Motomura, 2021). In sum, the earlier the onset of preterm labor, the greater the likelihood of underlying infection (Goldenberg, 2000; Goncalves, 2002).

Paradoxically, the incidence of culture-positive amnionic fluid collected by amniocentesis during spontaneous labor at term is similar to that with preterm labor (Gomez, 1994; Romero, 1993). It has been suggested that at term, amnionic fluid is infiltrated by bacteria as a consequence of labor, whereas in preterm pregnancies, bacteria represent an inciting cause. Thus, fetal infection, as defined by bacteria detected within amnionic fluid, has differing etiologies and consequences.

With chorioamnionitis, microbes may invade only maternal tissue and not amnionic fluid. Despite this, endotoxins can stimulate amnionic cells to secrete cytokines that enter amnionic fluid. This scenario may serve to explain the apparently contradictory observations concerning an association between amnionic fluid cytokines and preterm labor in cases in which microbes are not detected in the amnionic fluid.

Inflammatory Responses. These responses drive the pathogenesis of infection-induced preterm labor. Lipopolysaccharide (LPS) or other toxins elaborated by bacteria are recognized by receptors such as *toll-like receptors (TLRs)* (Janssens, 2003). These receptors are present on mononuclear phagocytes, decidual cells, cervical epithelia, and trophoblasts (Gonzalez, 2007; Holmlund, 2002). The expression of TLRs on maternal immune cells is necessary to recognize inflammatory stimuli in inflammation-mediated preterm birth (Cappelletti, 2020). Activation of TLRs induces a signaling cascade that activates production of chemokines such as interleukin 8 (IL-8) and cytokines such as IL-1β. Activation also recruits immune cells into the reproductive tract. Cytokines are produced by immune cells and by cells within the cervix, decidua, membranes, or fetus itself.

LPS-induced production of IL-1β in turn promotes a series of responses that include (1) increased synthesis of others, that is, IL-6, IL-8, and tumor necrosis factor alpha (TNF-α); (2) proliferation, activation, and migration of leukocytes; (3) modifications in extracellular matrix proteins; and (4) mitogenic and cytotoxic effects such as fever and acute-phase response (El-Bastawissi, 2000). In many tissues, including myometrium, decidua, and amnion, IL-1β also promotes prostaglandin formation that induces cervical ripening and loss of myometrial quiescence (Challis, 2002; Keelan, 2003). The importance of prostaglandins to infection-mediated preterm birth is supported by the observation that prostaglandin inhibitors can reduce the rate of LPS-induced preterm birth in both the mouse and nonhuman primate (Gravett, 2007; Timmons, 2014). Inhibition of cyclooxygenase 2 prevents inflammation-mediated preterm labor in the mouse. For these reasons, clinical approaches described on page 806 are being explored.

Proteases such as matrix metalloproteinases (MMPs) also are induced by inflammatory cytokines and function to break down extracellular matrix components such as collagen or elastic fibers. This disrupts the structural integrity of fetal membranes or the cervix. Current evidence from animal and human studies suggests that many aspects of infection-mediated preterm birth differ from pathways that regulate term parturition (Hamilton, 2012; Shynlova, 2013a,b; Willcockson, 2018).

Origin of Cytokines. Secretion of uterine cytokines is likely important for preterm labor. Cytokines produced in maternal decidua and myometrium have effects confined to that side, whereas cytokines produced in the membranes or in cells within the amnionic fluid will not be transferred to maternal tissues.

In general, resident and invading leukocytes produce the bulk of cytokines in cases of inflammation resulting from infection.

The presence of cytokines in amnionic fluid and their association with preterm labor is well documented. But, their exact cellular origin—with or without recoverable microorganisms—is not well defined. Amnionic fluid cytokines are most likely secreted by mononuclear phagocytes or neutrophils activated and recruited into the amnionic fluid (Tong, 2020). Thus, the amount of amnionic fluid IL-1β would be determined by the number of leukocytes recruited, their activational status, or the effect of amnionic fluid constituents on their IL-1β secretion rate.

Microbiota. Mucosal immunity and barrier function of the cervicovaginal epithelia, the vaginal microbiota composition, and their interplay among differing populations are major research topics (Elovitz, 2019; Fettweis, 2019; Serrano, 2019). To explore these, advanced genomic analysis techniques are used and show that the nonpregnant vagina hosts a complex microbial community (Gajer, 2012; White, 2011). And, the vaginal microbiome changes during normal pregnancy (Stout, 2017). Specifically, the diversity of microbe populations are reduced during pregnancy and become more stable.

Some but not all studies report an increased population of certain microbes—for example, *Gardnerella vaginalis* and *Ureaplasma urealyticum*—in women with preterm birth (Donders, 2009; Nelson, 2014). In contrast, Schuster and coworkers (2020) reported that asymptomatic vaginal *Candida* colonization was not associated with preterm birth. Differences in populations studied, preterm birth definitions, and data analysis complicate interpretation of these data. Currently, the strongest evidence for the role of the microbiome in preterm birth relates to the vaginal microbiota. The most consistent finding across almost all studies is the benefit of a vaginal microbiota characterized by *Lactobacillus crispatus* (Bayar, 2020).

Aagaard and colleagues (2014) suggested that the placenta contains a microbiome akin to the oral microbiome. Subsequent studies, however, have failed to confirm this (Lauder, 2016; Theis, 2019). Recently, de Goffau and associates (2019) found no evidence of bacteria in most of 537 placental samples from both complicated and uncomplicated pregnancies. Almost all samples pointed to acquisition of bacteria during labor and delivery or to contamination of laboratory reagents with the exception of *Streptococcus agalactiae*. *Thus, the human placenta does not appear to have a relevant microbiome* (Bayar, 2020).

■ Preterm Prelabor Rupture of Membranes

Previously referred to as preterm *premature* rupture of membranes, preterm *prelabor* rupture of membranes (PPROM) defines spontaneous membrane rupture before 37 completed weeks and before labor onset (American College of Obstetricians and Gynecologists, 2020g). Such rupture likely has various causes, but intrauterine infection, oxidative stress–induced DNA damage, and premature cellular senescence are major predisposing events (Dutta, 2016; Mercer, 2003). Associated risk factors are similar to those at term and include lower socioeconomical status, low body mass index, nutritional deficiencies, and cigarette smoking. Women with PPROM carry an enhanced risk for recurrence during a subsequent pregnancy (Bloom, 2001). Despite these known risk factors, none are identified in many cases.

Bacterial cultures of amnionic fluid support a role for infection in PPROM. One review of 18 studies and almost 1500 women with PPROM found that bacteria were isolated from amnionic fluid in a third of cases (Goncalves, 2002). Microbiome-mediated preterm birth and PPROM are current research areas (Bayar, 2020). One goal is to identify early risk markers for PPROM.

Molecular Changes

In pregnancies with PPROM, the amnion exhibits a higher degree of cell death and more apoptosis markers than in term amnion (Arechavaleta-Velasco, 2002; Fortunato, 2003). In vitro studies indicate that apoptosis is likely regulated by bacterial endotoxin, IL-1β, and TNF-α. In addition, oxidative stress initiated by events other than infection can induce DNA damage, premature senescence, and subsequent inflammation and proteolysis that leads to PPROM (Menon, 2020).

With membrane rupture, thrombin activity rises, which activates MMPs and prostaglandin synthesis. Studies by Mogami (2013) provide a mechanism by which bacterial endotoxin or TNF-α elicits release of fetal fibronectin (fFN) by amnion epithelial cells. The fFN then binds toll-like receptor 4 in the amnion mesenchymal cells to activate signaling cascades. These result in augmented prostaglandin E (PGE_2) synthesis and elevated activity of MMPs. Increasing prostaglandin levels promote cervical ripening and uterine contractions. Greater MMP concentrations allow collagen breakdown in the fetal membranes, resulting in premature rupture. Last, proteins involved in collagen synthesis or promoting its tensile strength are altered in membranes with premature rupture (Wang, 2006). Recently, Blois and associates (2020) introduced the concept of *galectins*, a family of glycan-binding proteins. They may serve as a mediator in fetal-maternal immune tolerance and work to prevent microbial infections that lead to preterm birth.

Both preterm labor and PPROM arise from distinct pathophysiological pathways but share inflammation as a common underlying mechanism. Excellent reviews are presented by Menon (2020) and Diemert (2020) and their coworkers.

■ Maternal-Fetal Stress

In this context, stress is defined as a condition that disturbs the normal physiological or psychological functioning of an individual. Since the 1940s, the association of maternal stress with birth outcomes has been explored. Results vary partly because of methodological difference in measuring stress (Hong, 2021). Quantitative measure is difficult, but considerable evidence shows that psychosocial stress in the form of racial discrimination—especially in black populations—results in poor health outcomes, including preterm birth (Salow, 2018). Psychological duress can include childhood stress, depression, or posttraumatic stress syndrome (Gillespie, 2017; Goldstein, 2017; Venkatesh, 2016). In one review of more than 50 studies, a significant link was found between low birthweight and preterm

birth in women impacted by intimate partner violence (Donovan, 2016).

One potential mechanism for stress-induced preterm birth is premature activation of the placental–adrenal endocrine axis. Another mechanism by which stress may translate to preterm birth is premature cellular senescence. As part of normal physiology, aging of fetal and decidual cells precipitates release of uterotonic signals for uterine activation at term. The interplay between preterm birth and maternal stress was recently reviewed by Hong and colleagues (2021).

CONTRIBUTING FACTORS

Several factors associated with preterm birth include pregnancy factors, lifestyle and behaviors, genetic and demographic features, and aspects of obstetrical history (Table 45-6). Disentangling association from causation remains a dilemma.

Prior Preterm Birth

The most important risk factor for preterm labor is a prior preterm birth. Data from nearly 16,000 women delivered at Parkland Hospital are instructive (Bloom, 2001). Namely, the recurrent preterm delivery risk for women with a preterm first delivery was threefold greater than that of women whose first neonate was born at term. More than a third of women whose first two newborns were preterm subsequently delivered a third preterm newborn. Most—70 percent—of the recurrent births occurred within 2 weeks of the gestational age of the prior preterm delivery. The causes of prior preterm delivery also recurred. Although women with prior preterm births are clearly at risk for recurrence, they represented only 10 percent of the total preterm births. Expressed another way, 90 percent of the preterm births at Parkland Hospital could not be predicted based on a history of preterm birth. Others have confirmed the importance of prior *spontaneous* preterm birth (Laughon, 2014). Moreover, prior *indicated* preterm birth was strongly associated with subsequent spontaneous preterm birth. Variable definitions of spontaneous and indicated may explain this association.

Ultimately, risk of recurrent preterm birth is influenced by three factors: the frequency of prior preterm deliveries, severity as measured by gestational age, and the order in which the prior preterm delivery occurred (McManemy, 2007). That is, an individual woman's risk for recurrent preterm birth is influenced by her past number and sequence of preterm and term births. For example, a risk of recurrent preterm birth for a gravida 3 para 2 woman with a prior preterm birth followed by a term birth is less than that for a woman with a prior term birth followed by preterm birth. Thus, the influence of reproductive history has a profound prognostic significance for risk of recurrence. This may also influence the supposed benefit attributed to interventions described later.

TABLE 45-6. Factors That May Contribute to the Genesis of Preterm Labor

Factor	Examples
Prior preterm birth	Spontaneous, indicated
Lifestyle	Smoking, poor diet, illicit drug use, stress, heavy physical activity
Genetic	Recurrent, familial, ethnoracial, immunoregulatory genes
Infection	*Mycoplasma* spp., bacterial vaginosis
Periodontal disease	Gingivitis
Interpregnancy interval	Long or short

Pregnancy Factors

Of these, *threatened abortion* in early pregnancy is associated with higher rates of later adverse outcomes. Weiss (2004) reported outcomes in nearly 14,000 women with vaginal bleeding at 6 to 13 weeks' gestation. Both light and heavy bleeding were associated with subsequent preterm labor, placental abruption, and pregnancy loss before 24 weeks. *Birth defects* in the fetus also may predispose to preterm birth. In a secondary analysis of data from the First- and Second-Trimester Evaluation of Risk (FASTER) trial, birth defects were associated with preterm birth and low-birthweight neonates (Dolan, 2007). Multifetal gestation is another well-recognized associate. Importantly, preterm delivery continues to be the major cause of the excessive perinatal morbidity and mortality for these pregnancies.

Lifestyle Factors

Extremes of maternal weight—both underweight and obese mothers—have an enhanced risk of preterm birth (Cnattingius, 2013; Girsen, 2016). Other maternal factors implicated include young or advanced maternal age, poverty, short stature, and vitamin C deficiency (Casanueva, 2005; Goldenberg, 2008; Leveno, 2009). Cigarette smoking, inadequate maternal weight gain, and illicit drug use affect the incidence and outcome of low-birthweight neonates (Chap. 47, p. 825).

Studies of work and physical activity related to preterm birth have yielded conflicting results (Goldenberg, 2008). Some evidence suggests that working long hours, fixed night shifts, and hard physical labor are probably linked to a higher risk of preterm birth (Cai, 2020). However, aerobic exercise in normal-weight women with uncomplicated singleton pregnancies appears to be safe and not associated with preterm birth (American College of Obstetricians and Gynecologists, 2020f; Di Mascio, 2016). One metaanalysis of physical activity found that leisure-time physical activity was associated with a reduced risk of preterm birth (Aune, 2017).

Because of the observational nature of many of the studies with the potential for confounding, the American College of Obstetricians and Gynecologists (2020b) has offered guidance for employment considerations during pregnancy. It is emphasized that accommodations that allow a woman to keep working are the most reliable way to guarantee pay, benefits, and job protection.

Genetic Factors

Evidence for a genetic component to preterm birth is supported by familial recurrent preterm births (Crider, 2005).

Genome-wide studies have identified genetic variants associated with gestational duration and preterm birth (Zhang, 2017). Common variants in *EBF1*, *EEFSEC*, and *AGTR2* genes have an association with preterm birth. Data sets, however, included only women with European ancestry, and thus future efforts will ideally include other populations. Recent large-scale transcriptome studies have identified additional loci associated with gestation length (Marinić, 2021; Sakabe, 2020).

Periodontal Disease

Gingivitis is a chronic anaerobic inflammation that affects as many as 50 percent of pregnant women in the United States (Goepfert, 2004). One metaanalysis of 17 studies showed that periodontal disease was significantly associated with preterm birth (Vergnes, 2007). To better study this relationship, 813 pregnant women between 13 and 17 weeks' gestation who had periodontal disease were randomly assigned to treatment during pregnancy or postpartum. Treatment during pregnancy improved periodontal disease, however, it failed to significantly alter preterm birth rates (Michalowicz, 2006). A workshop of the European Federation of Periodontology and the American Academy of Periodontology reaffirmed this position (Sanz, 2013).

Interpregnancy Interval

In one metaanalysis, intervals <18 months and >59 months were associated with greater risks for both preterm birth and small-for-gestational-age newborns (Conde-Agudelo, 2006). The causal effect of short interpregnancy intervals, however, has been questioned (Ball, 2014). A recent cohort study of more than three million births across four countries, including the United States, found that associations between interpregnancy intervals and preterm birth are modified by whether the previous pregnancy was preterm (Marinovich, 2021).

Infection

Antimicrobial Prophylaxis

As discussed on page 789, a link between some cases of preterm birth and infection seems irrefutable (Goldenberg, 2008). In several studies, antimicrobial treatment has been given to prevent preterm labor that was thought to stem from microbial invasion. Some of these strategies have targeted *Mycoplasma* species.

First, Andrews and associates (2006) reported results of a randomized trial in which they provided a course of azithromycin plus metronidazole every 4 months to 241 nonpregnant women whose last pregnancy resulted in spontaneous delivery before 34 weeks. Approximately 80 percent of the women with subsequent pregnancies had received study drug within 6 months of their subsequent conception. Such interconceptional antimicrobial treatment did not reduce the rate of recurrent preterm birth. From a subgroup analysis of this data, Tita and coworkers (2007) concluded that such use of antimicrobials may be harmful.

In another randomized study, 2661 women were given placebo or metronidazole plus erythromycin between 20 and 24 weeks' gestation followed by ampicillin plus metronidazole during labor (Goldenberg, 2006). This antimicrobial regimen did not reduce the rate of preterm birth or histological chorioamnionitis. As discussed later, antibiotic prophylaxis to prevent preterm birth is not currently recommended in women with preterm labor and intact membranes (Flenady, 2013).

Bacterial Vaginosis

In this condition, normal, hydrogen peroxide–producing, lactobacillus-predominant vaginal flora is replaced with anaerobes. For nearly 40 years, bacterial vaginosis has been recognized to be associated with spontaneous abortion, preterm labor, rupture of membranes, chorioamnionitis, and amnionic fluid infection (Gravett, 1986; Hillier, 1995). Unfortunately, screening and treatment have not prevented preterm birth (Haahr, 2016). Moreover, microbial resistance or antimicrobial-induced change in the vaginal flora results from regimens intended to eliminate bacterial vaginosis (Beigi, 2004; Carey, 2005).

COVID-19

Early reports suggested an increase in rates of preterm birth in pregnant women with COVID-19. However, population-level data show conflicting results on the changes, if any, in preterm birth rates (Berghella, 2020; Hedermann, 2021; Main, 2021). At Parkland Hospital, Adhikari and colleagues (2020) did not identify higher rates of preterm birth in 252 women with COVID-19 compared with 3122 gravidas who tested negative. However, women with severe infection are often delivered preterm for maternal indications (Pierce-Williams, 2020).

DIAGNOSIS

Symptoms

Contractions, pelvic pressure, menstrual-like cramps, watery vaginal discharge, and lower back pain are typical symptoms of preterm labor. These can also be seen with normal pregnancy and may be minimized by patients and providers. Early differentiation between true and false labor is difficult—especially before demonstrable cervical effacement and dilation. Uterine activity alone can be misleading because of *Braxton Hicks contractions* (Chap. 4, p. 52). Accordingly, the American College of Obstetricians and Gynecologists (2020e) defines preterm labor to be regular contractions accompanied by a change in cervical dilation, effacement, or both or to be regular contractions and cervical dilation of at least 2 cm at initial presentation.

Chao (2011) prospectively studied 843 women with a singleton fetus who presented to Parkland Hospital with preterm labor symptoms between $24^{0/7}$ and $33^{6/7}$ weeks, intact membranes, and cervical dilation <2 cm. Those whose cervix remained <2 cm were sent home with a diagnosis of false preterm labor. When analyzed against the general obstetrical population, women sent home had a similar rate of birth before 34 weeks—2 versus 1 percent. However, these women did have significantly higher rates of birth between 34 and 36 weeks—5 percent compared with 2 percent. Women with cervical dilation of 1 cm at discharge were significantly more likely to

deliver before 34 weeks compared with women without cervical dilation—5 percent versus 1 percent. Almost 90 percent of the 1-cm group delivered within 21 days of the initial presentation.

Cervical Change

Asymptomatic cervical dilation after midpregnancy is suspected to be a preterm delivery risk factor. Multiparity alone is not sufficient to explain cervical dilation discovered early in the third trimester. Cook (1996) longitudinally evaluated cervical status with transvaginal sonography between 18 and 30 weeks' gestation in nulliparas and multiparas who all subsequently gave birth at term. Cervical length and diameter were identical in both groups throughout these critical weeks. In a study from Parkland Hospital, routine digital cervical examinations were performed between 26 and 30 weeks in 185 asymptomatic women. Approximately 25 percent of women whose cervix was dilated 2 or 3 cm delivered before 34 weeks (Leveno, 1986a). Other investigators have verified cervical dilation as a predictor of increased preterm delivery risk (Copper, 1995).

Although women with dilation and effacement in the third trimester are at greater risk for preterm birth, detection does not necessarily improve pregnancy outcome. In one randomized study, 2719 women undergoing routine cervical examinations at each prenatal visit were compared with 2721 gravidas in whom serial examinations were not performed. Knowledge of antenatal cervical dilation did not affect any pregnancy outcome related to preterm birth or the frequency of interventions for preterm labor (Buekens, 1994). Thus, it seems that prenatal cervical examinations in asymptomatic women are neither beneficial nor harmful. Numerous cervical imaging technologies are under investigation for early, accurate prediction of cervical changes associated with preterm birth (Pizzella, 2020).

Ambulatory Uterine Monitoring

An external tocodynamometer belted around the abdomen and connected to an electronic waist recorder allows a woman to ambulate while uterine activity is recorded. Results are transmitted via telephone daily. Women are educated concerning signs and symptoms of preterm labor, and clinicians are kept apprised of their progress. The 1985 approval of this monitor by the U.S. Food and Drug Administration (FDA) prompted its widespread clinical use. Subsequently, it was proven that this expensive and time-consuming system did not reduce preterm birth rates (Collaborative Home Uterine Monitoring Study Group, 1995; Iams, 2002). Despite technology improvements, use of such monitoring is discouraged (American College of Obstetricians and Gynecologists, 2021c).

Biomarkers

Because clinical symptoms alone are not predictive of preterm birth, surrogate biomarkers have been evaluated. These include fetal fibronectin (fFN), phosphorylated insulin-like growth factor–binding protein 1 (phIGFBP-1), and placental alpha microglobulin 1 (PAMG-1). Their performance varies between studies and is influenced by demographic and other factors (Melchor, 2018).

Fetal Fibronectin

This glycoprotein is produced in 20 different molecular forms by various cell types, including hepatocytes, fibroblasts, endothelial cells, and fetal amnion cells. Present in high concentrations in maternal blood and amnionic fluid, fFN is thought to function in intercellular adhesion during implantation and in maintenance of placental adherence to uterine decidua (Leeson, 1996). Detected in cervicovaginal secretions in women who have normal pregnancies with intact membranes at term, fFN appears to reflect stromal remodeling of the cervix before labor. Qualitative and quantitative fFN levels are measured using enzyme-linked immunosorbent assays, and values exceeding 50 ng/mL are considered positive. Sample contamination by amnionic fluid and maternal blood should be avoided. Interventional studies based on fFN screening results in asymptomatic women have not demonstrated improved perinatal outcomes (Andrews, 2003; Esplin, 2017). The American College of Obstetricians and Gynecologists (2021c) does not recommend screening with fFN tests. In one review of 16 trials involving management based upon fFN results, the low quality of existing evidence and need for cost-effectiveness analyses were noted (Berghella, 2019).

Cervical Length Measurement

Progressively shorter cervical canals assessed sonographically are associated with increased rates of preterm birth (Iams, 1996). The sonographic technique is described in Chapter 14 (p. 254). The Society for Maternal-Fetal Medicine (2016b) has provided guidance for proper cervical length measurement and recommends that sonographers and practitioners obtain specific training through accreditation programs in the acquisition and interpretation of cervical length images.

Transvaginal cervical sonography is not affected by maternal obesity, cervix position, or shadowing from the fetal presenting part. Because of the inability to easily distinguish the lower uterine segment from the cervix in early gestation, transvaginal cervical length assessment is typically performed after 16 weeks' gestation. Such interrogation is currently limited to singleton gestations and not recommended for multifetal gestations outside of research trials (American College of Obstetricians and Gynecologists, 2021c).

Indications for cervical length measurement are controversial. For those women with a history of prior spontaneous preterm birth, the Society for Maternal-Fetal Medicine (2016b) recommends transvaginal cervical length screening. And, the American College of Obstetricians and Gynecologists (2021c) now also recommends screening for this indication. In women with singleton pregnancies but without a history of prior preterm birth, the Society for Maternal-Fetal Medicine and the College view cervical length screening as reasonable yet acknowledges that this remains an area of debate.

Biomarkers have been incorporated with hopes to improve screening performance. Esplin and colleagues (2017) prospectively studied 9410 nulliparas with singleton pregnancies. Universal screening of sonographically measured cervical length and quantitative measurement of vaginal fFN levels were evaluated as predictors of women who would spontaneously

deliver before 37 weeks. These measures had poor predictive performance as a screening test. Based on these findings, routine use of these screening tests in a low-risk population is not recommended. Of other markers, PAMG-1 has emerged as superior to predict potential preterm birth compared with fFN, particularly among symptomatic women (Nikolova, 2018; Pirjani, 2019; Wing, 2017). Incorporating results of cervicovaginal fluid proteomic markers and microRNAs obtained from peripheral blood also has been assessed (Parry, 2020; Winger, 2020). Although evidence seems promising, any firm recommendations should await larger clinical trials (Jones, 2020). This is particularly important given the challenges with accuracy and utility of screening, especially in low-risk women, who represent most of the population with preterm birth.

A second concern with screening is the efficacy of interventions to improve perinatal outcomes once cervical length screening, biomarkers, or both have isolated at-risk women. Cervical cerclage or vaginal progesterone have been evaluated, and their efficacy is described in the next section.

Bloom and Leveno (2017) subsequently critiqued the use of transvaginal cervical length screening in low-risk women and the promulgation of consensus guidelines. They highlighted the staggering costs encumbering the healthcare system in the United States as a result of such strategies. Similar concerns were raised by Kuusela and associates (2021) who evaluated cervical length screening among 11,456 asymptomatic gravidas.

PRETERM BIRTH PREVENTION

Prevention of preterm birth remains an elusive goal. Yet, experts continue to debate the optimal strategies to prevent or manage preterm birth (Medley, 2018). Dietary supplementations, for example, have not shown benefit (Makrides, 2019; Palacios, 2019). Still, recent reports suggest that prevention in selected populations may be achievable (Breslin, 2020; Goodfellow, 2021).

Cervical Cerclage

Cerclage placement may be used to prevent preterm birth in at least three circumstances. First, the procedure may benefit women who have a history of recurrent second-trimester loss and who are diagnosed with cervical insufficiency. A second instance is the woman identified during sonographic examination to have a short cervix. The third indication is a "rescue" cerclage, done emergently when cervical incompetence is recognized in women with threatened preterm labor. Cerclage placement in twin pregnancies for clinical indications is an evolving area (Li, 2019; Roman, 2020). In this chapter, however, cerclage placement will be in the context of a singleton pregnancy.

An accurate history is critical for management decisions. For recurrent abortion from cervical incompetence, historical clues are outlined in Chapter 11 (p. 205). For women with a short cervix incidentally detected by sonography, the benefit of cerclage placement appears directly related to whether the woman has a history of prior preterm birth. In those without a prior preterm birth, cerclage for a sonographically detected short cervix alone offers no advantage (Berghella, 2017). To and associates (2004) screened 47,123 women and randomly assigned the 253 women with a cervix measuring <15 mm, with or without a history of preterm birth, to cerclage or no cerclage groups. The frequency of preterm delivery before 33 weeks did not differ significantly between the two cohorts.

In contrast, women with a sonographically diagnosed short cervix *and* a history of preterm birth may benefit. Owen and colleagues (2009) randomly assigned 302 women with prior preterm birth plus a short cervix—defined as length <25 mm—to cerclage or no-procedure groups. The primary study outcome was not supported by the intervention. However, women with a cervical length <15 mm delivered before 35 weeks significantly less often following cerclage compared with women with no cerclage—30 versus 65 percent. This study suggested that recurrent preterm birth could be prevented in a subset of women with asymptomatic singleton gestations with both previous preterm birth and short cervical length.

These findings prompted a reassessment by Berghella and coworkers (2011), who performed a metaanalysis using individual patient data (Fig. 45-5). The primary outcomes from the included trials did not support cerclage placement. However, these investigators concluded that cerclage significantly prevented preterm birth and improved composite perinatal mortality and morbidity outcomes in women with prior spontaneous preterm birth, singleton gestation, and cervical length <25 mm.

One caveat in the interpretation of this cerclage data is the influence of obstetrical history. For example, all of the trials comprising the metaanalysis included preterm birth as early as 16 to 17 weeks' gestation. Defining these early second-trimester losses as preterm births, rather than cervical incompetence, is problematic. Thus, it is difficult to distinguish whether these women were treated in the context of cervical incompetence or of preterm labor at 16 weeks. Nonetheless, based on these findings, the American College of Obstetricians and Gynecologists (2021c) concluded that in women with a singleton pregnancy, prior spontaneous preterm birth, cervical length <25 mm, and gestational age <24 weeks, cerclage placement may be considered versus vaginal progesterone (p. 797).

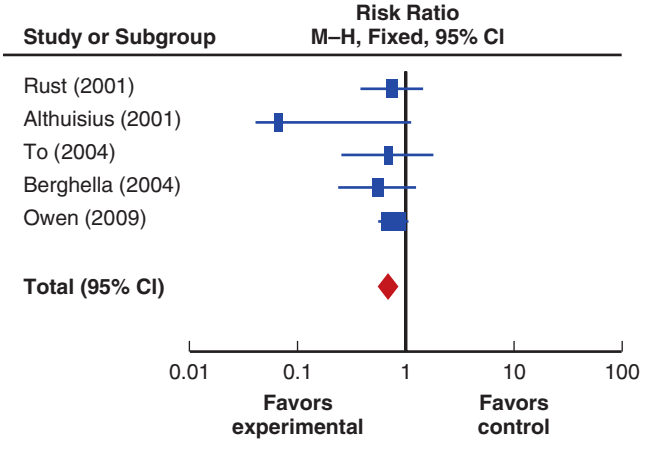

FIGURE 45-5 Cerclage versus no cerclage for prevention of recurrent preterm birth in women with a cervical length <25 mm. Forest plot analysis of composite perinatal mortality and morbidity. CI = confidence interval; M-H = Mantel-Haenszel.

Technique

The operative placement of cervical cerclage is shown in Chapter 11 (p. 206). Several emerging trends, however, merit comment. For example, indication for cerclage placement may influence selection of suture material (Battarbee, 2019). Tocolysis and antibiotics with cerclage placement is another controversy (Eleje, 2020). In a retrospective report of 142 cases, 72 received perioperative prophylaxis, which consisted of perioperative cefazolin and indomethacin, during physical examination–indicated cerclage placement. This practice was associated with a significant prolongation in gestational latency (Premkumar, 2020). At Parkland Hospital, we have not adopted such practices. Last, for women with a history of a failed cerclage, transabdominal cerclage appears to be superior to vaginal cerclage (Shennan, 2020).

Prophylaxis with Progestogen Compounds

In most mammals, *progesterone withdrawal* is considered to be a parturition-triggering event. During human parturition, however, maternal, fetal, and amnionic fluid progesterone levels remain elevated. It has been proposed that human parturition involves functional progesterone withdrawal mediated by decreased activity of progesterone receptors (Chap. 21, p. 406). It follows conceptually that progesterone administration may prevent preterm labor. This hypothesis has stimulated several studies of both 17-alpha hydroxyprogesterone caproate and vaginally administered progesterone in women with varying risks for preterm birth.

At present, reported benefits of either progestogen therapy are largely limited to women with singleton pregnancies. Progestogen prophylaxis specifically in multifetal gestations has not lowered preterm birth rates (Caritis, 2009; Dodd, 2019; Rehal, 2020; Rouse, 2007). Accordingly, both the American College of Obstetricians and Gynecologists (2021c) and the Society for Maternal-Fetal Medicine (2020b) support the use of progestogen therapy for prevention of preterm birth in select women with singleton pregnancies despite the challenges chronicled (Nelson, 2021). Either a history of prior preterm birth or no prior preterm birth but a sonographically identified short cervix is a criterion.

Prior Preterm Birth and Progestogen Compounds

The synthetic progestogen 17-alpha-hydroxyprogesterone caproate (17-OHPC) is the focus of current controversy. It remains the first, and only, drug approved by the FDA for prevention of recurrent preterm birth. This therapy was originally approved in 2011 through an accelerated process for orphan drugs and based on the findings of Maternal-Fetal Medicine Units (MFMU) Network study, described next. However, this approval and justification for continued use is now disputed (Chang, 2020; Food and Drug Administration, 2019, 2020; Greene, 2020; Nelson, 2021).

Maternal-Fetal Medicine Units Network Trial

In the MFMU Network trial, 463 women with a prior preterm birth were randomly assigned to receive weekly intramuscular injections of inert oil placebo or 17-OHPC from 16 through 36 weeks' gestation (Meis, 2003). Recurrence of preterm birth rates were 36 percent in women receiving 17-OHPC and 55 percent in those given placebo. This study was challenged because of the unexpectedly high preterm delivery rate in the placebo arm (Romero, 2013). One explanation for this high rate was asymmetry in the risks of recurrence. Indeed, 41 percent of the placebo group had ≥2 prior preterm births compared with only 28 percent in the 17-OHPC group. Another concern was that the injection dosage of 17-OHPC, which was 250 mg weekly, was empirically chosen (Caritis, 2012, 2014). Because of these reported challenges, the FDA granted approval but called for a confirmatory randomized clinical trial before final FDA approval (Food and Drug Administration, 2019). The multicenter, international, randomized trial was launched in 2009 but required 9 years to complete (Blackwell, 2020).

Pricing Concerns

Following the accelerated approval, drug-overpricing claims prompted concern (Cohen, 2011; Romero, 2013). In 2011, the FDA gave temporary approval to KV Pharmaceutical to market 17-OHPC under the brand name *Makena*. Because regulations prohibited compounding, there was no competitor for this relatively inexpensive drug, and *Makena* was priced at $1500 per injection. This caused widespread concern because the cumulative cost of *Makena* would be more than $30,000 per pregnancy.

Parkland Hospital, given these pricing concerns, contracted a local compounding pharmacy to provide 250-mg, single-dose vials of 17-OHPC in sesame oil at a cost of $25 per dose. Nelson and colleagues (2017) reported their findings from this program in a prospective study of 430 women given this compounded 17-OHPC. It was ineffective for prevention of recurrent preterm birth at 35 weeks or less compared with a historical cohort from Parkland Hospital. Moreover, 17-OHPC did not significantly reduce the rates of recurrent preterm birth regardless of prior preterm birth number or sequence. Moreover, plasma concentrations of 17-OHPC were not different at 24 weeks or 32 weeks between women delivered at ≤35 weeks and those delivered later.

Metabolism

Despite its widespread use, the mechanism of action for 17-OHPC remains unknown. Sharma and associates (2008) reported that the metabolism of 17-OHPC was predominantly mediated by the CYP3A enzymatic system. Thus, other agents that induce or inhibit this system or hepatic impairment may alter drug levels. They also showed that 17-OHPC is not converted after administration to the progesterone metabolite 17α-hydroxyprogesterone. The relative binding affinity of 17-OHPC to progesterone receptors approximates only 30 percent of that by progesterone (Attardi, 2007).

Caritis and colleagues (2012) examined 61 women receiving 17-OHPC therapy and found that the half-life was relatively long (median 16.2 days). Pharmacokinetic parameters were affected by maternal body habitus and varied widely between subjects. In addition, 17-OHPC crossed the placental barrier and was detectible in cord plasma 44 days after the

last maternal injection (Caritis, 2012). Despite this, evidence to date suggests that 17-OHPC is safe for the fetus (Food and Drug Administration, 2019). No abnormalities, including abnormal genitalia, were found in a 48-month follow-up study of infants exposed in the 2003 MFMU Network trial (Northen, 2007). Simons and coworkers (2021) also reported no effect of progestogens on child development in a systematic review comprising numerous developmental measurements.

PROLONG Trial

The FDA-required confirmatory trial was the PROLONG trial and completed in October 2018. A total of 1708 women were randomly assigned in a 2:1 ratio to receive 17-OHPC or placebo. This trial had two primary endpoints, which were birth <35 weeks' gestation and a neonatal composite. Data were analyzed for 1651 of the liveborn neonates (Table 45-7) (Blackwell, 2020). Progesterone was not effective in preventing recurrent preterm birth. In the analysis of various secondary outcomes, 17-OHPC treatment also lacked efficacy.

TABLE 45-7. Perinatal Outcomes of PROLONG Trial

Outcomes	17-OHPC n = 1130	Placebo n = 578	Relative Risk
Number assessed	1,113	574	0.95
PTB <$35^{0/7}$ wk	122 (11.0)	66 (11.5)	
Spontaneous	93 (8.4)	51 (8.9)	0.93
Indicated	28 (2.5)	14 (2.4)	1.03
Number assessed	1,112	572	
PTB <$37^{0/7}$ wk	257 (23.1)	125 (21.9)	1.06
Spontaneous	209 (18.8)	98 (17.1)	1.10
Indicated	46 (4.1)	26 (4.5)	0.91
Number assessed	1,116	574	0.92
PTB <$32^{0/7}$ wk	54 (4.8)	30 (5.2)	
Spontaneous	38 (3.4)	22 (3.8)	0.88
Indicated	15 (1.3)	7 (1.2)	1.11
Composite M&M	61 (5.6)	28 (5.0)	1.12
Death	6 (0.5)	3 (0.5)	0.98
BPD	6 (0.5)	1 (0.2)	3.02
RDS	54 (4.9)	26 (4.7)	1.06
NEC	2 (0.2)	2 (0.4)	0.5
IVH, grade 3 or 4	2 (0.2)	1 (0.2)	0.99
Sepsis	5 (0.5)	3 (0.5)	0.84

17-OHPC = 17-hydroxyprogesterone caproate; BPD = bronchopulmonary dysplasia; IVH = intraventricular hemorrhage; M&M = mortality and morbidity; NEC = necrotizing enterocolitis; PTB = preterm birth; RDS = respiratory distress syndrome.

FDA Recommendations

In October 2019, the FDA convened an Advisory Committee meeting to review 17-OHPC and the new data. Efficacy, side effects, and several subgroup analyses were studied, and none supported 17-OHPC efficacy (Fig. 45-6). The FDA concluded that the PROLONG trial did not demonstrate a treatment benefit of 17-OHPC in reducing the neonatal composite index or the rate of spontaneous preterm birth prior to 35 weeks' gestation. The Advisory Committee recommended to withdraw approval. In November 2020, the Center for Drug Evaluation and Research proposed that *Makena* (17-OHPC) be withdrawn from the market (Food and Drug Administration, 2020).

Response to the FDA position has been mixed. Both the American College of Obstetricians (2019a, 2021a) and Society for Maternal-Fetal Medicine (2020b) have issued statements endorsing continued use of 17-OHPC for prevention of recurrent preterm birth in women with singleton pregnancies. Endorsements by these organizations continue after publication of a metaanalysis by the Evaluating Progestogens for Preventing Preterm birth International Collaborative (EPPPIC)

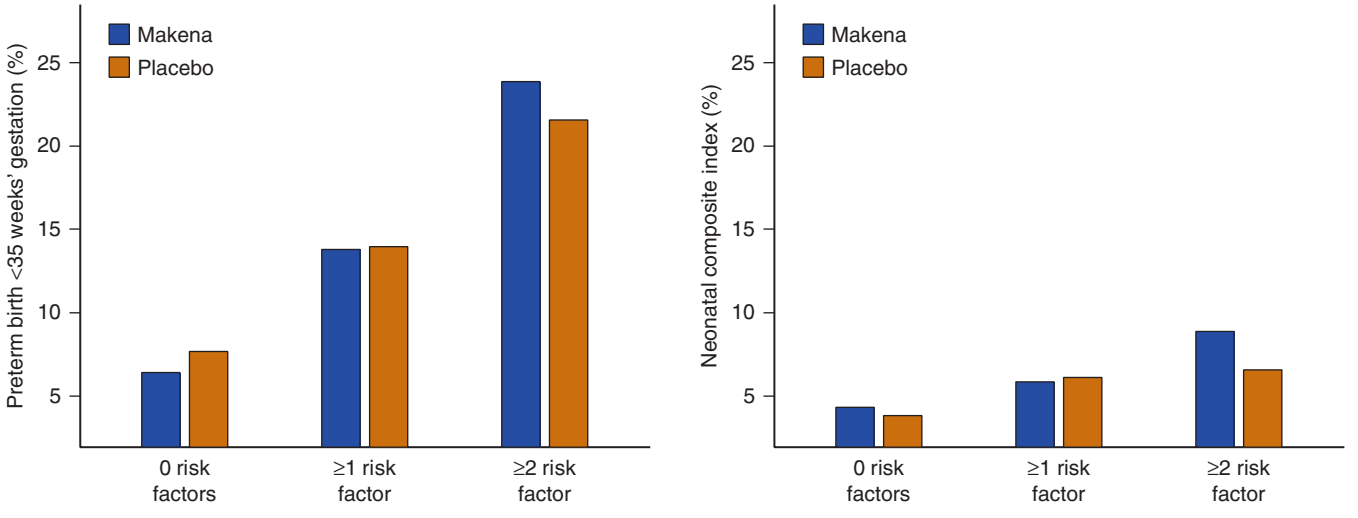

FIGURE 45-6 In analysis of co-primary endpoints for the PROLONG Trial, five of the included defining risk factors were noted to be different from those in the Maternal-Fetal Medicine Units Network trial (see text). These are black race, >1 prior spontaneous preterm birth, single or without a partner, substance use during pregnancy, and ≤12 years of formal education. The three groups examined in this post-hoc composite risk profile analysis were those with no risk factors, those with ≥1 risk factor, and those with ≥2 risk factors. Makena is the brand name of 17-OHPC.

Group (2021). These investigators summarized that vaginal progesterone and 17-OHPC both reduced birth rates before 34 weeks' gestation in high-risk singleton pregnancies. Notably, the findings for 17-OHPC did not reach statistical significance. Moreover, this metaanalysis grouped together trials of patients with differing risk profiles. It combined women with and without a prior preterm birth as well as women with and without a short cervix.

These positions have stimulated several dueling commentaries regarding its use (Chang, 2020; Godlewski, 2020; Greene, 2020; Sibai, 2020). At this time, the FDA has not withdrawn the accelerated approval. If formally withdrawn, however, a consequence may be continued "off-label" use, with the caveat that insurers may not provide payment coverage.

Progesterone Prophylaxis with Shortened Cervix

Three randomized trials are at the center of whether progestogen therapy should be used in women without prior preterm births but who have a shortened cervix (Table 45-8). In the first trial, 250 women with short cervices measuring ≤15 mm identified during routine prenatal care were nightly given 200-mg micronized progesterone vaginal capsules or placebo from 24 to 34 weeks' gestation (Fonseca, 2007). The rate of spontaneous delivery <34 weeks was significantly reduced by progesterone therapy. Importantly, this trial included nulliparas and also those with twins or prior preterm birth.

In the second trial, 465 women with a short cervix—10 to 20 mm—were given vaginal progesterone gel, 90 mg daily, or placebo (Hassan, 2011). Those receiving progesterone had significantly lower rates of preterm birth <33 weeks. This trial also included nulliparas and women with prior preterm births. According to Likis and colleagues (2012), the heterogeneity of these first two studies that included women with varied indications for progestogen treatment, combined with the fact that outcomes were not reported by risk factors such as nulliparity, made it impossible to interpret the efficacy of progesterone for specific indications.

The third study randomly assigned administration of 17-OHPC intramuscular injection or placebo between 16 and $22^{3/7}$ weeks' gestation to nulliparas with a singleton gestation and a cervical length <30 mm detected sonographically (Grobman, 2012). Treatment with 17-OHPC did not reduce the frequency of preterm birth <37 weeks. Regardless of cervical length, 17-OHPC was ineffective.

From these, vaginal progesterone, but not intramuscular 17-OHPC, appears to benefit women with a sonographically measured short cervix. Romero and Stanczyk (2013) provided a review to explain the conflicting evidence and argued that naturally occurring progesterone, which is used in the vaginal preparations, is not the same as synthetic 17-OHPC. Likewise, Furcron and coworkers (2015) found that 17-OHPC did not have local antiinflammatory effects at the maternal-fetal interface or cervix. Further, 17-OHPC did not protect against endotoxin-induced preterm birth.

From all these studies, the American College of Obstetricians and Gynecologists (2021c) concluded that universal cervical length screening in women without a prior preterm birth is not mandatory. However, this screening strategy could be considered in the context of treatment with vaginal progesterone.

Because of the preliminary results suggesting success of vaginally administered progesterone, the OPPTIMUM study was carried out—does progesterone prophylaxis to prevent preterm labor improve outcome? (Norman, 2016). High-risk women were defined as those with a prior spontaneous birth ≤34 weeks or with a cervical length ≤25 mm or a positive fFN test result combined with other clinical risk factors for preterm birth.

The primary outcomes of OPPTIMUM were unique in that both immediate obstetrical and childhood outcomes were examined. These were fetal death or birth <34 weeks; a composite of death, brain injury, or bronchopulmonary dysplasia; and a standardized cognitive score at age 2 years. Contrary to earlier reports, vaginal progesterone was not associated with a lower risk of preterm birth or composite neonatal adverse outcomes. In children at 2 years, vaginal progesterone had no long-term benefit or harm.

Progestogens Summary

Thus, evidence remains conflicting as to the efficacy of progestogens across various indications. Some have attempted to

TABLE 45-8. Randomized Trials of Progestogen Compounds Given Prophylactically to Prevent Preterm Labor

Investigator	Women Randomized	Cervical Length[a]	Progestogen Compound	Progestogen vs Placebo
Fonseca (2007)	n = 250; 5% nulliparous, 10% twins, 15% prior PTB; 8 hospitals: UK, Greece, Brazil, Chile	<15 mm	Progesterone, 200-mg vaginal capsules daily	Delivery <34 weeks: 19% vs 34%, $p = .02$
Hassan (2011)	n = 465; singletons only; 55% nulliparous; 13% prior PTB; 44 hospitals in 10 countries	10–20 mm	Progesterone, 90-mg vaginal gel daily	Delivery <33 weeks: 9% vs 16%, $p = .02$
Grobman (2012)	n = 657; singletons only; nulliparous only; 14 centers across US	<30 mm	17-OHPC, 250 mg IM weekly	Delivery <37 weeks: 25% vs 24%, p = NS

[a]Determined sonographically.
17-OHPC = 17-hydroxyprogesterone caproate; IM = intramuscularly; NS = nonsignificant; PTB = preterm birth; UK = United Kingdom; US = United States.

resolve these issues through systematic review and metaanalysis (Conde-Agudelo, 2018; da Fonseca, 2020; Jarde, 2019; Prior, 2017; Romero, 2018). However, virtually all evidence supporting progestogen use for a specific indication can be challenged in some way. At this time, we agree with Norman and colleagues (2016) that the results of recent studies should prompt a major review of progesterone use for preterm birth prophylaxis, a search to identify specific women who might benefit, and a redoubling of efforts to find alternative strategies to prevent preterm birth in women at risk.

Geography-based Public Health-care Programs

A well-organized prenatal system can lower preterm birth rates in high-risk indigent populations (Creasy, 1980). For example, in the Parkland Hospital prenatal clinic system, a declining preterm birth rate between 1988 and 2006 coincided with a substantial rise in prenatal visit attendance (Fig. 45-7) (Leveno, 2009). In the early 1990s, a concerted effort was made to improve access by creating seamless care that began with antenatal enrollment and extended through delivery and the puerperium. Prenatal clinics were placed strategically throughout Dallas County to provide convenient access for patients. Prenatal protocols are used by nurse practitioners at all clinic sites to guarantee homogeneous care. Women with high-risk pregnancy complications are referred to a hospital-based central clinic system. Here, maternal-fetal medicine clinics operate each weekday and are staffed by residents and midwives who are supervised by fellows and faculty.

A similar obstetrical care system for indigent women at the University of Alabama at Birmingham also has produced salutary results (Tita, 2011). Given the recent emphasis on access to care, especially among underserved minorities, these experiences remain relevant (United States Congress, 2019).

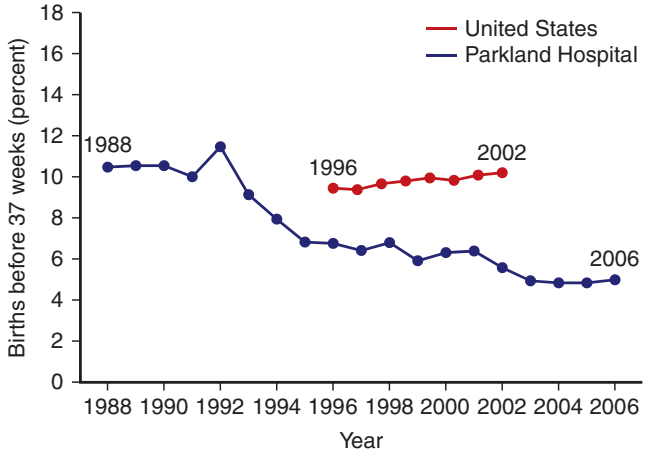

FIGURE 45-7 Percentage of births before 37 weeks' gestation at Parkland Hospital from 1988 to 2006 compared with that in the United States from 1996 to 2002. Analysis in both cohorts was limited to singleton liveborn infants ≥500 g who received prenatal care. (Reproduced with permission from Leveno KJ, McIntire DD, Bloom SL, et al: Decreased preterm births in an inner-city public hospital. Obstet Gynecol. 2009 Mar;113(3):578–584.)

Prenatal care is an important component of a comprehensive public health-care system that at least partially affects the preterm birth rate.

Aspirin

Acetylsalicylic acid (ASA) is a cyclooxygenase inhibitor with antiinflammatory and antiplatelet properties that has been used in pregnancy most commonly to prevent or delay onset of preeclampsia (Chap. 41, p. 705). Data now suggest that low-dose aspirin may also reduce spontaneous preterm birth rates (Andrikopoulou, 2018). In one randomized study of 11,976 nulliparas in six low- and middle-income countries, women were randomly assigned to receive low-dose aspirin (81 mg) or placebo initiated between $6^{0/7}$ and $13^{6/7}$ weeks' gestation (Hoffman, 2020). Low-dose aspirin decreased the incidence of birth <37 weeks and reduced the perinatal mortality rate. Although this trial did not differentiate spontaneous from indicated preterm birth, it requires replication in high-resource settings. The American College of Obstetricians and Gynecologists (2020c) does not recommend low-dose aspirin prophylaxis to prevent spontaneous preterm birth in the absence of preeclampsia risk factors.

MANAGEMENT OF PRETERM PRELABOR RUPTURE OF MEMBRANES

Methods used to diagnose ruptured membranes are detailed in Chapter 22 (p. 426). A history of vaginal leakage of fluid, either as a continuous stream or a gush, should prompt a speculum examination to visualize gross vaginal pooling of amnionic fluid, clear fluid from the cervical canal, or both. Confirmation of rupture of membranes is usually accompanied by sonographic examination to assess amnionic fluid volume, to identify the presenting part, and if not previously determined, to estimate gestational age. Once PPROM is identified, the general scheme shown in Table 45-9 can guide management.

Natural History

The time from PPROM to delivery is inversely related to the gestational age at which rupture occurs. Very few days are gained if membranes rupture during the third trimester compared with midpregnancy (Fig. 45-8) (Carroll, 1995).

In an earlier study from Parkland Hospital, 298 consecutive women with spontaneously ruptured membranes between 24 and 34 weeks' gestation were analyzed (Cox, 1988). PPROM constituted 1.7 percent of pregnancies during the study period. At the time they presented, 76 percent of the women were already in labor, and 5 percent were delivered for other complications. Thus, only 19 percent initially were suitable for expectant management. Ultimately, delivery was delayed 48 hours or more after membrane rupture in only 7 percent of the total study cohort. None of the neonates in this group died. This contrasted with a neonatal death rate of 8 percent in preterm newborns delivered within 48 hours of membrane rupture. Others have reported similar results (Nelson, 1994).

TABLE 45-9. Management of Prelabor Rupture of Membranes

$37^{0/7}$ weeks' gestation or older
- Deliver
- GBS prophylaxis as indicated (Table 67-3, p. 1195)
- Treat any intraamnionic infection

$34^{0/7}$–$36^{6/7}$ weeks' gestation
- Expectant management or deliver
- Neonatal consultation
- Consider single course of corticosteroids:
  - No prior corticosteroids
  - No chorioamnionitis
  - ≥24 hr anticipated from administration to delivery
  - <7 d anticipated from administration to delivery
- For delivery, GBS prophylaxis as indicated; For expectant care, GBS screening
- Treat any intraamnionic infection and deliver

$24^{0/7}$–$33^{6/7}$ weeks
- Expectant management, if no maternofetal indications favoring delivery
- Neonatal and perinatal consultations
- Single course of corticosteroids; rescue course suitable but not supported by robust data
- GBS screening on admission; for delivery, GBS prophylaxis as indicated
- Antibiotics recommended to prolong latency
- For pregnancies $<32^{0/7}$ weeks, magnesium sulfate for neuroprotection before anticipated delivery
- Treat any intraamnionic infection and deliver

Periviable: See Table 45-4

GBS = group B streptococcus.
American College of Obstetricians and Gynecologists 2019b; 2020g,h.

Hospitalization

Most clinicians hospitalize women with PPROM. Concerns regarding the costs of lengthy hospitalizations are usually moot, because most women enter labor within a week or less after membrane rupture. Carlan and coworkers (1993) randomly assigned 67 women with PPROM at <37 weeks' gestation to home or hospital management. The mean gestational age was 31 weeks. No benefits were found for hospitalization, and maternal hospital stays were reduced by 50 percent in those sent home—14 versus 7 days. Importantly, the investigators emphasized that this study was too small to conclude that home management was safe in regard to umbilical cord prolapse.

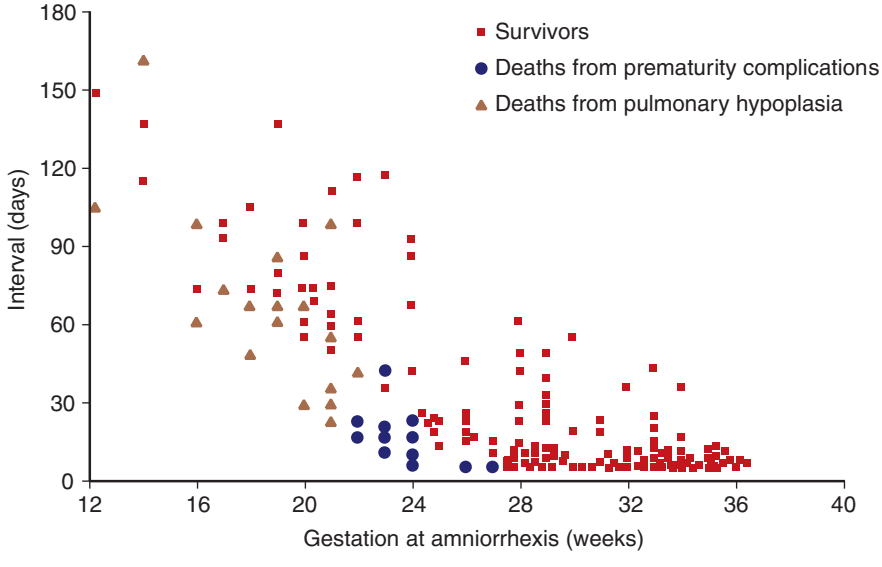

FIGURE 45-8 Relationship of time between preterm membrane rupture and delivery in 172 singleton pregnancies. (Reproduced with permission from Carroll SG, Blott M, Nicolaides KH: Preterm prelabor amniorrhexis: Outcome of live births. Obstet Gynecol 1995 Jul;86(1):18–25.)

If hospitalization is chosen, no consensus guides the optimal frequency of inpatient assessment. The American College of Obstetricians and Gynecologists (2020g) notes that an acceptable strategy would include periodic sonograms for fetal growth, fetal heart rate monitoring, and clinical surveillance for maternal infection—particularly fever. During the periviable period and at gestation ages before interventions would be planned, a short period of initial observation and consideration of outpatient monitoring in select cases is reasonable. Hospitalization would then be practiced at the time of viability.

Intentional Delivery

Before the mid-1970s, labor was usually induced in women with PPROM because of sepsis fears. Maternal infection risk and fetal prematurity risk vary according to the gestational age at membrane rupture, and management decisions incorporate this data. With periviable pregnancy, Morales (1993b) expectantly managed 94 singleton pregnancies with PPROM before 25 weeks. The average time gained was 11 days. Although 41 percent of infants survived to age 1 year, only 27 percent of the original cohort were neurologically normal. Similar results were reported by Farooqi (1998) and Winn (2000) and their colleagues. Management of these early pregnancies is discussed on page 785.

For PPROM in general, two randomized trials in the 1990s compared labor induction with expectant management (Cox, 1995; Mercer, 1993). In both of these studies, the balance of risk and benefit was difficult to ascertain, as neither immediate delivery nor expectant management was superior for neonatal outcomes. Lieman and associates (2005) found that neonatal outcomes did not improve with expectant management beyond 33 weeks. McElrath and coworkers (2003) found that prolonged latency after membrane rupture was not associated with a greater incidence of fetal neurological damage. An important correlate is that infection—specifically chorioamnionitis—is a recognized risk factor for neonatal neurological injury (Gaudet, 2001; Wu, 2000).

Bond and colleagues (2017) compared planned early birth with expectant management for women with PPROM before 37 weeks' gestation. They evaluated 12 randomized trials totaling 3617 women and 3628 newborns. No clinically important differences in the incidence of neonatal sepsis between women who immediately delivered and those managed expectantly were identified. Although the incidence of chorioamnionitis was lower, neonates of women randomized to early birth were more likely to be born at an earlier gestational age and encountered attendant perinatal sequelae. The authors concluded that in women with rupture of membranes before 37 weeks' gestation without contraindications to continuing the pregnancy, a policy of expectant management with careful monitoring was associated with better outcomes for both the mother and newborn. A subsequent metaanalysis of late-preterm prelabor rupture of membranes by Quist-Nelson and coworkers (2018) noted that immediate delivery and expectant management resulted in comparable rates of the composite of adverse neonatal outcomes.

Because of conflicting data and the controversies of immediate delivery compared with expectant management, the American College of Obstetricians and Gynecologists (2020g) cannot make firm recommendations. Clearly, gestational age is an important consideration. At $24^{0/7}$ to $33^{6/7}$ weeks, expectant management in the absence of nonreassuring fetal status, clinical chorioamnionitis, or placental abruption is recommended. At $34^{0/7}$ to $36^{6/7}$ weeks' gestation, delivery was once recommended, however, it is now considered reasonable to offer either expectant management or immediate delivery following consideration of risks and benefits, counseling, and shared decision-making. Expectant management should not go beyond $37^{0/7}$ weeks' gestation. Based upon limitations of access to care and resources, our current practices at Parkland Hospital continue to favor immediate delivery after 34 weeks' gestation.

Expectant Management

Several considerations arise during expectant management of PPROM (Boettcher, 2020; Shaddeau, 2020). One is digital cervical examination. Alexander and colleagues (2000) analyzed findings in women with membrane rupture expectantly managed between 24 and 32 weeks' gestation. They compared those who had one or two digital cervical examinations with women who were not examined. Those who were examined had a rupture-to-delivery interval of 3 days compared with 5 days in those not examined. This difference did not worsen maternal or neonatal outcomes. At Parkland Hospital, digital cervical examination is used judiciously in PPROM cases.

Rupture of membranes following second-trimester amniocentesis is uncommon (Chap. 17, p. 345). Compared with women with spontaneous rupture during the second trimester, Borgida and associates (2000) found that pregnancies complicated by PPROM after genetic amniocentesis resulted in significantly better perinatal outcomes. The perinatal survival rate was 91 percent. After counseling, affected women are typically managed expectantly as outpatients with serial surveillance of amnionic fluid volume and self-assessment of temperature (American College of Obstetricians and Gynecologists, 2020g). In the series cited above, the mean time to documentation of a normal amnionic fluid volume after amniocentesis approximated 2 weeks.

Tocolysis given with PPROM has been reported in few studies. In women with ruptured membranes and lack of labor, prophylactic tocolysis does not improve neonatal outcomes but is associated with greater chorioamnionitis rates (Mackeen, 2014). Similarly, therapeutic tocolysis—for those with ruptured membranes and labor—has not provided significant perinatal benefit (Garite, 1987).

Management of PPROM in the woman who has undergone cervical cerclage is complex (American College of Obstetricians, 2020g). McElrath and associates (2002) studied 114 women with a cerclage in place who later had ruptured membranes before 34 weeks. They were compared with 288 controls. Pregnancy outcomes were equivalent in both groups. Cerclage retention for more than 24 hours after PPROM may be associated with pregnancy prolongation, however, intrauterine infection and its consequences are risks (Giraldo-Isaza, 2011; Laskin, 2012). At Parkland Hospital, cerclage retention in the absence of infection or labor is currently practiced with close clinical surveillance in those with PPROM.

With PPROM in pregnancies before 26 weeks, the volume of amnionic fluid remaining after rupture appears to have prognostic importance (Carroll, 1995; Hadi, 1994). Although varied by report, current rates of pulmonary hypoplasia with PPROM before 24 weeks among surviving neonates can be as high as 30 percent (Kiver, 2018). This suggests that 23 weeks reflects a threshold for lung hypoplasia development (Chap. 7, p. 131). Further, when contemplating early expectant management, oligohydramnios and resultant limb compression deformities are influencing considerations.

For neonates born to women who have active herpetic lesions and who are expectantly managed, the infectious morbidity risk appears to be outweighed by risks associated with preterm birth (Chap. 68, p. 1216) (Major, 2003). Lewis and associates (2007) found that expectant management of women

with PPROM and noncephalic presentation was associated with a higher rate of umbilical cord prolapse, especially before 26 weeks.

Tissue sealants are often used to gain surgical hemostasis. Limited reports describe their use for repair of fetal membranes (Chap. 11, p. 203). Crowley and coworkers (2016) concluded that available data are currently insufficient to assess the value of sealing procedures for PPROM. We do not use these agents for this indication.

Clinical Chorioamnionitis

Infection is a major concern with membrane rupture. Although some cases remain subclinical, if chorioamnionitis is diagnosed, prompt efforts to effect delivery, preferably vaginally, are initiated. Because maternal leukocytosis alone is not a consistent finding, *fever is the only reliable indicator for the diagnosis of chorioamnionitis*. Institutional practices and protocols vary in defining the temperature threshold. Traditionally, a temperature ≥38°C (100.4°F) accompanying ruptured membranes has implied infection. At Parkland Hospital, we still adhere to this criterion.

In 2015, a workshop sponsored by the NICHD was convened and suggested renaming this condition *intraamnionic infection and inflammation—triple I* (Higgins, 2016). The merits of this terminology have been questioned (Barth, 2016). Nonetheless, the American College of Obstetricians and Gynecologists (2019b) revised both the definitions and temperature thresholds for intraamnionic infection. Using these new definitions, the diagnosis of suspected intraamnionic infection is made when the maternal temperature is ≥39.0°C or when the maternal temperature is 38.0 to 38.9°C and one additional clinical risk factor is present. The latter include low parity, multiple digital examinations, internal uterine and fetal monitors, meconium-stained amnionic fluid, and the presence of certain genital tract pathogens, such as group B streptococcus (GBS) and sexually transmitted agents. Isolated maternal fever is defined as any maternal temperature between 38.0°C and 38.9°C with no additional risk factors present, and with or without persistent temperature elevation.

With chorioamnionitis, fetal and neonatal morbidity are substantively increased. Alexander and colleagues (1998) studied 1367 very-low-birthweight neonates delivered at Parkland Hospital. Approximately 7 percent were born to women with overt chorioamnionitis, and their outcomes were compared with similar newborns without clinical infection. Those in the infected group had higher incidences of sepsis, respiratory distress, early-onset seizures, intraventricular hemorrhage, and periventricular leukomalacia. Yoon and colleagues (2000) found that intraamnionic infection in preterm neonates was associated with increased rates of cerebral palsy. In one study of more than 11 million singleton live births in the United States from 1995 to 1997, 1.6 percent of gravidas had fever during labor. This was a strong predictor of infection-related death in both term and preterm neonates (Petrova, 2001).

Antimicrobial Therapy

Various antimicrobials have been evaluated to forestall preterm delivery. Mercer and associates (1995) reviewed 13 randomized trials that evaluated antibiotics for PPROM before 35 weeks. Their metaanalysis indicated that only three of 10 outcomes were *possibly* benefited: (1) fewer women developed chorioamnionitis, (2) fewer newborns developed sepsis, and (3) pregnancy was more often prolonged 7 days in women given antibiotics. However, rates of other neonatal outcomes, including survival and respiratory distress, were unaffected.

In an MFMU Network trial, women with membrane rupture between 24 and 32 weeks' gestation were randomly assigned to expectant management combined with placebo or to a 7-day antibiotic regimen. Treatment included intravenous ampicillin plus erythromycin every 6 hours for 48 hours, which was followed by oral amoxicillin plus erythromycin, every 8 hours for 5 days. Neither tocolytics nor corticosteroids were given. Antimicrobial-treated women had significantly fewer newborns with respiratory distress, necrotizing enterocolitis, and composite adverse outcomes (Mercer, 1997). The latency period was also significantly longer. Specifically, 50 percent of women given an antimicrobial regimen remained undelivered after 7 days of treatment compared with only 25 percent of those given placebo. Also, a significantly greater number of treated pregnancies were undelivered at 14 and 21 days. Cervicovaginal GBS colonization did not alter these results.

Other studies have examined the efficacy of shorter treatment lengths and different antimicrobial combinations. Three-day treatments compared with 7-day regimens using either ampicillin or ampicillin-sulbactam appear equally effective in regard to perinatal outcomes (Lewis, 2003; Segel, 2003). Similarly, erythromycin compared with placebo offered a range of significant neonatal benefits. The substitution of azithromycin for erythromycin does not appear to impact maternal or neonatal outcomes, and the former has an improved side-effect profile (Dotters-Katz, 2020). An amoxicillin-clavulanate regimen is not recommended, however, because of its association with an increased incidence of neonatal necrotizing enterocolitis (Kenyon, 2004).

Some predicted that prolonged antimicrobial therapy in such pregnancies might have unwanted consequences (Carroll, 1996; Mercer, 1999). Stoll and associates (2002) studied 4337 neonates weighing from 400 to 1500 g and born from 1998 to 2000. Their outcomes were compared with those of 7606 neonates of similar birthweight born from 1991 to 1993 and prior to the practice of antibiotic prophylaxis. The overall rate of early-onset sepsis did not change between these two epochs. But, the rate of GBS sepsis dropped from 5.9 per 1000 births in the earlier group to 1.7 per 1000 births in the later group. Comparing these same epochs, the rate of *Escherichia coli* sepsis, however, rose from 3.2 to 6.8 per 1000 births. Almost 85 percent of isolates from the more recent cohort were resistant to ampicillin. Neonates with early-onset sepsis were more likely to die, especially if they were infected with coliforms. Long term, Kenyon and coworkers (2008a) found that antimicrobials given for women with PPROM had no effect on the health of children at age 7 years.

Corticosteroid Therapy

A single course of corticosteroids is recommended for pregnant women with PPROM between $24^{0/7}$ and $34^{0/7}$ weeks' gestation

(American College of Obstetricians and Gynecologists, 2020g). A single course of corticosteroids as early as $23^{0/7}$ weeks in those at risk for preterm delivery within 7 days may be considered. A similar controversy is found at the other end of the gestational age spectrum, $34^{0/7}$ to $36^{6/7}$ weeks' gestation and with rescue therapy (p. 803). These issues were summarized by Battarbee (2020) in a recent review.

MANAGEMENT OF PRETERM LABOR WITH INTACT MEMBRANES

Women with signs and symptoms of preterm labor with intact membranes are managed similarly to those with PPROM. If possible, delivery before 34 weeks' gestation is delayed. Drugs used to abate or suppress preterm uterine contractions are subsequently discussed.

Amniocentesis to Detect Infection

One of every 10 women with preterm labor and intact membranes will have intraamnionic infection that is largely subclinical (Yoon, 2019). Because of this, several tests have been used to diagnose intraamnionic infection (Andrews, 1995; Romero, 1993; Yoon, 1996). Although such infection can be identified with a positive test result, routine amniocentesis offers little value.

Corticosteroid Therapy

Glucocorticosteroids were found to accelerate lung maturation in preterm sheep fetuses, and Liggins and Howie (1972) evaluated them to treat women with preterm labor. Corticosteroid therapy was effective in lowering the incidence of respiratory distress syndrome (RDS) and neonatal mortality rates if birth was delayed for at least 24 hours after *initiation* of betamethasone. Infants exposed to corticosteroids in these early studies have now been followed into adulthood with no ill effects detected.

In 1995, a National Institutes of Health (NIH) Consensus Development Conference panel recommended corticosteroids for fetal lung maturation in threatened preterm birth. A subsequent NIH Conference (2000) summarized that data were insufficient to assess corticosteroid effectiveness in pregnancies complicated by hypertension, diabetes, multifetal gestation, fetal-growth restriction, or fetal hydrops. It was concluded, however, that administering corticosteroids to these women is reasonable.

One metaanalysis of 30 studies totaling 7774 women and 8158 infants quantified the benefit of a single course of corticosteroids (Roberts, 2017). Treatment was associated with lower rates of perinatal death, neonatal death, RDS, intraventricular hemorrhage, necrotizing enterocolitis, mechanical ventilation, and systemic infection in the first 48 hours of life. No obvious benefits were gained for chronic lung disease, death in childhood, or neurodevelopmental delay in childhood. Therapy was not associated with chorioamnionitis.

Parenthetically, corticosteroids given prophylactically to women at risk of preterm birth in low- and middle-income countries actually *increased* perinatal mortality rates (Althabe, 2015). Because of this unexpected finding, a multicountry randomized trial comparing dexamethasone to placebo and involving pregnant women between $26^{0/7}$ and $33^{6/7}$ weeks' gestation was recently completed (WHO ACTION Trials Collaborators, 2020). The trial was stopped early due to benefits of dexamethasone, which resulted in a significantly lower risk of stillbirth or neonatal death. The discrepancy between the two reports was attributed to inaccuracies in gestational age assessment (Rohwer, 2020).

A single course of corticosteroids is currently recommended for women between 24 and 34 weeks' gestation who are at risk for delivery within 7 days (American College of Obstetricians and Gynecologists (2020a). This recommendation for premature twins has been challenged (Viteri, 2016). For pregnancies at 23 weeks and at risk of delivery within 7 days, a single course of corticosteroids may be considered (p. 785). Administration of corticosteroids during the periviable period is linked to parental decisions regarding resuscitation and should be considered in that context (American College of Obstetricians and Gynecologists, 2019d).

Agent Selection

Betamethasone and dexamethasone are glucocorticoids that appear equivalent in stimulating fetal lung maturation (Murphy, 2007). Reduced rates of major preterm neonatal morbidities and increased rates of survival without neurosensory disability at age 2 years do not differ between them (Crowther, 2019; Elimian, 2007). A treatment course may be two 12-mg doses of betamethasone, and each dose is given intramuscularly 24 hours apart. With dexamethasone, 6-mg doses are given intramuscularly every 12 hours for four doses. Because treatment for less than 24 hours may be beneficial and reduce neonatal morbidity and mortality rates, a first dose of antenatal corticosteroids is administered regardless of the ability to complete additional doses before delivery (American College of Obstetricians and Gynecologists, 2020a).

Late-preterm Delivery

Antenatal betamethasone has been compared against placebo for neonates that are likely to deliver in the late-preterm period (Gyamfi-Bannerman, 2016). Although only 60 percent of 2831 women received both injections, the rate of respiratory complications measured as a composite outcome was significantly lower with corticosteroid use compared with placebo—11.6 versus 14.4 percent. Because of these findings, *consideration* for administration of a single course of betamethasone for women between $34^{0/7}$ and $36^{6/7}$ weeks is advocated by both the American College of Obstetricians and Gynecologists (2020a) and the Society for Maternal-Fetal Medicine (2016a).

Adoption of this practice has not been universal because of both short- and long-term neonatal safety concerns (Crowther, 2016; Kamath-Rayne, 2016). Specifically, in the newborns receiving betamethasone, rates of hypoglycemia were significantly greater (Gyamfi-Bannerman, 2016). Neonatal hypoglycemia is particularly worrisome for possible adverse long-term consequences that include developmental delay (Kerstjens, 2012). Another caveat is that the largest effects of betamethasone included a reduction in transient tachypnea of the newborn

(TTN), which is a self-limited condition with little clinical significance (Kamath-Rayne, 2016). Specifically, the rates of TTN were 6.7 and 9.9 percent in those given betamethasone and placebo, respectively. These rates are three- to fourfold higher than those reported by the Consortium on Safe Labor (2010). The latter was a retrospective, observational study from 19 hospitals across the United States that included 233,844 deliveries. Because of these issues, we do not provide corticosteroids beyond 34 weeks at Parkland Hospital at this time.

Repeated Courses

A single dose of intramuscular corticosteroids has been compared with repeated courses for lung maturation in two major randomized trials. Both found that repeated courses reduced neonatal respiratory morbidity rates, but the long-term consequences were much different. In one study, all women were given a primary course of betamethasone. If the preterm delivery risk persisted, they were assigned to serial weekly doses of betamethasone or placebo. These investigators found no adverse effects in the infants followed to age 2 years (Crowther, 2007).

In the second study, 495 women were randomly assigned to receive a single corticosteroid course that contained two doses or assigned to repeated courses that were given weekly (Wapner, 2007). In infants exposed to repeated courses, a nonsignificant rise in the cerebral palsy rate was identified. Still, exposure to the doubled betamethasone dose was worrisome because some experimental evidence supports the view that adverse effects are dose dependent (Bruschettini, 2006). We agree with Stiles (2007) who summarized these two studies as "early gain, long-term questions." At Parkland Hospital, our practice is to follow the recommendations of the American College of Obstetricians and Gynecologists (2020a) for single-course therapy.

Rescue Therapy

This refers to administration of a second corticosteroid dose when delivery becomes imminent and more than 7 days have elapsed since the initial dose. In one randomized trial, 326 women received placebo or a single 12-mg dose of betamethasone (Peltoniemi, 2007). Paradoxically, the rescue dose of betamethasone increased the risk of RDS. In another randomized study of 437 women with gestations <33 weeks, Garite and associates (2009) reported significantly lower rates of respiratory complications and neonatal composite morbidity with rescue corticosteroids versus placebo. Rates of perinatal mortality and other morbidities, however, did not differ. Another study found that treated infants had improved respiratory compliance (McEvoy, 2010). In a metaanalysis, Crowther and colleagues (2011) concluded that a single rescue course of corticosteroids should be considered in women whose prior course was administered at least 7 days previously and who were <34 weeks' gestation.

The American College of Obstetricians and Gynecologists (2020a) notes that a single rescue course of antenatal corticosteroids *should be considered* in women with fetuses <34 weeks' gestation whose prior course was administered at least 7 days previously. Effects of rescue therapy beyond 34 weeks are unknown. At Parkland Hospital, we currently do not provide additional courses of corticosteroids beyond the initial single-course therapy.

Magnesium Sulfate for Neuroprotection

Very-low-birthweight neonates whose mothers were treated with magnesium sulfate for preterm labor or preeclampsia were found to have a reduced incidence of cerebral palsy at 3 years (Grether, 2000; Nelson, 1995). Because of this, randomized trials were designed to investigate this hypothesis. In one trial, 1063 women at risk of delivery before 30 weeks' gestation were given magnesium sulfate or placebo (Crowther, 2003). Magnesium exposure improved some perinatal outcomes. Namely, rates of both neonatal death and cerebral palsy were lower in the magnesium-treated group. However, this study was not sufficiently powered. The multicenter French trial reported by Marret and associates (2008) had similar problems.

More convincing evidence for magnesium neuroprotection came from the randomized MFMU Network study—*Beneficial Effects of Antenatal Magnesium Sulfate—BEAM—study* (Rouse, 2008). In the study, 2241 women at imminent risk for preterm birth between 24 and 31 weeks' gestation were assigned to magnesium sulfate or placebo. Magnesium sulfate was given as a 6-g bolus over 20 to 30 minutes and was followed with a maintenance infusion of 2 g/hr. Magnesium sulfate was actually infusing at the time of delivery in approximately half of the treated women. Infusion continuation protocols vary by institution, including ours. In the BEAM study, after 12 hours with no signs of imminent delivery, the infusion was stopped and resumed if delivery again seemed imminent. If >6 hours had passed since discontinuation, another loading dose was given.

A 2-year assessment was available for 96 percent of the children in the BEAM trial (Table 45-10) (Rouse, 2008). The results can be interpreted differently depending on statistical methodologies employed. Some interpret these findings to mean that magnesium sulfate infusion prevents cerebral palsy regardless of the gestational age at which therapy is given. Those with a differing view conclude that this trial only supports use of magnesium sulfate for prevention of cerebral palsy potentially before 28 weeks.

Subsequently, Doyle and associates (2009) reviewed five randomized trials to assess neuroprotective effects. A total of 6145 infants were studied, and these reviewers concluded that magnesium sulfate exposure compared with no exposure significantly lowered risks for cerebral palsy. Rates of other neonatal morbidities did not differ significantly. It was calculated that treatment given to 63 women would prevent one case of cerebral palsy.

Controversy surrounding magnesium sulfate efficacy for neuroprotection prompted a debate at the 2011 annual meeting of the Society for Maternal-Fetal Medicine. Rouse (2011) spoke for the benefits of magnesium sulfate, whereas Sibai (2011) challenged that the reported benefits were falsely positive due to random statistical error in the metaanalysis by Doyle (2009). Another peculiarity is the apparent lack of dose-response for efficacy (McPherson, 2014).

Because none of the individual studies found a benefit from magnesium sulfate for fetal neuroprotection, the American College of Obstetricians and Gynecologists (2020d,g) concluded

TABLE 45-10. Magnesium Sulfate for the Prevention of Cerebral Palsy[a]

Perinatal Outcome[a]	Treatment		
	Magnesium Sulfate No. (%)	Placebo No. (%)	Relative Risk (95% CI)
Infants with 2-year follow-up	1041 (100)	1095 (100)	—
Fetal or infant death	99 (9.5)	93 (8.5)	1.12 (0.85–1.47)
Moderate or severe cerebral palsy:			
Overall	20/1041 (1.9)	3/1095 (3.4)	0.55 (0.32–0.95)
<28–31 weeks[b]	12/442 (2.7)	30/496 (6)	0.45 (0.23–0.87)
≥24–27 weeks[b]	8/599 (1.3)	8/599 (1.3)	1.00 (0.38–2.65)

[a]Selected results from the Beneficial Effects of Antenatal Magnesium Sulfate (BEAM) Study.
[b]Weeks' gestation at randomization.
CI = confidence index.

that those electing prophylaxis should develop specific guidelines, and this includes those with PPROM. In a recent prospective observational study of infants born at $22^{0/7}$ to $26^{6/7}$ weeks' gestation, exposure to both corticosteroids and magnesium sulfate was associated with lower rates of neurodevelopmental impairment and death compared with corticosteroids alone (Gentle, 2020). At Parkland Hospital, for the periviable fetus, we individualize management as shown in Table 45-4.

Antimicrobial Treatment

Results have been disappointing in studies of antibiotics given to *arrest* preterm labor. From one Cochrane metaanalysis, antimicrobial prophylaxis given to women with intact membranes did not reduce preterm birth rates or affect other clinically important short-term outcomes (Flenady, 2013). However, rates of short- and longer-term harm were higher for children of mothers exposed to antibiotics.

In the ORACLE Collaborative Group study of 6295 women with spontaneous preterm labor, intact membranes, but without evidence of infection, women were randomly assigned to receive antimicrobial or placebo therapy (Kenyon, 2001). The primary outcomes of neonatal death, chronic lung disease, and major cerebral abnormality were similar in both groups. In a follow-up of the ORACLE II trial, fetal exposure to antimicrobials in this setting was associated with an increased cerebral palsy rate at age 7 years compared with that in children without fetal exposure (Kenyon, 2008b). Moreover, although preterm birth is associated with bacterial vaginosis, treatment with clindamycin in more recent randomized trials has failed to lower preterm birth rates (Bellad, 2018; Subtil, 2018). Importantly, antimicrobial use described here is distinct from that given for GBS prophylaxis (Chap. 67, p. 1195).

Bed Rest

This has been one of the most often prescribed interventions, yet one of the least supported by evidence (McCall, 2013). An earlier systematic review concluded that evidence neither supported nor refuted bed rest for preterm birth prevention (Sosa, 2004). Moreover, possible harms are thromboembolic events, deconditioning, and bone loss (Kovacevich, 2000; Promislow, 2004). Grobman and associates (2013) reported that women with activity restriction were nearly 2.5 times more likely to have a preterm birth before 34 weeks. This finding, however, may reflect ascertainment bias. That is, women with restricted activity may have been assigned to bed rest because they were viewed to have a greater risk for preterm delivery. The Society for Maternal-Fetal Medicine (2020a) and the American College of Obstetricians and Gynecologists (2020f) recommend against activity restriction to reduce preterm birth rates.

Cervical Pessaries

Silicone rings, such as the Arabin pessary, have been used to support the cervix in women with a sonographically short cervix. In one study, 385 women with a cervical length ≤25 mm were provided a silicone pessary or expectant management (Goya, 2012). Newborns spontaneously delivered before 34 weeks' gestation in 6 percent of women in the pessary group compared with 27 percent in the expectant management group. In another randomized trial, almost 100 women with a cervical length <25 mm at 20 to 24 weeks' gestation received either pessaries or expectant management (Hui, 2013). The pessary did not lower the rate of delivery <34 weeks. Others have reported similar findings (Nicolaides, 2016). Moreover, authors of a recent systematic review totaling 4687 women and 7167 infants found that current evidence does not support pessary use to prevent preterm birth or improve perinatal outcomes in singleton or twin gestations with a short cervix or in unselected twin gestations (Conde-Agudelo, 2020). The Society for Maternal-Fetal Medicine (2017) currently recommends pessary prophylaxis only within research protocols.

Emergency or Rescue Cerclage

Some evidence supports the concept that cervical incompetence and preterm labor lie along a spectrum leading to preterm delivery. Consequently, cerclage placement after preterm labor begins to manifest clinically has been studied. Importantly, for

women with labor and active cervical change, cerclage is contraindicated.

In one study, 23 women with cervical incompetence before 27 weeks' gestation were randomly assigned to bed rest, with or without an adjunctive emergency McDonald cerclage (Althuisius, 2003). Delivery delay was significantly greater in the cerclage group compared with those assigned to bed rest alone—54 versus 24 days, respectively. Terkildsen and coworkers (2003) studied 116 women who underwent second-trimester emergency cerclage. Nulliparity, membranes extending beyond the external cervical os, and cerclage before 22 weeks' gestation were associated with a significantly lower chance of significant pregnancy continuation. More recently, a multicenter randomized trial assessed women with twin pregnancies and asymptomatic cervical dilation of 1 to 5 cm between $16^{0/7}$ and $23^{6/7}$ weeks' gestation (Roman, 2020). From a total of 30 enrolled women, 17 women received physical examination-indicated cerclage, and 13 women received no cerclage. Of note, all women who underwent cerclage received indomethacin and antibiotics. In the cerclage group, the preterm birth rate was significantly decreased at all evaluated gestational ages, and specifically, cerclage lowered the birth rate for those <28 weeks by 50 percent. From these limited reports, for women facing a poor pregnancy prognosis due to cervical dilation at midgestation, emergency or rescue cerclage with appropriate counseling is reasonable. At this time, however, it is unclear if such interventions truly confer a benefit or merely increase the risk of membrane rupture and infection (Hawkins, 2017).

■ Tocolysis

Although several drugs have been used to prevent or inhibit preterm labor, none is completely effective. The American College of Obstetricians and Gynecologists (2020e) has concluded that tocolytic agents do not markedly prolong gestation but may delay delivery in some women for up to 48 hours. This may allow transport to an obstetrical center with higher-level neonatal care and permit time for a course of corticosteroid therapy. Although delivery may be delayed to administer corticosteroids, evidence does not support that tocolytic therapy has any direct favorable effect on neonatal outcomes or that any prolongation of pregnancy afforded by tocolytics alone translates into statistically significant neonatal benefit.

Beta-adrenergic agonists, magnesium sulfate, calcium-channel blockers, or indomethacin are the recommended tocolytic agents for short-term use. The gestational age range for tocolytic use is debatable (Mendez-Figueroa, 2020). But, because the perinatal outcomes in preterm neonates are generally good after 34 weeks' gestation, most do not recommend use of tocolytics after 33 weeks.

In many women, tocolytics stop contractions temporarily but rarely prevent preterm birth. Moreover, the American College of Obstetricians and Gynecologists (2020e) has concluded that maintenance therapy with tocolytics is ineffective for preventing preterm birth. No trial has ever convincingly shown reduced rates of any important adverse outcome by a tocolytic drug compared with placebo (Walker, 2016).

β-Adrenergic Receptor Agonists

Several compounds stimulate β-adrenergic receptors to reduce intracellular ionized calcium levels and prevent activation of myometrial contractile proteins (Chap. 21, p. 403). Of β-mimetic drugs in the United States, ritodrine and terbutaline have been used in obstetrics, but only ritodrine is FDA-approved for preterm labor.

Ritodrine was voluntarily withdrawn from the United States market in 2003, but a discussion of ritodrine is included here to present issues with β-mimetic drug use. In a randomized trial at Parkland Hospital, intravenous ritodrine delayed delivery for 24 hours but without other benefits (Leveno, 1986b). Additional studies confirmed a delivery delay up to 48 hours (Canadian Preterm Labor Investigators Group, 1992).

Importantly, β-agonist infusion resulted in serious and even fatal maternal side effects. Pulmonary edema is a special concern, and its cause is multifactorial. Risk factors include tocolytic therapy with β-agonist drugs, multifetal gestation, concurrent corticosteroid therapy, tocolysis for more than 24 hours, and intravenous infusion of large volumes of crystalloid. β-Agonist agents cause retention of sodium and water, and with time—usually 24 to 48 hours—these can cause volume overload (Hankins, 1988). The drugs have been implicated in increased capillary permeability, cardiac rhythm disturbances, and myocardial ischemia. For example, in an earlier study, tocolysis was the third most common cause of acute respiratory distress and death in pregnant women during a 14-year period in Mississippi (Perry, 1998).

Terbutaline is commonly used in the United States to forestall preterm labor. Like ritodrine, it may cause pulmonary edema (Angel, 1988). Low-dose terbutaline can be administered long-term by subcutaneous pump, but randomized trials fail to show benefit for such therapy (Guinn, 1998; Wenstrom, 1997). Oral terbutaline also is ineffective (How, 1995; Parilla, 1993). In one trial, 203 women with arrested preterm labor at 24 to 34 weeks' gestation were randomly assigned to receive 5-mg terbutaline tablets or placebo every 4 hours (Lewis, 1996). Of outcomes, delivery rates at 1 week, median days of pregnancy extension, mean gestational age at delivery, and incidence of preterm labor relapse were similar in both groups.

Because of serious maternal side effects, the FDA (2011) issued a warning regarding terbutaline use for preterm labor. The American College of Obstetricians and Gynecologists (2020e) recommends only short-term inpatient use of terbutaline as a tocolytic or as acute therapy for uterine tachysystole. Subcutaneous dosages of 0.25 mg are commonly used for the latter indication.

Magnesium Sulfate

Ionic magnesium in a sufficiently high concentration can alter myometrial contractility. It functions as a calcium antagonist, and when given in pharmacological doses, it may inhibit labor. Magnesium sulfate treatment has been associated with pulmonary edema (Samol, 2005). As discussed in Chapter 41 (p. 720), this has not been our experience at Parkland Hospital with treatment of tens of thousands of preeclamptic women with intramuscular or intravenous magnesium sulfate.

In one randomized trial, 54 women with preterm labor received magnesium sulfate, ritodrine, or placebo. Few differences in outcomes were identified (Cotton, 1984). Cox and coworkers (1990) randomly assigned 156 women to receive magnesium sulfate or infusions of normal saline. Magnesium sulfate–treated women and their neonates had identical outcomes compared with those given placebo. Because of these findings, this method of tocolysis was abandoned at Parkland Hospital. Similarly, Crowther and associates (2014) concluded that magnesium sulfate to treat preterm labor was ineffective and potentially harmful. Last, the FDA (2013) has warned against prolonged use of magnesium sulfate given to arrest preterm labor because of bone thinning and fractures in fetuses exposed for more than 5 to 7 days. This was attributed to low calcium levels in the fetus. Yule and associates (2020) demonstrated the influence of magnesium sulfate on maternal serum calcium levels.

Prostaglandin Inhibitors

These compounds are intimately involved in the contractions of normal labor (Chap. 21, p. 413). Antagonists act by inhibiting prostaglandin synthesis or by blocking their action on target organs.

Indomethacin, a nonselective cyclooxygenase inhibitor, was first used as a tocolytic in one study of 50 women (Zuckerman, 1974). Studies that followed reported the efficacy of indomethacin in halting contractions and delaying preterm birth (Muench, 2003; Niebyl, 1980). Morales and coworkers (1989, 1993a), however, compared indomethacin with either ritodrine or magnesium sulfate and found no difference in their efficacy to forestall preterm delivery. Berghella and associates (2006) reviewed four trials of indomethacin given to women with a sonographically determined short cervix and found such therapy to be ineffective to halt labor. But, as discussed earlier, its use with cerclage is gaining favor.

Most studies have limited indomethacin use to 24 to 48 hours because of concerns for oligohydramnios, which can develop with therapeutic doses. If amnionic fluid is monitored, oligohydramnios can be detected early, and it is reversible with drug discontinuation. There has also been considerable debate on the association of necrotizing enterocolitis or early ductus arteriosus closure and use of indomethacin (Doni, 2020; Hammers, 2015; Muench, 2001). Two metaanalyses of the effects of antenatal indomethacin on neonatal outcomes had conflicting findings (Amin, 2007; Loe, 2005). In one review of 20 studies, cyclooxygenase inhibitors, including indomethacin, provided no clear benefit compared with placebo or any other tocolytic agent (Reinebrant, 2015).

Calcium-channel Blockers

Myometrial activity is directly related to cytoplasmic free calcium, and reduced calcium concentrations inhibit contractions. Calcium-channel blockers inhibit, by various mechanisms, calcium entry through cell membrane channels.

From study results, calcium-channel blockers, especially nifedipine, are safer and more effective tocolytic agents than β-agonist drugs (King, 2003; Papatsonis, 1997). Comparing magnesium sulfate and nifedipine, one study of 192 women at 24 to 33 weeks' gestation found no substantial differences in efficacy or adverse effects (Lyell, 2007). Comparing nifedipine and atosiban in 145 women with preterm labor between 24 and 33 weeks, another randomized study showed that neither agent was superior to delay delivery. Neonatal morbidity rates were equivalent (Salim, 2012).

Flenady and coworkers (2014b) reviewed 38 trials of calcium-channel blockers for preterm labor and concluded that these agents have benefits compared with placebo. It is problematic, however, that this conclusion stemmed from a trial with unclear risk of selection bias and a three-arm study of 84 women that was not blinded (Ara, 2008; Zhang, 2002). More recently, Hawkins and associates (2021) performed a randomized, placebo-controlled trial of nifedipine for acute tocolysis of preterm labor at Parkland Hospital. Acute tocolysis with nifedipine did not affect preterm birth rates. However, the study results were obtained following an interim analysis demonstrating futility for study continuation.

Importantly, the combination of nifedipine and magnesium sulfate for tocolysis is potentially dangerous. Ben-Ami (1994) and Kurtzman (1993) and their coworkers reported that nifedipine enhances the neuromuscular blocking effects of magnesium, which can interfere with pulmonary and cardiac function. In one small study of 54 women with preterm labor who received either magnesium sulfate plus nifedipine or no tocolytic, neither benefit nor harm was found (How, 2006).

Other Agents

Atosiban is a nonapeptide oxytocin analogue and an oxytocin-receptor antagonist that is used in European countries to forestall labor. In randomized trials, atosiban failed to improve relevant neonatal outcomes and was linked with significant neonatal morbidity (Flenady, 2014a; Moutquin, 2000; Romero, 2000). The FDA has denied approval of atosiban for use in the United States because of these findings.

Nitric oxide donors are potent smooth-muscle relaxants that affect the vasculature, gut, and uterus. In randomized clinical trials, nitroglycerin administered orally, transdermally, or intravenously was ineffective or showed no superiority compared with other tocolytics. In addition, maternal hypotension is a common side effect (Bisits, 2004; Lees, 1999).

■ Labor and Delivery

Fetal heart rate and uterine contractions are monitored with preterm labor. We prefer continuous electronic monitoring. Fetal tachycardia, especially with ruptured membranes, suggests sepsis. Some evidence supports that intrapartum acidemia may intensify some of the neonatal complications usually attributed to preterm delivery. For example, Morgan and associates (2017) found that metabolic acidemia significantly raised the risks related to prematurity in neonates delivered <34 weeks' gestation. Low and colleagues (1995) observed that intrapartum acidosis—umbilical artery blood pH <7.0—had an important role in neonatal complications. GBS infections are common and dangerous in the preterm neonate, and antimicrobial prophylaxis should be provided (Chap. 67, p. 1195).

For delivery, perinatal outcome data do not support routine episiotomy or forceps delivery to protect the "fragile" preterm

fetal head. Staff proficient in resuscitative techniques commensurate with the gestational age and fully oriented to any specific problems should be present at delivery. The importance of specialized personnel and facilities for preterm newborn care is underscored by the improved survival rates of these neonates when delivered in tertiary-care centers. For community-based hospitals, multidisciplinary team-based simulation for preterm delivery can improve performance (Barbato, 2020).

Preterm newborns frequently have intracranial germinal matrix bleeding that can extend to more serious intraventricular hemorrhage. It was hypothesized that cesarean delivery to obviate trauma from labor and vaginal delivery might prevent these complications. This has not been validated by subsequent studies (Malloy, 1991). At Parkland Hospital, cesarean delivery is reserved for usual obstetrical indications.

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CHAPTER 46

Postterm Pregnancy

The adjectives *postterm*, *prolonged*, *postdates*, and *postmature* are used interchangeably to describe pregnancies that have exceeded a duration considered to be the upper limit of normal. We eschew use of the term *postdates* because the real issue in many postterm pregnancies is uncertainty in the estimated date of delivery (EDD). *Postmature* is reserved for the uncommon clinical fetal syndrome in which the newborn has recognizable features indicating a pathologically prolonged pregnancy. Thus, *postterm* or *prolonged pregnancy* is our preferred term for an extended pregnancy.

The definition of postterm pregnancy is one that exceeds $42^{0/7}$ weeks or is ≥294 days from the first day of the last menstrual period (LMP). Importantly, this is 42 "completed weeks." Pregnancies between $41^{1/7}$ and $41^{6/7}$ weeks, although in the 42nd week, do not complete 42 weeks until the seventh day has elapsed. These are considered *late term* (American College of Obstetricians and Gynecologists, 2019e, 2020b).

ESTIMATED GESTATIONAL AGE

The current definition of postterm pregnancy assumes that ovulation occurs 2 weeks after the LMP. Thus, some pregnancies may not actually be postterm because of error in menstrual date recall or delayed ovulation. Even with exactly recalled menstrual dates, there still is imprecision, and first-trimester sonography is the most accurate method to establish or confirm gestational age (American College of Obstetricians and Gynecologists, 2019b, 2020b). Several studies support this (Bennett, 2004; Joseph, 2007). If available, gestational ages calculated from the LMP and from the first accurate ultrasound are reconciled as shown in Table 14-1 (p. 248), and the EDD is recorded (American College of Obstetricians and Gynecologists, 2019c).

INCIDENCE

Of the 3.75 million neonates born in the United States during 2019, 0.3 percent were delivered at ≥42 weeks (Martin, 2021). This rate has declined because of improved pregnancy dating accuracy and earlier intervention. To identify predisposing factors for postterm pregnancy, one analysis of the Danish Birth Cohort found only prepregnancy body mass index ≥25 and nulliparity to be significantly associated (Olesen, 2006). Others reported similar associations (Arrowsmith, 2011; Mission, 2015). Nulliparas with a long midpregnancy cervical length (third or fourth quartile) are twice as likely to deliver after 42 weeks (van der Ven, 2016). Last, the risk for adverse pregnancy outcomes in postterm pregnancies increases with advancing maternal age (Kortekaas, 2020).

The tendency for some mothers to have repeated postterm births suggests that some prolonged pregnancies are biologically determined. In one study, if a mother and daughter had a prolonged pregnancy, the risk for the daughter to have a subsequent postterm pregnancy was significantly increased

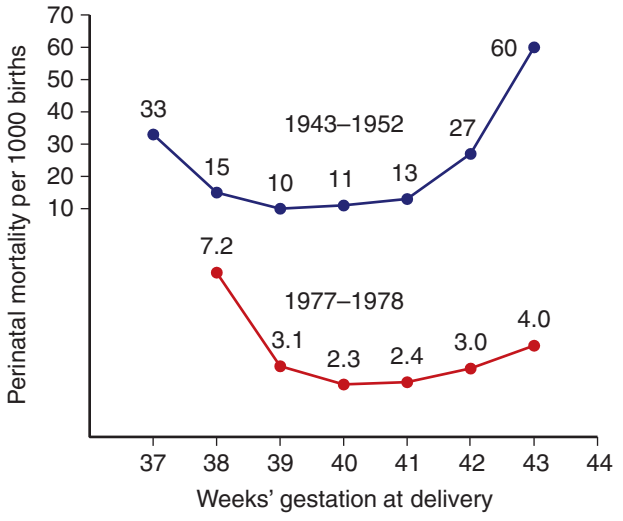

FIGURE 46-1 Perinatal mortality rates in late pregnancy according to gestational age of all births in Sweden during 1943–1952 compared with those during 1977–1978. The partially compressed scale is used for convenience in depiction. (Adapted from Bakketeig, 1991; Lindell, 1956.)

(Oberg, 2013). Maternal, not paternal, genes influence prolonged pregnancy (Laursen, 2004). For example, genes from one locus of chromosome 2q13 are associated with gestational duration (Liu, 2019). As discussed in Chapter 5 (p. 102), rare fetal-placental factors that predispose to postterm pregnancy include anencephaly, adrenal hypoplasia, and X-linked placental sulfatase deficiency (Ayyavoo, 2014; MacDonald, 1965).

PERINATAL MORTALITY AND MORBIDITY

Rates of stillbirth, neonatal death, and infant morbidity all rise after the EDD. Data from times before widespread intervention for postterm pregnancies are most illustrative. In two large Swedish studies, the perinatal mortality rate reached a nadir at 39 to 40 weeks' gestation and rose thereafter (Fig. 46-1). This trend is also reported for the United States (MacDorman, 2009). The major causes of morbidity in these studies include gestational hypertension, prolonged labor with cephalopelvic disproportion, birth injuries, and hypoxic-ischemic encephalopathy (Table 46-1). Similar outcomes were reported in 78,022 women with postterm pregnancies delivered before routine labor induction was adopted in Denmark (Olesen, 2003). A slight increase in cerebral palsy rates and two-point lower intelligence quotient (IQ) scores have been reported in postterm births (Moster, 2010; Williams, 2020; Yang, 2010). Conversely, data do not associate autism with postterm birth (Gardener, 2011).

Alexander and colleagues (2000a) reviewed 56,317 singleton pregnancies delivered at ≥40 weeks between 1988 and 1998 at Parkland Hospital. Labor was induced in 35 percent of pregnancies completing 42 weeks. The rate of cesarean delivery for dystocia or fetal distress was significantly greater at 42 weeks compared with earlier gestations. More newborns of postterm pregnancies were admitted to intensive care units. Notably, the incidence of neonatal seizures and deaths was doubled at 42 weeks.

TABLE 46-1. Adverse Maternal and Perinatal Outcomes Associated with Postterm Pregnancy

Maternal	Perinatal
Fetal macrosomia	Stillbirth
Oligohydramnios	Postmaturity syndrome
Preeclampsia	NICU admission
Cesarean delivery	Meconium aspiration syndrome
Labor dystocia	Neonatal convulsions
Fetal jeopardy	Hypoxic-ischemic encephalopathy
Shoulder dystocia	Birth injuries
Postpartum hemorrhage	Infection
Forceps delivery	Childhood obesity
Perineal lacerations	

NICU = neonatal intensive care unit.
From Amark, 2021; Kortekaas, 2020; Lindquist, 2021; MacDorman, 2009; Maoz, 2019; Middleton, 2018; Olesen, 2003.

Smith (2001) has challenged analyses such as these because the population at risk for perinatal mortality in a given week consists of all ongoing pregnancies rather than just the births in a given week. He calculated perinatal mortality rates using only births in a given week of gestation from 37 to 43 completed weeks compared with the cumulative probability—the *perinatal index*—of death when all ongoing pregnancies are included in the denominator. Using this computation, delivery at 38 weeks' gestation had the lowest risk for perinatal death. In current practice, perinatal death is balanced against morbidity associated with immaturity. This shapes the rationale for delaying delivery until 39 weeks' gestation unless a comorbidity warrants earlier intervention (American College of Obstetricians and Gynecologists, 2019d).

PATHOPHYSIOLOGY

Postmaturity Syndrome

The postmature newborn is unique, and features include wrinkled, patchy, peeling skin; a long, thin body that suggests wasting; and advanced maturity in that the neonate is open-eyed, unusually alert, and appears old and worried (Fig. 46-2). Skin wrinkling can be prominent on the palms and soles, and nails are typically long. Most postmature neonates are not technically growth restricted because their birthweight seldom falls below the 10th percentile for gestational age (Chap. 47, p. 825). However, severe growth restriction—which logically must have preceded completion of 42 weeks—may be present.

The incidence of postmaturity syndrome in newborns at 41, 42, or 43 weeks, respectively, has not been conclusively determined, but the syndrome complicates 10 to 20 percent of pregnancies at 42 completed weeks (American College of Obstetricians and Gynecologists, 2020b). Associated oligohydramnios substantially raises the likelihood of postmaturity. Trimmer and associates (1990) reported that 88 percent of fetuses were postmature if there was oligohydramnios, defined by a sonographic maximal vertical amnionic fluid pocket that measured ≤1 cm at 42 weeks.

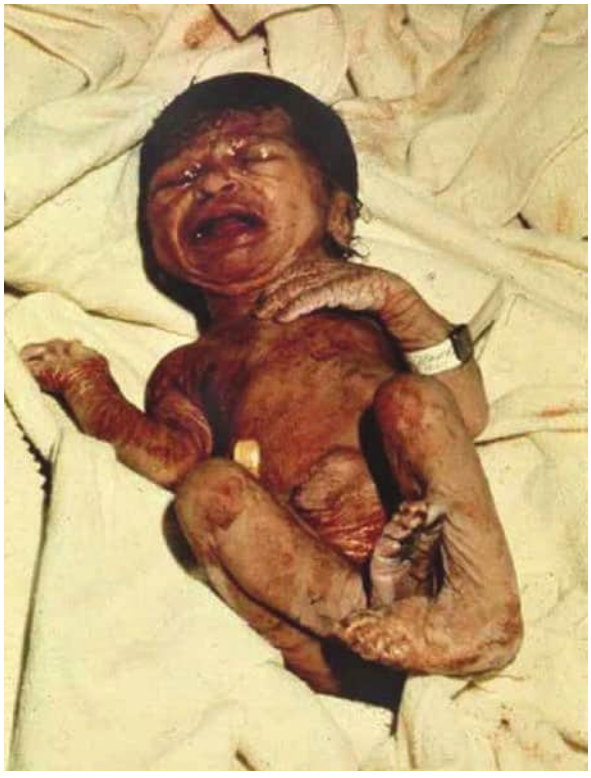

FIGURE 46-2 Postmaturity syndrome. Neonate delivered at 43 weeks' gestation with thick, viscous meconium coating the desquamating skin. Note the long, thin appearance and wrinkling of the hands.

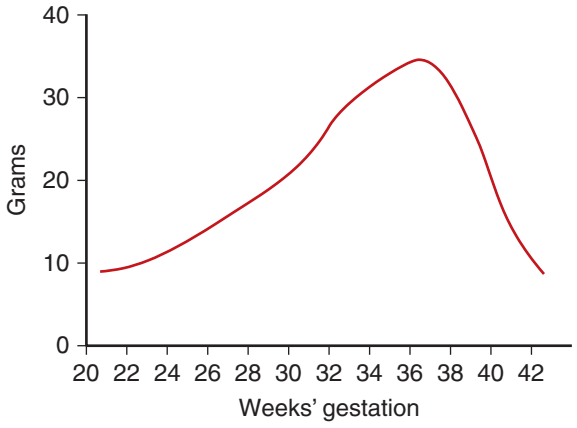

FIGURE 46-3 Mean daily fetal growth during previous week of gestation. (Redrawn from Hendricks CH: Patterns of fetal and placental growth: the second half of pregnancy. Obstet Gynecol 24:357, 1964.)

Placental Dysfunction

Many believe that postterm pregnancy is an abnormal state. Redman and Staff (2015) suggest that limited placental capacity, characterized by dysfunctional syncytiotrophoblast, explains the greater risks of the postmaturity syndrome. A murine model of stillborn fetuses supports this theory (Rahman, 2017).

Clifford (1954) proposed that the associated skin changes follow loss of the protective effects of vernix caseosa. He also attributed the postmaturity syndrome to placental senescence, although he did not find placental degeneration histologically. Still, the concept that postmaturity stems from placental insufficiency has persisted despite an absence of morphological or significant quantitative findings (Larsen, 1995; Redman, 2015; Rushton, 1991). However, the rate of placental apoptosis—programmed cell death—is significantly greater at 41 to 42 completed weeks compared with that at 36 to 39 weeks (Smith, 1999). Several proapoptotic genes such as *kisspeptin* are upregulated in postterm placental explants compared with the same genes in term ones (Torricelli, 2012). The clinical significance of such apoptosis is unclear.

Jazayeri and coworkers (1998) investigated cord blood erythropoietin levels in 124 appropriately grown newborns delivered from 37 to 43 weeks. The only known stimulator of erythropoietin is decreased partial oxygen pressure. Thus, they sought to assess whether fetal oxygenation was compromised due to placental aging in postterm pregnancies. All women had an uncomplicated labor and delivery. Cord blood erythropoietin levels were significantly elevated in pregnancies reaching 41 weeks or more. Although Apgar scores and acid-base studies were normal, these researchers concluded that fetal oxygenation was decreased in some postterm gestations.

However, the postterm fetus typically continues to gain weight and thus be unusually large at birth. This suggests that placental function is not severely compromised. Indeed, continued fetal growth is the norm—albeit at a slower rate beginning at 37 completed weeks (Fig. 46-3). Nahum and associates (1995) confirmed that fetal growth continues until at least 42 weeks. However, umbilical blood flow does not increase concomitantly (Link, 2007).

Fetal Distress and Oligohydramnios

The principal reasons for increased risks to postterm fetuses were described by Leveno and colleagues (1984). Both antepartum fetal jeopardy and intrapartum nonreassuring fetal status were found to be the consequence of cord compression associated with oligohydramnios. In their analysis of 727 postterm pregnancies, intrapartum nonreassuring fetal status detected with electronic monitoring was not associated with late decelerations characteristic of uteroplacental insufficiency. Instead, one or more prolonged decelerations such as shown in Figure 46-4 preceded three fourths of emergency cesarean deliveries for nonreassuring fetal heart rate tracings. In all but two cases, there were also variable decelerations. Another common fetal heart rate pattern, although not ominous by itself, was the saltatory baseline. As described in Chapter 24 (p. 453), these findings are consistent with cord occlusion as the proximate cause of the nonreassuring tracings. Other correlates included oligohydramnios and viscous meconium. Schaffer and coworkers (2005) implicated a nuchal cord in abnormal intrapartum fetal heart rate patterns, meconium, and compromised newborn condition in prolonged pregnancies.

Normally, the volume of amnionic fluid continues to decline after 38 weeks, and logically oligohydramnios may become problematic. Moreover, meconium release into an already reduced amnionic fluid volume results in thick, viscous fluid that may cause *meconium aspiration syndrome* (Chap. 33, p. 600). The risk for this increases to 5 percent at 42 weeks (Ward, 2020).

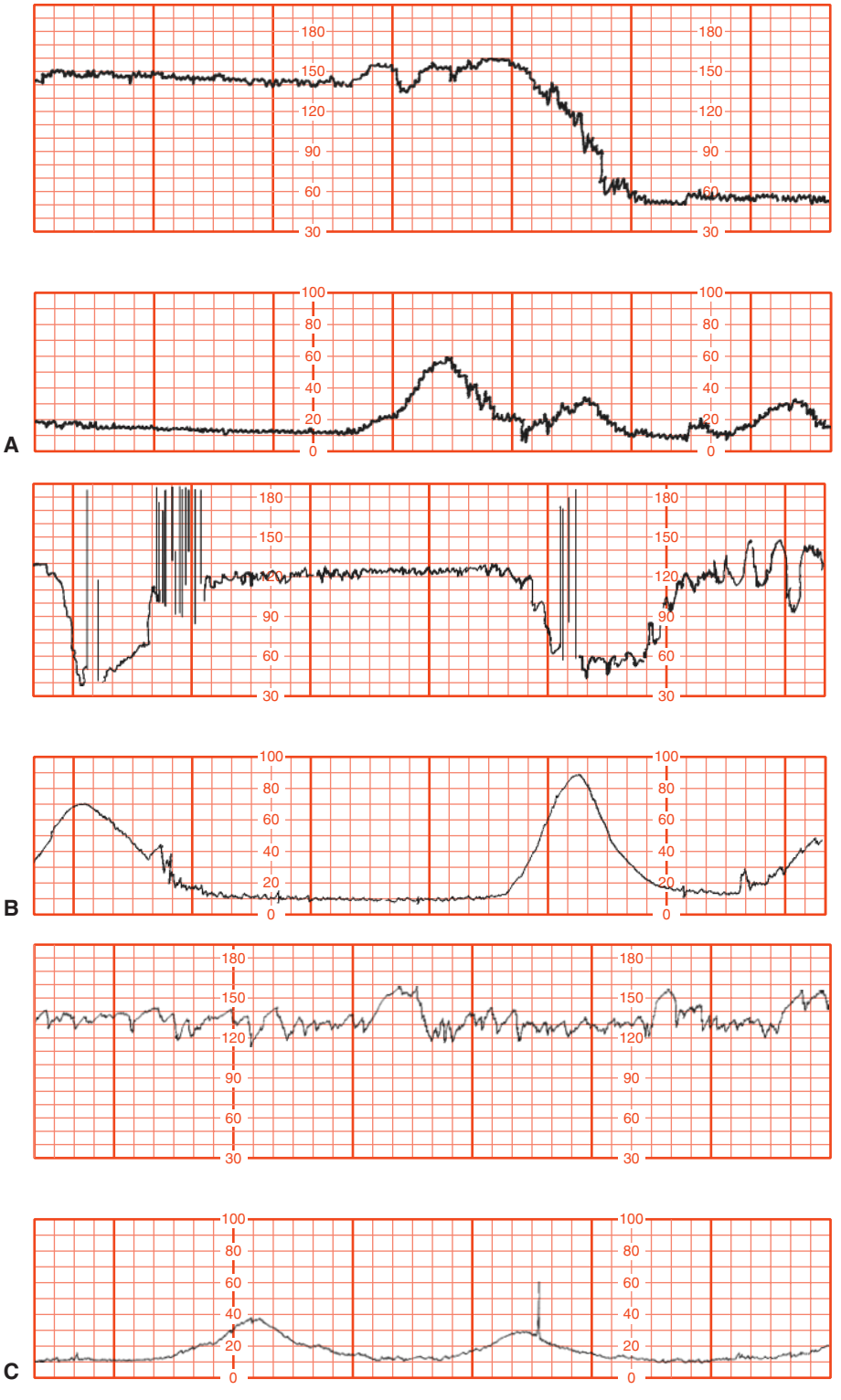

FIGURE 46-4 A. Prolonged fetal heart rate deceleration before emergency cesarean delivery in a postterm pregnancy with oligohydramnios. **B.** Variable decelerations in a postterm pregnancy with oligohydramnios. **C.** Saltatory baseline fetal heart rate showing oscillations exceeding 20 bpm and associated with oligohydramnios in a postterm pregnancy. (Reproduced with permission from Leveno KJ, Quirk JG, Cunningham FG, et al: Prolonged pregnancy, I. Observations concerning the causes of fetal distress, Am J Obstet Gynecol. 1984 Nov 1;150(5 Pt 1):465–473.)

Fetal-growth Restriction

In the late 1990s, the clinical significance of fetal-growth restriction in the otherwise uncomplicated pregnancy became more fully appreciated. Data from the National Swedish Medical Birth Registry showed that stillbirths were more common among growth-restricted newborns who were delivered after 42 weeks (Clausson, 1999; Divon, 1998). Indeed, a third of postterm stillborn neonates were growth restricted. During this time in Sweden, labor induction and antenatal fetal testing usually commenced at 42 weeks. In a study from Parkland Hospital, Alexander and colleagues (2000d) analyzed outcomes for 355 neonates from gestations ≥42 weeks and with birthweights <3rd percentile. These outcomes were compared with those of 14,520 similarly aged newborns above the 3rd percentile. Morbidity and mortality rates were significantly higher in the growth-restricted neonates. Moreover, a fourth of all stillbirths associated with prolonged pregnancy were in this comparatively small number of growth-restricted fetuses.

COMPLICATIONS

Oligohydramnios

Recognized postterm complications include oligohydramnios and fetal macrosomia. In 38 postterm pregnancies, Trimmer and colleagues (1990) sonographically measured hourly fetal urine production using sequential bladder volume measurements. Diminished urine production was found to be associated with oligohydramnios. Using Doppler waveforms, Oz and associates (2002) concluded that fetal renal blood flow is reduced in postterm pregnancies complicated by oligohydramnios. The lack of increasing umbilical blood flow postterm may be a possible cause (Link, 2007).

Diminished amnionic fluid volume at any gestational age signifies increased fetal risk. Unfortunately, an exact method to define this decreased volume is lacking. Currently, sonographic measurement of the deepest vertical pocket or calculation of the amnionic

fluid index (AFI) are options (Chap. 14, p. 257). One study of postterm pregnancies attempted to determine which amnionic fluid volume criteria best predicted normal and abnormal outcomes (Fischer, 1993). The smaller the amnionic fluid pocket, the greater the likelihood of clinically significant oligohydramnios. However, normal amnionic fluid volume did not preclude abnormal outcomes. One randomized trial assigned 500 women with postterm pregnancies to assessment using either AFI or the deepest vertical pocket (Alfirevic, 1997). The authors concluded that the AFI overestimated the number of abnormal outcomes in postterm pregnancies.

Regardless of the criteria used to diagnose oligohydramnios in postterm pregnancies, most investigators have found a higher incidence of some measure of "fetal compromise" during labor. Thus, oligohydramnios by most definitions is a clinically meaningful finding. Conversely, reassurance of continued fetal well-being in the presence of "normal" amnionic fluid volume is tenuous. This may be related to how quickly pathological oligohydramnios can develop.

Macrosomia

The velocity of fetal weight gain peaks at approximately 37 weeks (see Fig. 46-3). Although growth velocity slows at that time, most fetuses continue to gain weight. According to Duryea and associates (2014), the 95th percentile at 42 weeks is 4475 g. Even so, in one study, brachial plexus injury was not related to postterm gestation (Walsh, 2011).

Intuitively, it seems that both maternal and fetal morbidity associated with macrosomia would be mitigated with timely induction to preempt further growth. This, however, does not appear to be the case. The American College of Obstetricians and Gynecologists (2020a) concludes that current evidence does not support such a practice in women at term with suspected fetal macrosomia. Moreover, the College notes that in the absence of diabetes, vaginal delivery is not contraindicated for women with an estimated fetal weight up to 5000 g (Chap. 27, p. 501). Obvious problems with all such recommendations are substantive variations in fetal weight estimation.

ANTEPARTUM MANAGEMENT

After completing 42 weeks, labor induction is recommended to help avoid the just-described morbidity and mortality. For late-term gestations, some intervention is indicated, but the method and timing are not unanimous. The decision focuses on whether labor induction is warranted or if expectant management with fetal surveillance is best. In a survey done more than 15 years ago, 73 percent of members of the American College of Obstetricians and Gynecologists reported routinely induced women at 41 weeks (Cleary-Goldman, 2006). Most of the remainder performed twice-weekly fetal antepartum testing until 42 completed weeks.

Induction Factors

A cervix that is soft, dilated, and effaced improves labor induction success. However, investigators have used differing criteria in studies of prolonged pregnancy. Harris and coworkers (1983) defined an unfavorable cervix by a Bishop score <7 and reported this in 92 percent of women at 42 weeks (Chap. 26, p. 488). Others found that 40 percent of women with a 41-week gestation had an "undilated cervix" (Hannah, 1992). In a study of 800 women undergoing induction for postterm pregnancy at Parkland Hospital, women without cervical dilation had a twofold higher cesarean delivery rate for "dystocia" (Alexander, 2000b). Instead, a cervical length ≤3 cm measured with transvaginal sonography predicted successful induction (Yang, 2004). In a similar study, cervical length ≤25 mm positively predicted spontaneous labor or successful induction (Vankayalapati, 2008).

Several investigators have evaluated prostaglandin E_2 (PGE_2) and E_1 (PGE_1) for induction in women with an unfavorable cervix and postterm pregnancy. A study by the Maternal–Fetal Medicine Units Network (1994) found that PGE_2 gel was not more effective than placebo. Alexander and associates (2000c) treated 393 women with a postterm pregnancy with PGE_2, regardless of cervical "favorability," and reported that almost half of the 84 women with cervical dilation of 2 to 4 cm entered labor with PGE_2 use alone. Prostaglandins and other agents used for cervical ripening are discussed in Chapter 26 (p. 488).

Sweeping or stripping of the membranes to induce labor and thereby prevent postterm pregnancy has been evaluated. A metaanalysis of 44 studies found that membrane stripping slightly increased spontaneous labor and lowered induction rates (Finucane, 2020). However, this practice did not lower the cesarean delivery rate. Other trials have found that sweeping membranes did not reduce the need to induce labor (Hill, 2008; Kashanian 2006; Wong, 2002). Drawbacks of membrane stripping included pain, vaginal bleeding, and irregular contractions without labor.

The station of the fetal head within the pelvis is another predictor of successful postterm pregnancy induction. Shin and colleagues (2004) studied 484 nulliparas who underwent induction after 41 weeks' gestation. The cesarean delivery rate was directly related to station. The rate was 6 percent if the vertex before induction was at –1 station; 20 percent at –2 station; 43 percent at –3 station; and 77 percent at –4 station.

Induction versus Fetal Testing

The less than optimal benefits from induction with an unfavorable cervix lead some clinicians to prefer fetal antepartum testing beginning at 41 completed weeks. In a Canadian study, 3407 women were randomly assigned at ≥41 weeks to induction or to fetal testing (Hannah, 1992). Labor induction resulted in a small but significant reduction in the cesarean delivery rate compared with fetal testing—21 versus 24 percent, respectively. There were only two stillbirths in the fetal testing group.

The Maternal–Fetal Medicine Network then performed a randomized trial of induction versus fetal testing beginning at 41 weeks' gestation (Gardner, 1996). Fetal surveillance included nonstress testing and sonographic estimation of amnionic fluid volume performed twice weekly in 175 women. Perinatal outcomes were compared with those of 265 women also at 41 weeks but randomly assigned to induction with or without

TABLE 46-2. Selected Maternal and Perinatal Outcomes from SWEPIS Trial

Outcome	Induction (n = 1381)	Expectant (n = 1379)	*p* value
Maternal			
Gestational age (days)	289 ± 1.3	292 ± 2.7	—
Labor (hours)	7.1 ± 5.4	8.3 ± 5.9	<0.001
Cesarean delivery	10.4%	10.7%	0.79
Operative vaginal delivery	6.4%	6.6%	0.87
Perinatal			
Primary composite	2.4%	2.2%	0.9
Perinatal mortality	0	6/1000	0.03
Meconium aspiration	0.1%	0.2%	1.00
Macrosomia (>4500 g)	4.9%	8.3%	<0.001
NICU stay (days)	3.4 ± 3	4.6 ± 5.6	NS

g = grams; NICU = neonatal intensive care unit; NS = not significant; SWEPIS = SWEdish Post-term Induction Study.

cervical ripening. There were no perinatal deaths, and the cesarean delivery rate did not differ between groups. The results of this study support the validity of either management scheme.

In another study of women reaching 41 completed weeks' gestation, those who entered spontaneous labor prior to $42^{0/7}$ weeks had a lower cesarean delivery rate than those who did not spontaneously labor but who underwent induction after $42^{0/7}$ weeks (Alexander, 2001). Cesarean delivery rates were significantly increased—19 versus 14 percent—in the induced group because of failure to progress.

A study from Denmark is also instructive (Zizzo, 2017). In 2011, the Danish national guidelines were changed from labor induction at $42^{0/7}$ weeks with no fetal surveillance to labor induction at $41^{2/7}$ to $41^{6/7}$ weeks with fetal surveillance beginning at $41^{0/7}$ weeks. They compared two 3-year epochs—one before and one after 2011. The rate of pregnancies that progressed past $42^{0/7}$ weeks decreased from 2.85 to 0.62 percent. Concurrently, as expected, the induction rate rose significantly, and this was accompanied by a drop in the perinatal mortality rate—22 to 13 per 1000 births. The cesarean delivery rate was not changed. A similar before-and-after observational study reported that induction at ≥42 weeks' gestation was associated with a significantly lower cesarean delivery rate—15 versus 19.4 percent (Bleicher, 2017).

To further address the question, the SWEdish Post-term Induction Study—SWEPIS—was a randomized trial that included 2760 low-risk pregnancies at 41 weeks' gestation. The trial compared outcomes with induction of labor at 41 weeks against expectant management and induction at 42 weeks. As shown in Table 46-2, maternal and perinatal outcomes were not different with the exception of perinatal mortality and macrosomia (Wennerholm, 2019). The study was stopped early because of a significantly higher perinatal mortality rate in the expectantly management group. The investigators concluded that these results should be interpreted with caution because the primary composite outcomes were not significantly different.

Management Strategies

At this time, evidence is insufficient to mandate a management strategy between 40 and 42 completed weeks. Thus, induction of labor or initiation of fetal surveillance at 41 weeks' gestation is a reasonable option. The American College of Obstetricians and Gynecologists and the Society for Maternal-Fetal Medicine (2021) suggest that fetal surveillance should be done once or twice weekly beginning at 41 0/7 weeks. After completing 42 weeks, labor induction is recommended. A management algorithm by the American College of Obstetricians and Gynecologists (2020b) is summarized in Figure 46-5. In light of the recent studies that show an increased stillbirth rate associated with expectant management at 41 weeks, it is likely that routine induction will eventually become preferable in most circumstances.

When gestational age is uncertain, the American College of Obstetricians and Gynecologists (2019b) recommends delivery at 41 weeks' gestation using the best clinical estimate of gestational age. The College also recommends against amniocentesis for fetal lung maturity.

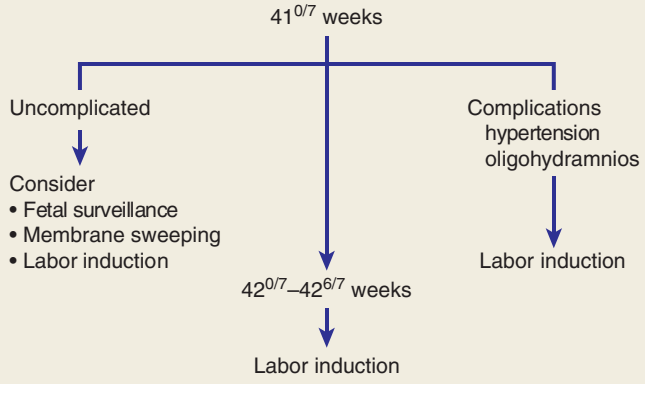

FIGURE 46-5 Algorithm for management of postterm pregnancy.

INTRAPARTUM MANAGEMENT

Labor is a particularly dangerous time for the postterm fetus. Thus, women whose pregnancies are known or suspected to be postterm ideally come to the hospital as soon as they suspect labor. While being evaluated for active labor, fetal heart rate and uterine contractions are monitored electronically for variations consistent with fetal compromise (Chap. 24, p. 457).

During labor, the decision to perform amniotomy is problematic. Further reduction in fluid volume following amniotomy can enhance the possibility of cord compression. Conversely, after membrane rupture, a scalp electrode and an intrauterine pressure catheter can be placed. These usually provide more precise data concerning fetal heart rate and uterine contractions. Amniotomy also aids identification of thick meconium.

Thick meconium in the amnionic fluid is particularly worrisome. The viscosity probably signifies the lack of liquid and thus oligohydramnios. Aspiration of thick meconium may cause severe pulmonary dysfunction and neonatal death (Chap. 33, p. 600). According to the American College of Obstetricians and Gynecologists (2019a), amnioinfusion does not prevent meconium aspiration syndrome. However, it remains a reasonable treatment approach for repetitive variable decelerations (Chap, 24, p. 459). Suctioning the pharynx once the head is delivered is not recommended (American College of Obstetricians and Gynecologists, 2019a; Wyckoff, 2020). If the depressed newborn has meconium-stained fluid, intubation is performed.

The likelihood of a successful vaginal delivery is reduced appreciably for the nullipara who is in early labor with thick, meconium-stained amnionic fluid. Thus, if a woman is remote from delivery, strong consideration should be given to prompt cesarean delivery, especially when cephalopelvic disproportion is suspected or either hypotonic or hypertonic dysfunctional labor is evident. Some practitioners choose to avoid oxytocin use in these cases.

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CHAPTER 47

Fetal-Growth Disorders

Disorders of fetal growth occur at both ends of the spectrum, either fetal-growth restriction or macrosomia. Each poses concern because of associated morbidities and potential mortality. However, in both categories most of these newborns are ultimately deemed normal and healthy but merely constitutionally small or large. The clinical challenge thus lies in the evaluation and management of suspected fetal-growth disorders.

NORMAL FETAL GROWTH

Fetal growth may be divided into three phases. The initial phase of hyperplasia occurs in the first 16 weeks and is characterized by a rapid rise in cell number. The second phase, which extends up to 32 weeks' gestation, includes both cellular hyperplasia and hypertrophy. After 32 weeks, fetal mass accrues by cellular hypertrophy, and it is during this phase that most fetal fat and glycogen accumulate. The corresponding fetal-growth rates during these three phases approximate 5 g/d at 15 weeks' gestation, 15 g/d at 24 weeks', and 30 g/d at 34 weeks' (Grantz, 2018; Williams, 1982).

In the National Institute of Child Health and Human Development Fetal Growth Studies, serial sonographic evaluations were performed in 1733 nonobese, low-risk pregnancies at 12 sites across the United States (Grantz, 2018). As shown in Figure 47-1, growth velocity peaked at 35 weeks' gestation (Grantz, 2018).

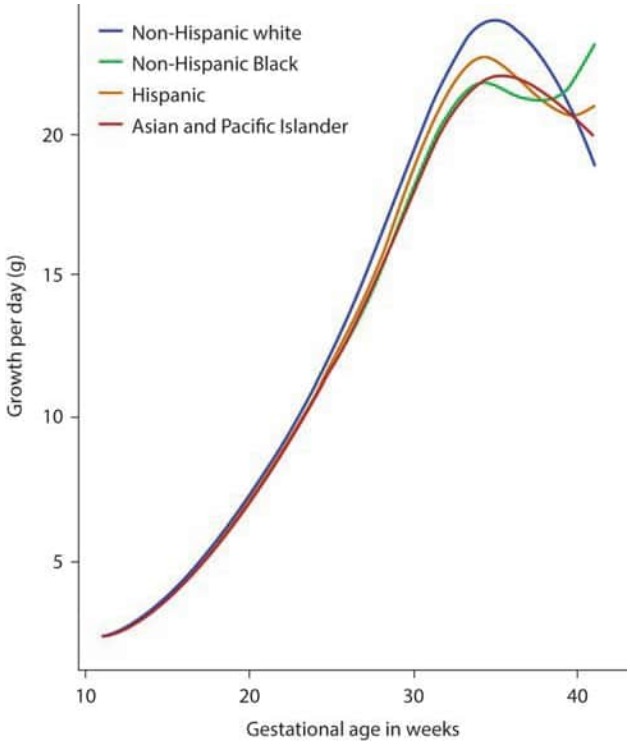

FIGURE 47-1 Fetal weight gain in grams per day by race/ethnicity throughout gestation.

The investigators demonstrated that fetal growth varies considerably and that it is *not* highly correlated with fetal birthweight percentile. Some fetuses with initial estimated weights below the 5th percentile maintained their growth velocity and ultimately weighed more at birth than other fetuses whose weight percentiles were initially higher but whose growth was slower. Such findings support our understanding that large and small fetal weight percentiles reflect constitutional size in some but indicate disordered growth in others. They further highlight the importance of serial sonography when abnormal growth is a concern.

Normal Birthweight

Accurate gestational age assessment is critical for determining whether birthweight is normal. Current normative data are based on birthweights from pregnancies in which gestational age is established using an *obstetrical estimate* that includes sonography and discussed in Chapter 14 (p. 248) (American College of Obstetricians and Gynecologists, 2019b). The birthweight percentiles shown in Table 47-1 were derived using data from more than 3 million liveborn singletons delivered across the United States in 2011 (Duryea, 2014). As shown in Figure 47-2, use of a birthweight percentile curve in which gestational age is based on a last menstrual period alone yields significantly larger weights for a given gestational age, particularly in the preterm period. The accuracy of a birthweight reference thus has potential to affect the prevalence of neonates diagnosed as small or large for gestational age.

The curve by Duryea and associates (2014) is most accurately termed a *population reference*, rather than a *standard*. A population reference incorporates pregnancies of varying risks, along with the resulting outcomes, both normal and abnormal. In contrast, a standard incorporates normal pregnancies with normal outcomes. Because population references include preterm births, which are more likely to be growth restricted, it has been argued that the associated birthweight data overestimate impaired fetal growth (Mayer, 2013; Zhang, 2010).

TABLE 47-1. 2011 Gestational Age Birthweight (g) Percentiles for 3,252,011 Singleton Live Births in the United States

	Percentile				
Age (wk)	5th	10th	50th	90th	95th
24	539	567	680	850	988
25	540	584	765	938	997
26	580	637	872	1080	1180
27	650	719	997	1260	1467
28	740	822	1138	1462	1787
29	841	939	1290	1672	2070
30	952	1068	1455	1883	2294
31	1080	1214	1635	2101	2483
32	1232	1380	1833	2331	2664
33	1414	1573	2053	2579	2861
34	1632	1793	2296	2846	3093
35	1871	2030	2549	3119	3345
36	2117	2270	2797	3380	3594
37	2353	2500	3025	3612	3818
38	2564	2706	3219	3799	3995
39	2737	2877	3374	3941	4125
40	2863	3005	3499	4057	4232
41	2934	3082	3600	4167	4340
42	2941	3099	3686	4290	4474

From Duryea, 2014, with permission.

FIGURE 47-2 Fetal-growth curves for births in the United States in 2011. Curves vary depending on whether gestational age was calculated from the last menstrual period or from an improved obstetrical estimate, derived in part using sonography. (Modified with permission from Duryea EL, Hawkins JS, McIntire DD, et al: A revised birth weight reference for the United States. Obstet Gynecol. 2014 Jul;124(1):16–22.)

Physiology of Fetal Growth

Fetal development is believed to be determined by maternal provision of substrate and its placental transfer, whereas fetal growth potential is governed by the genome. The precise cellular and molecular mechanisms leading to normal fetal growth are incompletely understood. Considerable evidence supports the role of insulin and insulin-like growth factors in fetal growth and weight gain regulation (Luo, 2012). These growth factors are produced by virtually all organs and are potent stimulators of cell division and differentiation. Other hormones implicated in fetal growth include leptin and other adipokines, which are derived from adipose tissue. Fetal leptin concentrations rise during gestation, and they correlate both with birthweight and with neonatal fat mass (Briffa, 2015; Ökdemir, 2018; Simpson, 2017).

Both excessive and diminished maternal glucose availability also have the potential to affect fetal growth (Chap. 7, p. 135). That said, growth-restricted neonates do not typically show pathologically low glucose concentrations in cord blood (Pardi, 2006). Fetal-growth restriction in response to glucose deprivation generally results only after long-term severe maternal caloric deprivation (Lechtig, 1975). Conversely, hyperglycemia more consistently results in excessive growth. The Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) Study Cooperative Research Group (2008) found that elevated cord C-peptide levels, which reflect fetal hyperinsulinemia, are associated with greater birthweight. This relationship was noted even in women with maternal glucose levels below the threshold for diabetes.

Excessive transfer of lipids has similarly been implicated in fetal overgrowth (Delhaes, 2018). Free or nonesterified fatty acids in maternal plasma may be transferred to the fetus via facilitated diffusion or after liberation of fatty acids from triglycerides by trophoblastic lipases (Gil-Sánchez, 2012). Independent of prepregnancy body mass index (BMI), higher maternal free fatty acid levels during the latter half of pregnancy correlate with birthweight (Crume, 2015). Greater intake of certain fatty acids, particularly omega-3, is associated with greater birthweight (Calabuig-Navarro, 2016).

Placental fatty acid metabolism and transfer may be dysregulated in fetal-growth restriction and in maternal conditions associated with fetal overgrowth. For example, levels of endothelial lipase are reduced with deficient fetal growth, and this enzyme is overexpressed in placentas of women with diabetes (Gauster, 2007, 2011). Others have reported that diabetes and obesity are associated with altered placental lipid-transport gene expression (Segura, 2017). Obesity is also linked with greater expression of fatty acid binding/transport proteins within the trophoblast (Myatt, 2016). These alterations lead to an abnormal accumulation of lipids that can result in pathological placental inflammation and dysfunction (Calabuig-Navarro, 2016; Myatt, 2016; Yang, 2016).

FETAL-GROWTH RESTRICTION

Fundamental to understanding fetal-growth restriction (FGR) is an appreciation of the strengths and limitations of its defining criteria. A diagnosis based on *estimated fetal weight* alone does not indicate disease but rather a fetus that is in an at-risk category. Benefits of definitions such as the one used by the American College of Obstetricians and Gynecologists are ease of application and promotion of consistency across care settings. However, if applied to an otherwise low-risk population, a 10th-percentile threshold will label nearly 10 percent of fetuses as growth restricted, although most are merely *constitutionally small* rather than compromised. Moreover, a threshold will fail to identify at-risk fetuses with a weight above that threshold but who have not reached their growth potential. Thus, the definition is intended to strike a balance between false-positive and false-negative diagnoses.

Definition

Various criteria and thresholds have been used to define FGR. These have included estimated fetal weights (EFW) below the 3rd, 5th, or 10th percentiles; similar abdominal circumference (AC) percentiles; a specified decline in the EFW percentile or AC percentile over serial assessments; and various abnormal Doppler findings (Lees, 2020). All definitions are based solely on prenatal sonography and rely on accurate gestational age assessment.

Currently, the American College of Obstetricians and Gynecologists (2021a) and the Society for Maternal-Fetal Medicine (2020) recommend defining FGR as either an EFW <10th percentile for gestational age or an AC <10th percentile for gestational age. Use of the AC threshold may correctly identify one additional small-for-gestational age (SGA) newborn for every 14 sonograms performed in the last month of pregnancy (Blue, 2018). Importantly, management recommendations are further stratified based on lower percentile thresholds and findings such as oligohydramnios or abnormal umbilical artery Doppler velocimetry, as discussed subsequently (p. 829).

To more precisely identify growth-restricted fetuses, investigators have derived customized growth charts that incorporate variables such as maternal height and weight, race or ethnicity, parity, and fetal sex. However, customized growth curves do not improve outcomes and thus are not recommended (American College of Obstetricians and Gynecologists, 2021a; Chiossi, 2017; Costantine, 2013; Grobman, 2013; Zhang, 2011).

FGR should be differentiated from SGA, which is a postnatal designation based on birthweight percentile. When considering FGR *detection*, investigators study the proportion of SGA neonates identified as FGR during prenatal sonography. However, FGR often does not equate to SGA because of the inherent error of sonographic measurement. One population-based study of routine third-trimester sonography found that 50 percent of those with suspected FGR had birthweights above the 10th percentile (Monier, 2015). Those with false-positive diagnoses of FGR were delivered 2 weeks earlier in gestation, which raises concerns about potential iatrogenic sequelae of routine screening.

Importantly, as many as 70 percent of SGA newborns are not pathologically growth restricted. Indeed, such children have normal outcomes and are thought to be appropriately grown when maternal ethnic group, parity, weight, and height are considered (Unterscheider, 2015). In a Swedish study of 130,000 term births, the maternal and paternal birthweights were estimated to account for 6 and 3 percent of variance in birthweight, respectively (Mattsson, 2013). Additionally, as shown in Figure 47-3, most adverse outcomes occur in newborns smaller

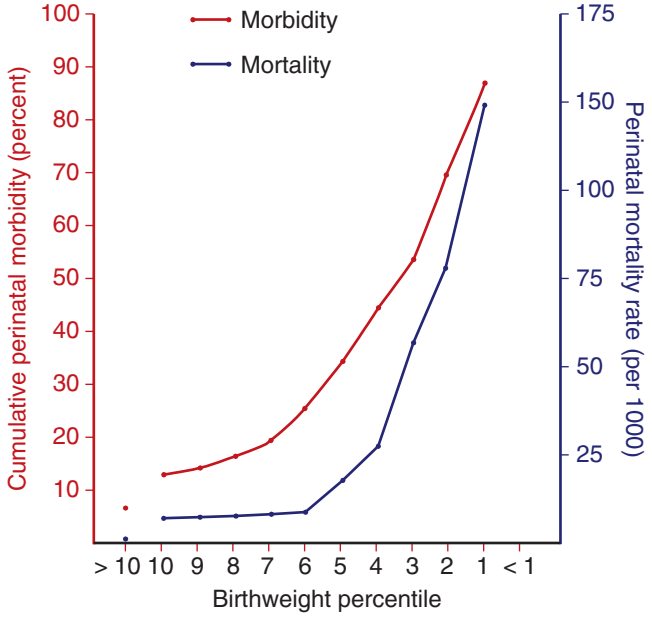

FIGURE 47-3 Relationship between birthweight percentile and perinatal mortality and morbidity rates in 1560 small-for-gestational-age fetuses. A progressive increase in both mortality and morbidity rates is observed as birthweight percentile decreases.

than the 3rd percentile (Manning, 1995). In a review of more than 80,000 singleton term births from Parkland Hospital, McIntire and colleagues (1999) found that neonatal mortality and most neonatal morbidity rates rose only at birthweights at or below the 3rd percentile.

Small-but-normal neonates do not show evidence of the postnatal metabolic derangements commonly associated with deficient fetal growth. Moreover, these intrinsically small newborns remain significantly smaller during surveillance to 2 years compared with appropriate-for-gestational-age sized neonates. However, they do not show differences in measures of metabolic risk that included glucose and insulin levels (Milovanovic, 2012). As discussed later, true SGA newborns carry short- and long-term metabolic risks.

Detection

Identification of truly impaired fetal growth remains a challenge. Ideally, it involves detecting fetuses who meet the aforementioned definition and also discerning those at risk for compromise. There are three main tenets:

1. The diagnosis relies on accurate gestational age assessment, optimally confirmed with sonography in the first or early second trimester (Table 14-1, p. 248). If gestational age is uncertain and the diagnosis is suspected, serial sonography is considered.
2. In low-risk pregnancies, the diagnosis is suspected based on clinical abdominal examination after 24 weeks' gestation in which the fundal height lags by ≥3 cm. Sonography is then performed.
3. If the pregnancy is at risk for FGR, based on factors reviewed in the next section, sonography is considered to assist with detection. This is performed at approximately 32 weeks' gestation. Care is individualized, and in some cases sonography may be needed every 4 weeks to assess fetal growth. One example of the latter is twin gestations, because fundal height cannot evaluate individual twin growth (Chap. 48, p. 851).

Uterine Fundal Height

At each prenatal visit after 20 weeks' gestation, fundal height is assessed to *screen* for fetal-growth impairment (Chap. 10, p. 182). The measurement in centimeters approximates the gestational age in weeks. The uterine size-date discrepancy may be unrelated to fetal size. However, if the measurement differs by ≥3 cm in the absence of an obvious explanation, sonography is generally performed.

Serial fundal height measurement is the only routine screening for FGR that is endorsed by the American College of Obstetricians and Gynecologists and Society for Maternal-Fetal Medicine (2021a). International consensus also indicates that carefully performed serial fundal height measurements are a simple, safe, inexpensive, and reasonably accurate method to screen for FGR (McCowan, 2018).

Limitations of fundal height screening are well documented. The overall sensitivity of fundal height to detect FGR ranges from 11 to 25 percent (Goetzinger, 2012; Grantz, 2021; Roex, 2012; Sparks, 2011). Detection rates are lower in obese women than in those with normal BMI (Goetzinger, 2012).

Sonographic Assessment

Studies of routine screening for FGR using third-trimester sonography have yielded variable results, and detection of SGA neonates ranges from <20 percent to >60 percent (Hammad, 2016; Monier, 2015; Sovio, 2015; Wanyonyi, 2021). One reason for poor detection is that sonography performed at any point in gestation will fail to detect pregnancies in which FGR develops *later*. Also, it will miss those needing delivery for FGR *before* the sonographic examination was performed. Compounding this is that EFW is an imperfect metric. Given that most SGA neonates are constitutionally small, it is not unexpected that the recurrence risk for FGR approximates 20 percent. Many of these cases are merely smaller mothers having smaller healthy children in successive pregnancies.

Routine third-trimester sonography to assess fetal growth is not recommended because it has not been demonstrated to improve outcomes (American College of Obstetricians and Gynecologists, 2021a). Indeed, a Cochrane database analysis of 13 trials with 34,980 women found that routine late-pregnancy ultrasound for a low-risk or an unselected population was not associated with maternal or fetal benefit (Bricker, 2015).

Pathophysiology

Fetal-growth restriction is one of the "major obstetrical syndromes" associated with defects in early placentation (Brosens, 2015). Mechanisms leading to abnormal trophoblastic invasion are likely multifactorial, and both vascular and immunological etiologies have been proposed. For example, *atrial natriuretic peptide converting enzyme*, also known as *corin*, plays a critical role in trophoblastic invasion and remodeling of the uterine spiral arteries (Cui, 2012). These processes are impaired in corin-deficient mice, which also develop evidence of preeclampsia. Moreover, mutations in the gene for corin are reported in women with preeclampsia (Chen, 2015).

Several immunological abnormalities are associated with FGR. This raises the prospect of maternal rejection of the "paternal semiallograft." Rudzinski and colleagues (2013) studied C4d, a component of complement that is associated with humoral rejection of transplanted tissues. They found this to be highly associated with chronic villitis—88 percent of cases versus only 5 percent of controls—and with reduced placental weight. In a study of 10,204 placentas, chronic villitis was associated with placental hypoperfusion, fetal acidemia, and FGR and its sequelae (Greer, 2012). Kim and coworkers (2015) extensively reviewed chronic inflammatory placental lesions and their association with fetal-growth restriction, preeclampsia, and preterm birth.

Risk Factors

Risk factors for impaired fetal growth may be divided into three overlapping categories or "compartments": those in the mother, the fetus, or the placenta. Some of these are depicted in Figure 47-4. Many causes of FGR are prospectively considered risk factors, because impaired fetal growth is not consistent in all affected women.

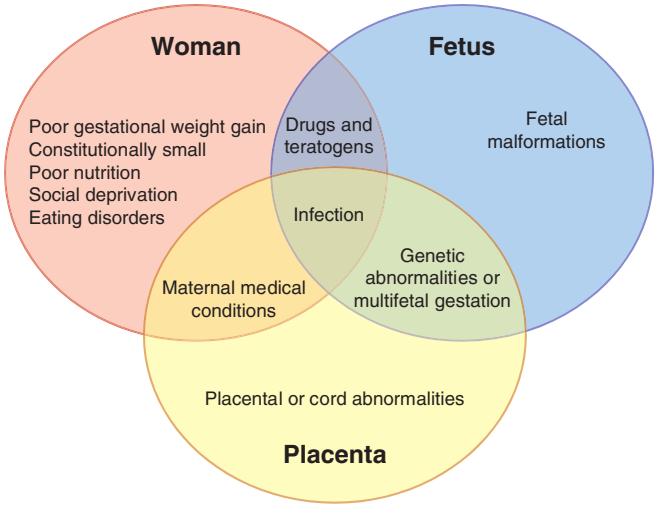

FIGURE 47-4 Risk factors and causes of impaired fetal growth centering on the mother, fetus, and placenta.

Gestational Weight Gain and Nutrition

Maternal weight gain during pregnancy is positively correlated with fetal size (Hutcheon, 2019). Among women with gestational diabetes, gestational weight gain is also associated with both neonatal birthweight and adiposity (Blackwell, 2016). In contrast, a gestational weight gain during the second and third trimesters that is less than that recommended by the Institute of Medicine is associated with increased risk of an SGA neonate in women of all weight categories except class II or III obesity (Durie, 2011) (Chap. 10, p. 183). The best-documented effect of famine on fetal growth was in the winter of 1944 in Holland. For 6 months, the German occupation army restricted dietary intake to 500 kcal/d for civilians, including pregnant women. As a result, the average birthweight declined by 250 g (Stein, 1975).

Undernourished women may benefit from micronutrient supplementation. In one study, almost 32,000 Indonesian women were randomly assigned to receive micronutrient supplementation or only iron and folate tablets (Prado, 2012). Offspring of those receiving the supplement had lower risks of early infant mortality and low birthweight and had improved childhood motor and cognitive abilities. A Cochrane review of 20 trials involving 141,849 women concluded that supplementation of micronutrients may lower the risk of low birthweight (Keats, 2019). The importance of antenatal vitamins and trace metals is discussed in Chapter 10 (p. 185).

Socioeconomic Factors

The effect of social deprivation on birthweight is interconnected with lifestyle factors such as smoking, alcohol or other substance abuse, and poor nutrition. With appropriate modifying interventions, women with psychosocial factors were significantly less likely to deliver a low-birthweight newborn and also had fewer preterm births and other pregnancy complications (Coker, 2012).

Food insecurity, late entry into prenatal care, and limited access to healthcare are all contributors to fetal-growth restriction (Bryant, 2010). Hall (2020) found that in a military population with equal access to healthcare, racial differences in late entry to prenatal care and FGR persist. An Australian study showed that the proportion of pregnancies affected by fetal-growth restriction increased as levels of social disadvantage rose (Langridge, 2011).

Vascular and Renal Disease

Especially when complicated by superimposed preeclampsia, chronic vascular disease commonly restricts fetal growth (Chap. 53, p. 948). Maternal vascular disease as evidenced by abnormal uterine artery Doppler velocimetry early in pregnancy is associated with higher rates of preeclampsia, SGA neonates, and delivery before 34 weeks (He, 2020; Poon, 2019). Using Washington state birth certificate data, Leary and colleagues (2012) found that maternal ischemic heart disease was associated with a 16-percent risk of having an SGA newborn.

Chronic renal insufficiency is frequently associated with underlying hypertension and vascular disease. Nephropathies are commonly accompanied by restricted fetal growth (Cunningham, 1990; Feng, 2015; Saliem, 2016). These relationships are considered further in Chapter 56 (p. 1004).

Pregestational Diabetes

Fetal-growth restriction in newborns of women with diabetes may be related to congenital malformations or may follow substrate deprivation from advanced maternal vascular disease (Chap. 60, p. 1072). The likelihood of restricted growth increases with worsening White classification, particularly nephropathy (Klemetti, 2016). That said, the prevalence of serious vascular disease associated with diabetes in pregnancy is low.

Chronic Hypoxia

Conditions associated with chronic hypoxia include asthma, maternal cyanotic heart disease, other chronic pulmonary disease, cigarette smoking, and living at high altitude. When exposed to a chronically hypoxic environment, some fetuses have significantly reduced birthweight. Smoking causes a dose-dependent reduction in fetal growth, resulting in an average birthweight 200 g below that of newborns of nonsmokers (D'Souza, 1981). For each 1000-meter rise in altitude, the birthweight declined 150 g in a study of more than 1.8 million births in Austria (Waldhoer, 2015).

Anemia

In most cases, maternal anemia does not impair fetal growth. Exceptions include sickle-cell disease and other inherited anemias (Desai, 2017; Thame, 2016). Importantly, curtailed maternal blood-volume expansion is linked to FGR (de Haas, 2017; Stott, 2017). This is further discussed in Chapter 4 (p. 59).

Antiphospholipid Syndrome

Adverse obstetrical outcomes including fetal-growth restriction have been associated with three types of antiphospholipid antibodies: *anticardiolipin antibodies, lupus anticoagulant*, and *anti-β2 glycoprotein-I antibodies*. Mechanistically, a "two-hit" hypothesis suggests that initial endothelial damage is then followed by intervillous placental thrombosis. More specifically, oxidative damage to certain membrane proteins is followed by antiphospholipid antibody binding, which leads to immune-complex formation and ultimately to thrombosis (Giannakopoulos, 2013). This syndrome is considered in detail in Chapters 55 (p. 979) and 62 (p. 1115). Women with more than one type of antiphospholipid

antibody are at higher risk for FGR compared with those with only one antibody (Saccone, 2017). Also, *anti-β_2 glycoprotein-I antibodies* may have a stronger association with FGR, particularly early-onset disease.

Placental, Cord, and Uterine Abnormalities

Several placental abnormalities are associated with poor fetal growth, which is presumed secondary to uteroplacental insufficiency. These are discussed further throughout Chapter 6 and include chronic placental abruption, extensive infarction, chorioangioma, velamentous cord insertion, and umbilical artery thrombosis. Abnormal placental implantation leading to endothelial dysfunction may also limit fetal growth (Brosens, 2015). This pathology is implicated in pregnancies complicated by preeclampsia (Chap. 40, p. 694). Last, some uterine malformations are linked to impaired fetal growth (Chap. 3, p. 43).

Multifetal Gestation

Pregnancy with two or more fetuses is more likely to be complicated by diminished growth of one or more fetuses compared with that of singletons (Fig. 47-5). Serial sonography is recommended for this reason. With the understanding that normal twin growth may be less than that of singletons, we use a chorionicity-specific twin nomogram to diagnose FGR at Parkland Hospital. Discordance in estimated fetal weight also is considered when evaluating twin growth (Chap. 48, p. 851).

Medications and Other Substances

Fortunately, most medications do not affect fetal growth. Selected medications and other substances that have been associated with FGR due to fetotoxicity are discussed in Chapter 8. Examples include cyclophosphamide and other antineoplastic drugs, significant lead exposure, and drugs such as cocaine and methamphetamine. Alcohol and tobacco each have potent effects on fetal growth. FGR is included among the diagnostic criteria for fetal alcohol syndrome, and cigarette smoking is associated with a two- to threefold increased risk of FGR (Werler, 1997).

Maternal and Fetal Infections

Viral, bacterial, protozoan, and spirochetal infections have been implicated in up to 5 percent of FGR cases and are discussed in Chapters 67 and 68. The best known of these are *rubella* and *cytomegalovirus infection*. Both promote calcifications in the fetus that are associated with cell death, and infection earlier in pregnancy correlates with worse outcomes. Toda and colleagues (2015) described a Vietnamese epidemic in which 39 percent of 292 term newborns with congenital rubella syndrome were low birthweight. In one study of 238 primary cytomegalovirus infections, no severe cases were observed when infection occurred after 14 weeks' gestation (Picone, 2013). These investigators later identified sonographic findings in 30 of 69 cases of congenital infection, and growth restriction was noted in 30 percent of these 30 cases (Picone, 2014).

Tuberculosis and *syphilis* also are associated with poor fetal growth. Both extrapulmonary and pulmonary tuberculosis are linked with low birthweight (Chap. 54, p. 965). Sobhy (2017) analyzed 13 studies that included a total of 3384 women with active tuberculosis. The odds ratio was 1.7 for low birthweight. The etiology is uncertain, however, the adverse effects on maternal health, compounded by effects of poor nutrition and poverty, are important (Jana, 2012). Congenital syphilis is more common, and paradoxically, the placenta is almost always larger and heavier than normal due to edema and perivascular inflammation (Chap. 68, p. 1208). Congenital syphilis is strongly linked with preterm birth and thus low-birthweight newborns (Sheffield, 2002).

Congenital infection with *toxoplasma gondii* is associated with FGR. Capobiango (2014) described 31 Brazilian pregnancies complicated by congenital toxoplasmosis. Only 13 percent were treated antepartum for toxoplasmosis, and low birthweight complicated nearly 40 percent of all the pregnancies. *Congenital malaria* may similarly cause low birthweight and poor fetal growth. Briand and colleagues (2016) emphasize the importance of prophylaxis early in pregnancy for women at risk.

Congenital Malformations

In a classic review of more than 13,000 fetuses with major malformations and chromosomal abnormalities, the rate of growth restriction was double the population prevalence (Khoury, 1988). The birth defect most strongly linked with FGR is gastroschisis. Nelson (2015) reviewed 111 fetuses with gastroschisis and found that a third had birthweights <10th percentile. Congenital cardiac abnormalities are also associated with a slight increase in FGR risk. In a recent review of 1789 singleton neonates with isolated congenital cardiac abnormalities, the prevalence of SGA was 13 percent, which was 3 percent higher than the general-population risk (Ghanchi, 2021). With few exceptions, the identification of growth restriction in the setting of a structural malformation further increases the risk for an underlying genetic syndrome. If not already performed, amniocentesis with chromosomal microarray analysis should be offered.

Genetic Abnormalities

Many genetic syndromes are strongly linked with prenatal-growth impairment or postnatal failure to thrive. Among live-born neonates with autosomal trisomies, trisomy 21 is associated with an SGA prevalence of 15 to 30 percent (Herrera, 2020; Khoury, 1988). With trisomies 13 and 18, the risk of SGA is significantly greater, 50 percent and >80 percent, respectively (Khoury, 1988). In trisomy 18, the combination of fetal abnormalities plus FGR and hydramnios is particularly common. The crown-rump length in fetuses with trisomy 18 and 13, unlike

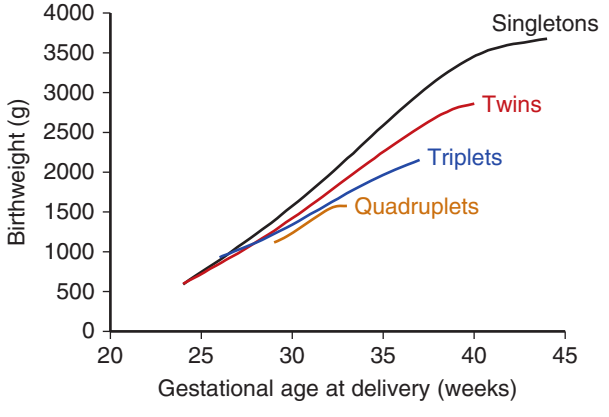

FIGURE 47-5 Birthweight and gestational age relationships in multifetal gestations without malformations delivered at Parkland Hospital.

that with trisomy 21, is also typically shorter than expected (Bahado-Singh, 1997; Schemmer, 1997). Poor fetal growth similarly complicates Turner syndrome, and the severity correlates with increasing haploinsufficiency of the short arm of the X chromosome (Fiot, 2016). In contrast, poor growth is not characteristic of an increased number of X chromosomes (Ottesen, 2010; Wigby, 2016). Discussed in Chapter 16 (p. 318), *confined placental mosaicism* is a recognized cause of FGR.

Management

If FGR is detected, efforts are made to assess the fetal condition and search for possible causes. The risk for stillbirth is increased, and early-onset growth restriction is especially problematic. General tenets of management include serial evaluation of fetal growth every 3 weeks and at least weekly evaluation of amnionic fluid and umbilical artery Doppler velocimetry. A fetus with slow but progressing EFW is more reassuring than one that has plateaued growth. This is supplemented with antepartum evaluation of fetal well-being, which is usually nonstress testing or biophysical profile (American College of Obstetricians and Gynecologists, 2021a) (Chap. 20, p. 387). Consideration is also given to performing a detailed fetal anatomic survey and amniocentesis to assess for underlying genetic abnormalities or infection—particularly with early-onset FGR. A management algorithm is shown in Figure 47-6.

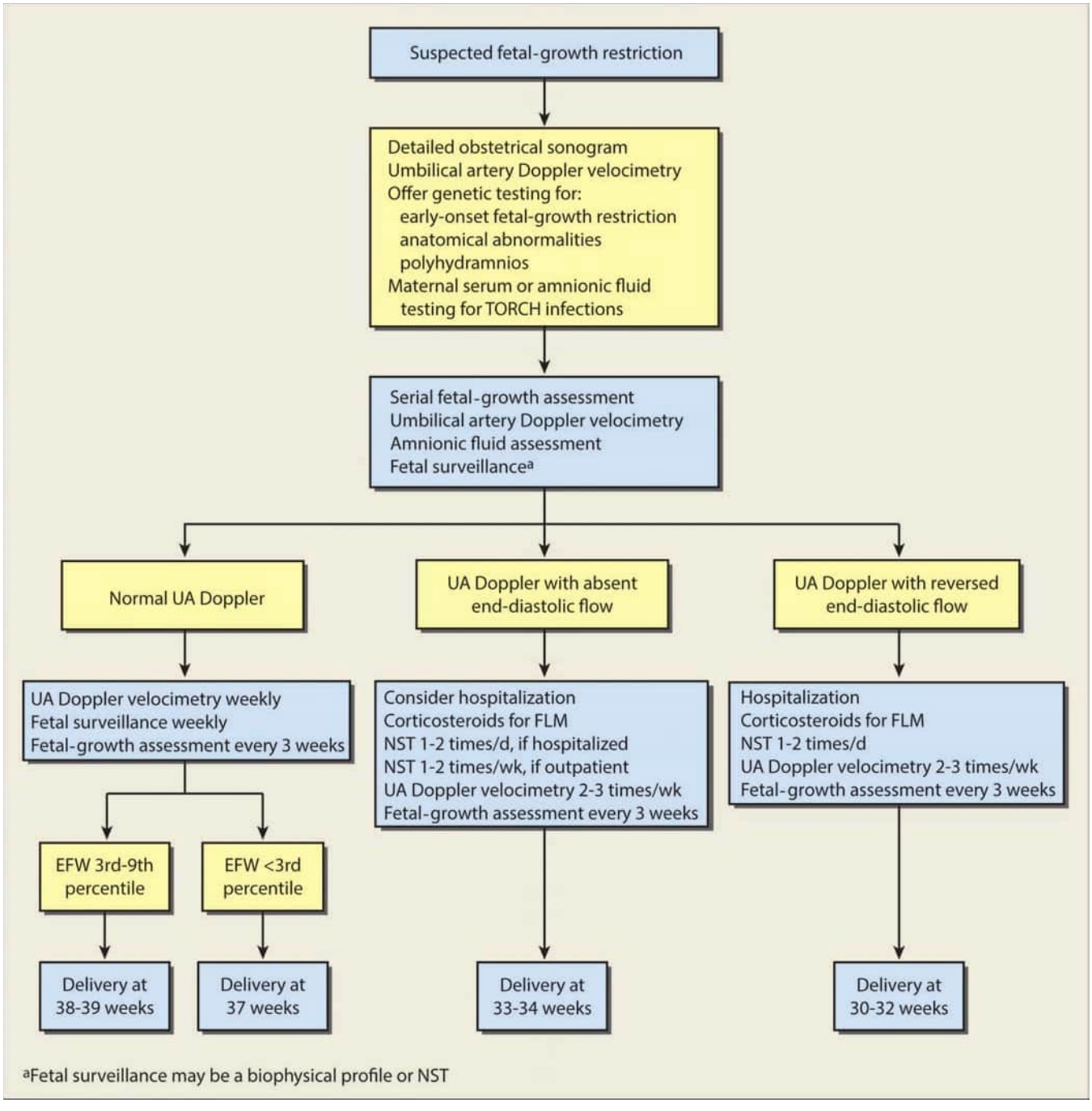

FIGURE 47-6 Algorithm for management of fetal-growth restriction. EFW = estimated fetal weight; FLM = fetal lung maturity; NST = nonstress test; TORCH = toxoplasmosis, other, rubella, cytomegalovirus, herpesvirus; UA = umbilical artery.

Delivery timing balances the risks of fetal death with the hazards of preterm birth. Several multicenter studies address these problems, but unfortunately, none has elucidated the optimal timing of delivery. For the preterm fetus, the only randomized trial of delivery timing is the Growth Restriction Intervention Trial (GRIT) (Thornton, 2004). This trial involved 548 women between 24 and 36 weeks' gestation. Women were randomly assigned to immediate delivery or to delayed delivery until the situation worsened. The primary outcome was perinatal death or disability after reaching age 2 years. Mortality rates did not differ through 2 years of age. Moreover, children aged 6 to 13 years did not show clinically significant differences between the two groups (Walker, 2011). The Disproportionate Intrauterine Growth Intervention Trial at Term (DIGITAT) study examined the delivery timing of growth-restricted fetuses who were 36 weeks' gestation or older. The 321 enrolled women were randomly assigned to labor induction or to expectant management. Composite neonatal morbidity rates did not differ, except that neonatal admissions were lower after 38 weeks' gestation in a secondary analysis (Boers, 2010, 2012). Secondary analyses of DIGITAT did not identify a clear subgroup that benefited from labor induction, and neurodevelopmental and behavioral outcomes at age 2 were similar in both groups (Tajik, 2014; Van Wyk, 2012).

Doppler Velocimetry

Umbilical artery Doppler flow studies are central to the evaluation and management of the fetus with growth restriction (Chap. 14, p. 262). Abnormalities represent the negative progression from fetal adaptation to failure. Specifically, initially increased impedance to flow in the umbilical artery may progress to absent end-diastolic flow and then reversed end-diastolic flow (Fig. 47-7). This negative progression correlates with hypoxia, acidosis, and fetal death. In one prospective series of 1116 fetuses with EFW <10th percentile, only 1 percent of those with normal umbilical artery Doppler studies had adverse outcomes compared with 12 percent of fetuses with Doppler abnormalities (O'Dwyer, 2014). The stillbirth risk in the setting of absent and reversed end-diastolic flow is 7 percent and 19 percent, respectively (Caradeux, 2018). Because of these findings, the American College of Obstetricians and Gynecologists (2021a,b) and Society for Maternal-Fetal Medicine (2020) recommend serial umbilical artery Doppler studies in the management of FGR.

Doppler abnormalities in other vessels may convey information regarding pathophysiology, but interrogation of these is not recommended for routine management of the pregnancy complicated by FGR (American college of Obstetricians and Gynecologists, 2021a; Society for Maternal-Fetal Medicine, 2020). Doppler abnormalities of the *ductus venosus* (Fig. 14-12, p. 264) reflect increased central venous pressure from decreased cardiac compliance and higher right ventricular end-diastolic pressure. Fetuses with abnormal ductus venosus Doppler flow have a 20-percent risk for stillbirth, and this increases to 46 percent in cases with a reversed A-wave (Caradeux, 2018). Second, pulsatile flow in the umbilical vein waveform (Fig. 14-12) indicates cardiac dysfunction. Last, cerebral vasodilation is the fetal adaptative response to hypoxemia in the setting of growth restriction. The cerebroplacental ratio (CPR)—defined as middle cerebral artery pulsatility index divided by umbilical artery pulsatility index—is a measure of this adaptation and may be abnormal in severe cases of FGR. An abnormal CPR <1 has been associated with greater risk for earlier delivery, lower birthweight, cesarean delivery, neonatal intensive care unit admission, and perinatal death (DeVore, 2015; Flood, 2014). However, a metaanalysis of 18,731 fetuses found the CPR was not predictive of adverse perinatal outcomes (Vollgraff, 2021).

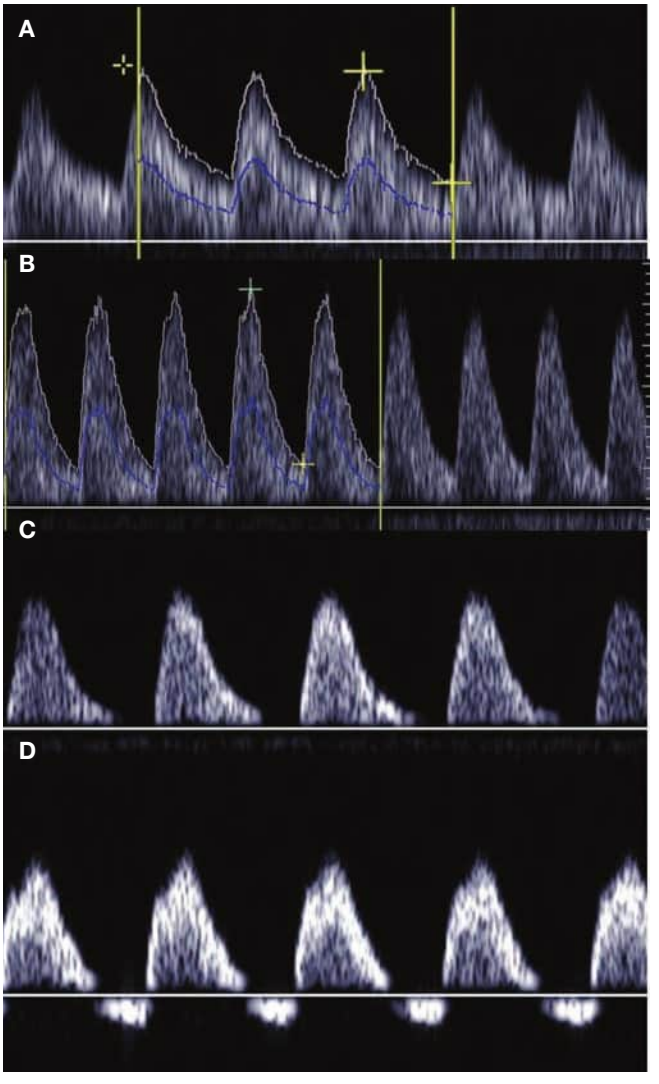

FIGURE 47-7 Doppler velocity waveforms. **A.** Normal waveform with normal S/D ratio. **B.** Increased impedance to flow with abnormally elevated S/D ratio. **C.** Absent end-diastolic flow. **D.** Reversed end-diastolic flow.

Management of the Near-term Fetus

Delivery of a suspected growth-restricted fetus with normal umbilical artery Doppler velocimetry, normal amnionic fluid volume, and reassuring fetal testing can likely be deferred until 37 to 38 weeks' gestation (see Fig. 47-6). Expectant management can be guided using antepartum evaluation of fetal well-being described in Chapter 20. If oligohydramnios is present, delivery between $36^{0/7}$ and $37^{6/7}$ weeks' gestation is recommended (American College of Obstetricians and Gynecologists, 2021c;

Society for Maternal-Fetal Medicine, 2020). With a normal fetal heart rate pattern, vaginal delivery is planned. Notably, some of these fetuses do not tolerate labor.

Management of the Fetus Remote from Term

If growth restriction is identified in a fetus before 34 weeks, and amnionic fluid volume and fetal surveillance findings are normal, observation is recommended. As long as interval fetal growth and fetal surveillance test results are normal, pregnancy is allowed to continue (see Fig. 47-6). Reassessment of fetal growth is typically made no sooner than 3 weeks later. Weekly outpatient assessment of umbilical artery Doppler velocimetry and amnionic fluid volume is combined with fetal well-being testing. If umbilical artery Doppler studies indicate absent or reversed end-diastolic flow, inpatient surveillance is undertaken. During hospitalization, more frequent sonographic evaluations and antenatal testing of fetal well-being and close proximity to labor and delivery are advantages.

With growth restriction remote from term, no specific treatment ameliorates the condition. Evidence does not support diminished activity or bed rest to accelerate growth or improve outcomes. Nutrient supplementation, attempts at plasma volume expansion, oxygen therapy, antihypertensive drugs, heparin, and aspirin are all ineffective (American College of Obstetricians and Gynecologists, 2021a).

Management decisions hinge on assessment of the relative risks of fetal death during expectant management versus the risks from preterm delivery. Reassuring results from fetal well-being tests may allow observation with continued maturation. However, long-term neurological outcome, which theoretically may suffer from additional weeks in an inhospitable intrauterine environment, is a concern (Baschat, 2014; Lees, 2015; Thornton, 2004). Baschat and associates (2009) showed that neurodevelopmental outcome at 2 years in growth-restricted fetuses was best predicted by birthweight and gestational age. Doppler abnormalities are generally not associated with poor childhood cognitive developmental scores among low-birthweight fetuses delivered in the third trimester (Llurba, 2013). These findings emphasize that adverse neurodevelopmental outcomes cannot always be predicted.

Intrapartum Management

When lagging fetal growth is the result of placental insufficiency due to poor maternal perfusion or reduction of functional placenta, the fetal condition may be aggravated by labor. Equally important, oligohydramnios raises the likelihood of cord compression during labor. For these and other reasons, the frequency of cesarean delivery is increased.

The risk of neonatal hypoxia or meconium aspiration is also greater. Thus, care for the newborn should be provided immediately by an attendant who can skillfully clear the airway and ventilate a neonate as needed (Chap. 32, p. 586). The severely growth-restricted newborn is particularly susceptible to hypothermia and may also develop other metabolic derangements such as hypoglycemia, polycythemia, and hyperviscosity. Risk is greatest at the lowest extremes of birthweight (Baschat, 2009, 2014; Llurba, 2013).

Outcomes

Lessons learned from SGA neonates inform concerns about FGR. More than 50 years ago, Battaglia and Lubchenco (1967) classified SGA neonates as those whose weights were below the 10th percentile for their gestational age. The mortality rate of SGA neonates born at 38 weeks was 1 percent compared with 0.2 percent in those with larger birthweights. More recent data also indicate that the overall stillbirth rate among SGA neonates approximates 1 percent, which is twice as high as the population prevalence (Getahun, 2007).

The risk for abnormal neurological development also is greater in SGA neonates. In an analysis of nearly 3000 newborns born before 27 weeks' gestation, those weighing <10th percentile had a nearly fourfold higher risk of neonatal death or neurodevelopmental impairment and a nearly threefold greater risk of cerebral palsy compared with non-SGA neonates (De Jesus, 2013). In another analysis of more than 91,000 otherwise uncomplicated pregnancies, newborns with birthweights <5th percentile had a higher risk of low 5-minute Apgar score, respiratory distress, necrotizing enterocolitis, and neonatal sepsis than appropriate-weight neonates. The risks of stillbirth and neonatal death were sixfold and fourfold higher, respectively (Mendez-Figueroa, 2016).

Newborns at the lowest birthweight percentiles are at greatest risk for adverse outcome. In one study of more than 44,561 neonates, only 14 percent of those weighing <1st percentile at birth survived to discharge (Griffin, 2015). Poor motor, cognitive, language and attention, and behavioral outcomes in growth-restricted newborns unfortunately persist into early childhood and adolescence (Baschat, 2014; Levine, 2015; Rogne, 2015).

Early-onset Growth Restriction

Perinatal morbidities are further increased in the 30 percent of FGR pregnancies diagnosed prior to 32 weeks' gestation (Savchev, 2014). Thus, this gestational age is used to demarcate early-onset from late-onset growth restriction (Society for Maternal-Fetal Medicine, 2020). Early-onset FGR is typically more severe and more commonly associated with placental dysfunction and maternal hypertension than late-onset growth restriction (Aviram, 2019; Dall'Asta, 2017). Pregnancies with early-onset FGR have greater rates of umbilical artery Doppler abnormalities compared with those with late onset. Similar to pregnancies complicated by preeclampsia, increased maternal serum levels of antiangiogenic factors that include soluble vascular endothelial growth factor receptor 1 (sVEGFR-1) and soluble fms-like tyrosine kinase 1 (sFlt-1) are reported in pregnancies complicated by early-onset growth restriction (Kingdom, 2018; Korzeniewski, 2016) (Chap. 40, p. 694).

Barker Hypothesis

Thirty years ago, Barker (1992) hypothesized that *adult* mortality and morbidity are related to fetal and infant health. This includes both under- and overgrowth. In the context of FGR, numerous reports describe a relationship between suboptimal fetal nutrition and a higher risk of subsequent adult hypertension, atherosclerosis, type 2 diabetes, and metabolic

derangement (Colella, 2018; Jornayvaz, 2016). The degree to which low birthweight mediates adult disease is controversial, as weight gain in early life also appears important (Breij, 2014; Kerkhof, 2012; McCloskey, 2016).

Evidence suggests that FGR may affect organ development, particularly that of the heart. Individuals with low birthweight demonstrate cardiac structural changes and dysfunction that persist through childhood, adolescence, and adulthood (Crispi, 2018). In one study, 80 infants who were born SGA before 34 weeks' gestation were compared at 6 months with 80 normally grown infants (Cruz-Lemini, 2016). The ventricle in SGA infants was more globular, resulting in systolic and diastolic dysfunction. In another study, echocardiography in 418 adolescents showed that low birthweight was associated with a thicker left ventricular posterior wall (Hietalampi, 2012). However, these findings have unclear long-term significance (Cohen, 2016).

Growth restriction is also associated with postnatal structural and functional renal changes. Luyckx and Brenner (2015) concluded that both low and high birthweight, maternal obesity, and gestational diabetes adversely affect in-utero development of the kidney and its health into adulthood. However, other variables that include childhood nutrition, acute kidney injury, excessive childhood weight gain, and obesity also worsen long-term renal function.

Prevention

Ideally, prevention begins before conception. Maternal medical conditions are treated, and medications are modified to help lower FGR risks. Smoking cessation is critical. Other risk factors are tailored to the maternal condition, such as antimalarial prophylaxis for women living in endemic areas and correction of nutritional deficiencies. Treatment of mild to moderate hypertension does not reduce the incidence of SGA newborns (Chap. 53, p. 950).

Currently, no pharmacologic therapies prevent growth restriction. Considerable study of low-dose aspirin therapy has not demonstrated consistent benefit in low-risk pregnancies. Daily aspirin therapy did not reduce the risk for SGA neonates in a randomized trial of 1700 women (Rolnik, 2017). Two large metaanalyses involving more than 20,000 women did find that low-dose aspirin was associated with a significantly lower risk of FGR, whether initiated prior to or after 16 weeks' gestation (Meher, 2017; Roberge, 2017). A Cochrane database analysis showed a small reduction in the risk of SGA neonates with maternal aspirin therapy (Duley, 2019). However, these studies included women at risk for preeclampsia, and the modest decrease in the risk for growth restriction was a secondary finding. Because evidence in women without risk factors for preeclampsia is lacking, aspirin therapy for the prevention of FGR is not recommended (American College of Obstetricians and Gynecologists, 2020a, 2021a; Society for Maternal-Fetal Medicine, 2020)

FETAL MACROSOMIA

Definition

The term *macrosomia* is used rather imprecisely to describe a fetus whose estimated weight exceeds a threshold—typically 4000 g, 4500 g, or even 5000 g (American College of Obstetricians and Gynecologists, 2019a). Although obstetricians generally agree that neonates weighing <4000 g are not excessively large, a similar consensus has not been reached for the definition of macrosomia.

TABLE 47-2. Birthweight Distribution of 354,509 Liveborn Infants at Parkland Hospital between 1988 and 2012

	Births		Maternal Diabetes	
Birthweight (g)	No.	%	No.	%
500–3999	322,074	90.9	13,365	86.2
4000–4249	19,106	5.4	1043	6.7
4250–4499	8391	2.4	573	3.7
4500–4649	3221	0.9	284	1.8
4750–4999	1146	0.3	134	0.7
5000–5249	385	0.1	57	0.4
5250–5499	127	0.04	31	0.2
5500 or more	59	0.02	14	0.09
Total	354,509		15,501	

Large for gestational age (LGA) denotes a fetus or newborn whose weight exceeds the 90th percentile for gestational age. Similar to SGA, the term LGA does not imply that growth is necessarily abnormal. Indeed, most such neonates are simply constitutionally larger than their peers. The 90th percentile for birthweight at 39 weeks' gestation approximates 3900 g (Duryea, 2014). Thus, most LGA neonates would not meet any of the common definitions of macrosomia.

In the United States in 2019, 6.4 percent of all newborns weighed 4000 to 4499 g; 0.9 percent weighed 4500 to 4999 g; and 0.1 percent were born weighing ≥5000 g (Martin, 2021). Similarly, during a 30-year period at Parkland Hospital, during which more than 350,000 singletons were born, only 1.4 percent of neonates weighed ≥4500 g (Table 47-2). We are of the view that the upper limit of fetal growth, above which growth can be deemed abnormal, is likely to be two standard deviations above the mean. This represents perhaps 3 percent of births. At 40 weeks, such a threshold would correspond to approximately 4500 g.

Detection

Because current methods fail to accurately estimate excessive fetal size, macrosomia cannot be definitively diagnosed until delivery (American College of Obstetricians and Gynecologists, 2019a). Inaccuracy in estimates of fetal weight, by either fundal height measurement or sonography, are often attributable to maternal obesity. In one study of 502 patients with sonographic estimated fetal weights >4000 g within 2 weeks of delivery, the risk of birthweight overestimation was >50 percent (Zafman, 2020). Of those who underwent cesarean delivery for suspected LGA, almost 30 percent delivered a neonate weighing <4000 g.

Pathophysiology

Particularly in women with diabetes and elevated cord blood levels of insulin-like growth factor 1, fetal macrosomia is asso-

TABLE 47-3. Risk Factors for Fetal Macrosomia

Obesity
Diabetes
Postterm gestation
Multiparity
Large size of parents
Advancing maternal age
Previous macrosomic infant
Racial and ethnic factors

ciated with greater neonatal fat mass and morphological heart changes. Pedersen (1954) first proposed that hyperglycemia leads to fetal hyperinsulinemia and fetal overgrowth. This has been extended to organ dysmorphia, for example, increased interventricular septal thickness in neonates of mothers with gestational diabetes (Aman, 2011; Garcia-Flores, 2011). The cardiopulmonary vasculature also is adversely affected by diabetes in pregnancy. In 3277 cases of persistent pulmonary hypertension of the newborn, maternal obesity, diabetes, and both deficient and excessive fetal growth were independent risk factors (Steurer, 2017). Long-term metabolic consequences of fetal macrosomia in the setting of maternal obesity are discussed in Chapter 51 (p. 907).

Risk Factors

Some factors associated with fetal macrosomia are listed in Table 47-3. Many are interrelated. Advancing age usually correlates with multiparity and risk for diabetes, and obesity is similarly associated with diabetes. In one study, the birth prevalence of macrosomia exceeded 24 percent among obese women in China, and macrosomia rates were approximately 2.5-fold higher for prolonged pregnancy and gestational diabetes (Wang, 2017). As shown in Table 47-2, maternal diabetes is strongly associated with neonates weighing >4000 g. In a prospective study of 682 consecutive pregnancies complicated by diabetes, women with type 1 diabetes were significantly more likely than women with type 2 diabetes to have a neonate weighing above the 90th and 97.7th percentiles (Murphy, 2011). Higher third-trimester glucose concentration correlates with fetal macrosomia, and hemoglobin A_{1c} and fasting glucose values are independent predictors of macrosomia risk (Cyganek, 2017). Notably, maternal diabetes is associated with only a small percentage of the total number of LGA newborns.

Management

Several interventions have been proposed to interdict suspected or "impending" fetal overgrowth. Exercise in pregnancy is beneficial to the mother, does not increase the risk for growth impairment, and decreases macrosomia risk. One metaanalysis of 28 studies involving 5322 women concluded that exercise reduces the risk of an LGA newborn or birthweight >4000 g without raising the risk of an SGA neonate or birthweight <2500 g (Wiebe, 2015). Similarly, others have concluded that aerobic exercise increases the likelihood of a normal weight neonate (Di Mascio, 2016; Perales, 2016).

For women with diabetes, insulin therapy and glycemic control may lower the prevalence of neonatal macrosomia but have not consistently translated into reduced cesarean delivery rates. Fetal macrosomia, irrespective of the diagnosis of diabetes mellitus, is strongly associated with maternal obesity and excessive gestational weight gain (Durie, 2011; Durst, 2016; Harper, 2015). Currently recommended weight gains for pregnancy according to maternal BMI are described in Chapter 10 (p. 183).

"Prophylactic" Labor Induction

Some clinicians have induced labor when fetal macrosomia was suspected in nondiabetic women. The rationale for this approach was to obviate further fetal growth and, in theory, reduce the risk of delivery complications or cesarean delivery. In a systematic review of 11 studies of expectant management compared with labor induction for suspected macrosomia, labor induction significantly increased cesarean delivery rates without improving perinatal outcomes (Sanchez-Ramos, 2002). In contrast, Magro-Malosso and colleagues (2017) performed a metaanalysis of four randomized trials involving 1190 women and concluded that labor induction at ≥38 weeks' gestation for suspected macrosomia significantly reduces the frequency of fetal overgrowth and fractures. In one of these studies, 822 women with suspected LGA fetuses were randomly assigned either to early-term delivery or to expectant management (Boulvain, 2015). There was a higher rate of vaginal delivery that was marginally significant and a lower composite measure of morbidity. The authors cautioned that any benefits should be balanced with the risks of early-term labor induction and delivery. Namely, a review of early-term births indicates that elective delivery before 39 weeks' gestation does not improve maternal outcomes and is associated with worse neonatal outcomes (Tita, 2016). We agree with the American College of Obstetricians and Gynecologists (2019a, 2020b) that current evidence does not support a policy for early labor induction or delivery before 39 weeks' gestation.

Elective Cesarean Delivery

With the delivery of macrosomic neonates, shoulder dystocia and its attendant risks described in Chapter 27 (p. 501) are major concerns. That said, 9 percent of these injuries still follow cesarean delivery (Johnson, 2020). Therefore, planned cesarean delivery on the basis of suspected macrosomia to prevent brachial plexopathy is an unreasonable strategy in the *general population* (Chauhan, 2005). Ecker and coworkers (1997) analyzed 80 cases of brachial plexus injury in 77,616 consecutive newborns at Brigham and Women's Hospital. They concluded that an excessive number of otherwise unnecessary cesarean deliveries would be needed to prevent a single brachial plexus injury in neonates born to women without diabetes. Others echoed these sentiments in their analysis of nondiabetic mothers (Rouse, 1996; Van der Looven, 2020).

Conversely, planned cesarean delivery may be a reasonable strategy for *diabetic* women with an estimated fetal weight >4250 or >4500 g. Conway and Langer (1998) described a protocol of routine cesarean delivery for sonographic estimates of ≥4250 g in diabetic women. This management significantly lowered the shoulder dystocia rate from 2.4 to 1.1 percent.

TABLE 47-4. Maternal and Fetal Outcomes for 208,090 Pregnancies Delivered at Parkland Hospital from 1998 through 2012

Outcome[a]	<4000 g n = 187,119	4000–4499 g n = 17,750	4500–4999 g n = 2849	≥5000 g n = 372	*p* value
Cesarean total	46,577 (25)	5,362 (30)	1204 (42)	224 (60)	<0.001
Scheduled	12,564 (7)	1,481 (8)	316 (11)	65 (17)	<0.001
Dystocia	7589 (4)	1388 (8)	337 (12)	46 (12)	<0.001
Shoulder dystocia	437 (0)	366 (2)	192 (7)	56 (15)	<0.001
3rd- or 4th-degree laceration	7296 (4)	932 (5)	190 (7)	37 (10)	<0.001
Labor induction	26,118 (13)	2499 (14)	420 (15)	39 (10)	0.141
Prolonged second stage	6905 (4)	899 (5)	147 (5)	14 (4)	<0.001
Chorioamnionitis	13,448 (7)	1778 (10)	295 (10)	35 (9)	<0.001
pH <7.0	925 (0.5)	96 (0.6)	20 (0.7)	4 (1.1)	0.039
Apgar <7 @ 5 minutes	1898 (1.0)	80 (0.5)	22 (0.8)	10 (2.7)	<0.001
ICN admission	4266 (2.2)	123 (0.7)	36 (1.3)	9 (2.4)	<0.001
Fractured clavicle	1880 (1.0)	616 (3.5)	125 (4.4)	16 (4.3)	<0.001
Mechanical ventilation	2305 (1.2)	54 (0.3)	11 (0.4)	9 (2.4)	<0.001
Hypoglycemia	480 (0.2)	89 (0.5)	31 (1.1)	12 (3.2)	<0.001
Hyperbilirubinemia	5829 (3.0)	305 (1.7)	60 (2.1)	12 (3.2)	<0.001
Erb palsy	470 (0.2)	224 (1.3)	74 (2.6)	22 (5.9)	<0.001
Neonatal death	402 (0.2)	3 (0)	2 (0.1)	1 (0.3)	<0.001

[a]Outcome data presented as n (%).
ICN = intensive care nursery.

In summary, we agree with the American College of Obstetricians and Gynecologists that elective delivery for the fetus that is suspected to be overgrown is inadvisable, particularly before 39 weeks' gestation. Last, we also conclude that elective cesarean delivery is not indicated when estimated fetal weight is <5000 g among women without diabetes and <4500 g among women with diabetes (American College of Obstetricians and Gynecologists, 2019a, 2020b).

Outcomes

The adverse consequences of excessive fetal growth are considerable. Neonates with a birthweight of at least 4000 g have cesarean delivery rates exceeding 50 percent. This is particularly true with maternal obesity or diabetes or with birthweights >5000 g (Cordero, 2015; Crosby, 2017; Hehir, 2015). Neonatal morbidity is higher in LGA neonates compared with those with lower birthweights. Macrosomic newborns have higher rates of shoulder dystocia, obstetrical brachial plexus injuries, and birth fractures (Beta, 2019; Chauhan, 2017). Rates of shoulder dystocia vary greatly and can reach nearly 30 percent for macrosomic neonates when maternal diabetes is comorbid (Cordero, 2015). In general obstetrical populations that include diabetic mothers, dystocia rates are at least 5 percent for neonates with birthweights ≥5000 g (Crosby, 2017; Hehir, 2015). The risk for stillbirth is greater with macrosomia, and this risk rises with increasing birth weight (Salihu, 2020). Rates of postpartum hemorrhage, perineal laceration, and maternal infection, which are related complications, also are higher in mothers delivering overgrown newborns. Table 47-4 shows maternal and neonatal outcomes by birthweight for neonates >4000 g delivered at Parkland Hospital.

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CHAPTER 48

Multifetal Pregnancy

Multifetal pregnancies may result from two or more fertilization events, from a single fertilization followed by a splitting of the zygote, or both. In part because of infertility therapy, the twin birth rate in the United States was 3.2 percent in 2019. For higher-order multifetal births, the number peaked in 1998 at 0.2 percent of all births. Subsequent efforts in the reproductive endocrinology community to curb this rate have led to declines. Specifically, the rate of triplets or more declined by 55 percent from 1998 to 2019 (Martin, 2021).

Multifetal gestations remain problematic for both the mother and her fetuses. For the fetus, multifetal births accounted for 3 percent of all live births in 2013 but for 15 percent of all infant deaths. Specifically, the infant mortality rate for twins was more than four times the rate for singletons, and for triplets it was 12-fold higher (Matthews, 2015). Neonates from multifetal gestations also make up a disproportionate percentage of very-low-birthweight newborns in the United States (Martin, 2021). These two outcomes in singletons and twins from Parkland Hospital are shown in Table 48-1. Risks for congenital malformations and preterm birth are greater with multifetal gestation and discussed later.

The mother may also experience higher morbidity and mortality rates, and these rise with the number of fetuses (Society for Maternal-Fetal Medicine, 2019). In one study of more than 44,000 multifetal pregnancies, the risks for preeclampsia, postpartum hemorrhage, and maternal death were twofold higher than these rates in singleton gestations (Walker, 2004). Rates of placenta previa and placenta accreta spectrum are increased (Miller, 2021a). Moreover, compared with rates for singletons,

TABLE 48-1. Selected Outcomes in Singleton and Twin Pregnancies Delivered at Parkland Hospital from 1988 through 2021

Outcome	Singletons (No.)	Twins (No.)
Pregnancies	456,120	5366
Births[a,b]	456,120	10,732
Stillbirths	2532 (5.6)	258 (24.0)
Neonatal deaths	918 (2.1)	186 (18.2)
Perinatal deaths	3453 (7.6)	444 (41.4)
Very low birthweight (<1500 g)	4450 (10.0)	1109 (108.8)

[a]Birth data are represented as number (per 1000).
[b]Denominator for neonatal deaths and very low birthweight is liveborn infants.
Data from Dr. Don McIntire.

the peripartum hysterectomy rate was threefold greater for twins and 24-fold higher for triplets or quadruplets in one study (Francois, 2005).

MECHANISMS OF MULTIFETAL GESTATIONS

Dizygotic versus Monozygotic Twinning

Multifetal gestations are often described by *zygosity*, *amnionicity*, and *chorionicity*, which are the number of zygotes, amnions, and chorions, respectively. Twin fetuses most often result from fertilization of two separate ova, which yields *dizygotic* or *fraternal twins*. Less often, twins arise from a single fertilized ovum that then divides to create *monozygotic* or *identical twins*.

Dizygotic twins are not in a strict sense true twins because they result from the maturation and fertilization of two ova during a single ovulatory cycle. Genetically, these twins are like any other pair of siblings. Twins of opposite sex are almost always dizygotic. Rarely, somatic mutations or chromosome aberration in one monozygotic twin can yield differing gender karyotype or phenotype. For example, postzygotic loss of the Y chromosome in one 46,XY twin creates a phenotypically female twin with 45,X Turner syndrome.

Monozygotic twins, although they have the same genetic heritage, also are usually not identical. For example, the division of one fertilized zygote into two does not necessarily yield equal sharing of protoplasmic material. In addition, monozygotic twins may be discordant for genetic mutations because of a postzygotic mutation, or they may have the same genetic disease but with marked variability in its expression. In female fetuses, skewed lyonization can produce differential expression of X-linked traits or diseases. Last, sesquizygosity is a rare event of dispermic fertilization that leads to monozygotic twins. Some cases may have sex discordance (Gabbett, 2019).

Monozygotic Twinning

Mechanisms underlying monozygotic twinning are poorly understood. One association is assisted reproductive technology (ART) and in-vitro fertilization (IVF). The monozygotic twinning incidence is twofold greater in pregnancies conceived using blastocyst transfer compared with transfer of a later-stage embryo. The predisposition to splitting may stem from culture media effects (Busnelli, 2019).

The outcome of the monozygotic twinning process depends on when division occurs as depicted in Figure 48-1. If zygotes divide within the first 72 hours after fertilization, two embryos, two amnions, and two chorions develop, and a *monozygotic, dichorionic, diamnionic* twin gestation evolves. Two distinct placentas or a single, fused placenta may develop. If division occurs between days 4 through 8, a *monozygotic, monochorionic, diamnionic* twin pregnancy results. By 8 days, the chorion and the amnion have already differentiated, and division results in two embryos within a common amnionic sac, which is a *monozygotic, monochorionic, monoamnionic* twin gestation. Conjoined twins result if division initiates later.

Rarely, monochorionic twins may be dizygotic. Mechanisms are unclear. In one review of 31 cases, nearly 80 percent were conceived after ART procedures, and 90 percent were associated with chimerism (Peters, 2017).

Factors Affecting Twinning

Dizygotic twinning is much more common than monozygotic splitting of a single oocyte, and its incidence is positively influenced by infertility treatment and by maternal age, race, heredity, and size. By contrast, the frequency of monozygotic twin births is relatively constant worldwide—approximately one set per 250 births. This incidence is generally independent of most demographic factors, except ART.

Of *infertility therapies*, ovulation induction with clomiphene citrate or with follicle-stimulating hormone (FSH) plus human chorionic gonadotropin (hCG) remarkably enhances the likelihood of multiple concurrent ovulations. Moreover, with IVF, the greater the number of embryos that are transferred, the greater the risk of twins or more. In 2017, ART contributed to 1.9 percent of all newborns in the United States and to 14.7 percent of all neonates in multifetal gestations (Sunderam, 2020). The American Society for Reproductive Medicine (2017) revised their guidelines regarding the number of embryos or blastocysts transferred during IVF to reduce the incidence of multifetal pregnancies. For example, women younger than 35 years are encouraged to receive a single-embryo transfer, regardless of embryo stage. These practices have effectively lowered multifetal rates (Martin, 2021).

Advancing maternal age and *delayed childbearing* are other important risk factors (Adashi, 2018; Otta, 2016). One explanation is FSH levels, which rise with age and lead to greater ovarian stimulation (Beemsterboer, 2006). Higher levels of FSH have been linked with dizygotic twinning (Lambalk, 1998). Another explanation may be a higher use of ART in older women. *Paternal age* has also been linked to twinning, but its effect is felt to be small (Abel, 2012).

Different races and ethnic groups vary in their frequency of multifetal births. In the United States in 2019, the twin birth rate was 4.1 percent in black women, 3.3 percent in whites, and 2.5 in Hispanics (Martin, 2021). In one rural community in Nigeria, twinning occurred once in every 20 births (Knox, 1960). These marked differences in twinning frequency may stem from racial variations in FSH levels (Nylander, 1973).

Heredity is another factor, and maternal influence appears to supersede that of the father. In a study of 4000 genealogical records, women who themselves were a dizygotic twin gave birth to twins at a rate of one set per 58 births (White, 1964). Women who were not a twin, but whose husbands were a dizygotic twin, gave birth to twins at a rate of one set per 116 pregnancies. Genome-wide association studies have identified potentially contributory genes, and two are related to FSH (Mbarek, 2016). However, the contribution of these variants to the overall incidence of twinning is likely small (Hoekstra, 2008).

Maternal size is another risk factor. Nylander (1971) showed an increasing gradient in the twinning rate in taller, heavier women. These had a twinning rate 25 to 30 percent higher than short, nutritionally deprived women. Likewise, another study found an association between greater maternal weight

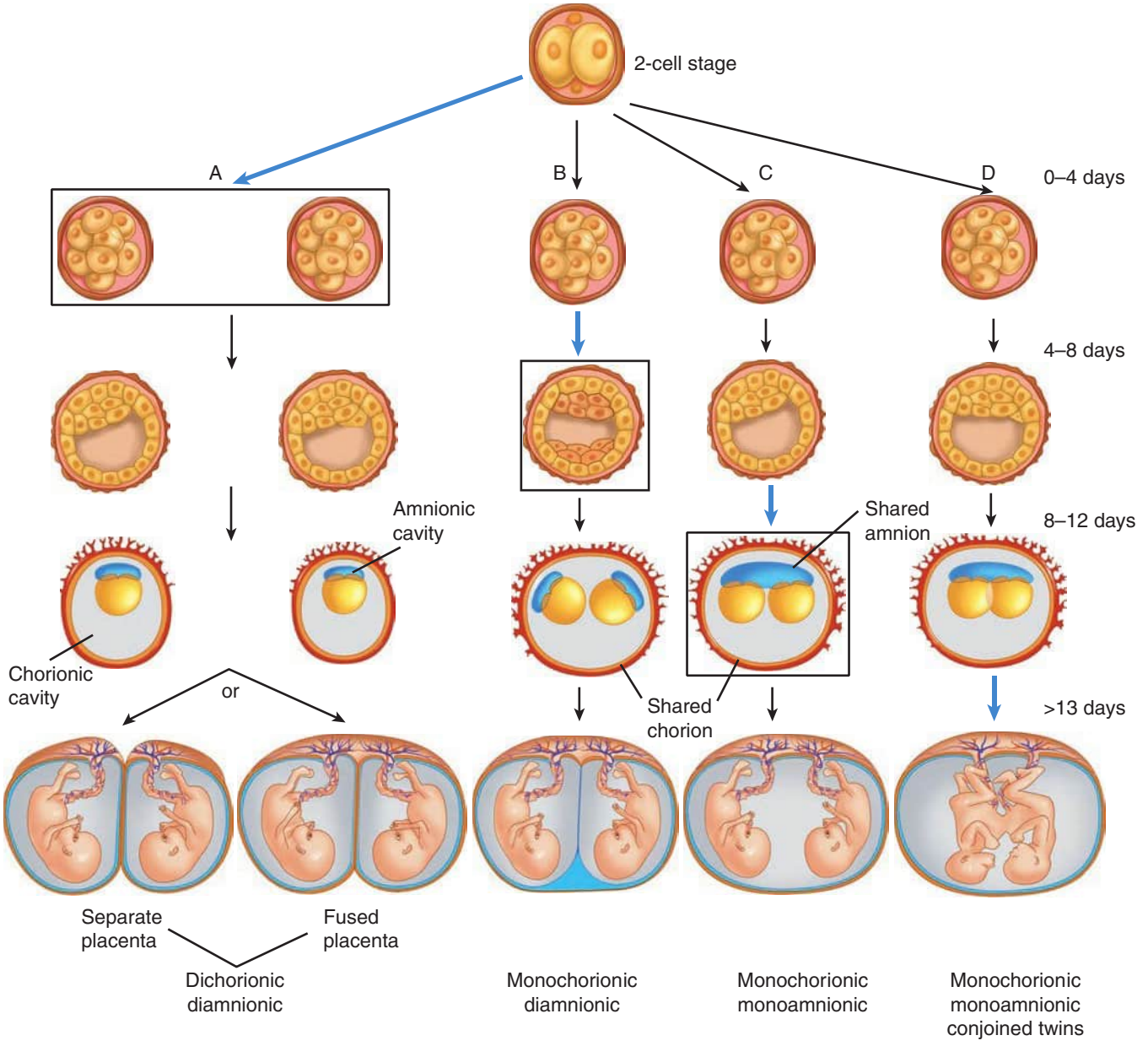


FIGURE 48-1 Mechanism of monozygotic twinning. Black boxing and blue arrows in columns A, B, and C indicate timing of division. **A.** At 0 to 4 days postfertilization, an early conceptus may divide into two. Division at this early stage creates two chorions and two amnions (dichorionic, diamnionic). Placentas may be separate or fused. **B.** Division between 4 to 8 days leads to formation of a blastocyst with two separate embryoblasts (inner cell masses). Each embryoblast will form its own amnion within a shared chorion (monochorionic, diamnionic). **C.** Between 8 and 12 days, the amnion and amnionic cavity form above the germinal disc. Embryonic division leads to two embryos with a shared amnion and shared chorion (monochorionic, monoamnionic). **D.** Differing theories explain conjoined twin development. One describes an incomplete splitting of one embryo into two. The other describes fusion of a portion of one embryo from a monozygotic pair onto the other.

and dizygotic twinning (Reddy, 2005). Evidence acquired during and after World War II suggests that twinning correlates more with nutrition than with body size. Widespread undernourishment in Europe during those years was associated with a marked fall in the dizygotic twinning rate (Bulmer, 1959).

■ Superfecundation and Superfetation

Superfecundation is fertilization of two ova within the same menstrual cycle but not at the same coitus nor necessarily by sperm from the same male. The latter leads to *heteropaternity* (Silver, 2021).

In *superfetation*, an interval as long as or longer than a menstrual cycle intervenes between fertilizations. Superfetation is not known to occur spontaneously and is likely due to ART (Lantieri, 2010). Pseudo-superfetation often results from markedly unequal growth of twins with the same gestational age.

DIAGNOSIS OF MULTIFETAL GESTATION

■ Clinical Evaluation

Early diagnosis can help with management of the associated risks posed by twins. Accurate fundal height measurement can

TABLE 48-2. Incidence of Some Complications Related to Twin Characteristics

Type of Twinning	Twins	Rates of Twin-Specific Complications in Percent			
		Fetal-Growth Restriction	Preterm Delivery[a]	Placental Vascular Anastomosis	Perinatal Mortality
Dizygotic	80	25	40	0	10–12
Monozygotic	20	40	50	—	15–18
Diamnionic/dichorionic	6–7	30	40	0	18–20
Diamnionic/monochorionic	13–14	50	60	100	30–40
Monoamnionic/monochorionic	<1	40	60–70	80–90	58–60
Conjoined	0.002 to 0.008	—	70–80	100	70–90

[a]Delivery before 37 weeks.

be an initial tool. With multiples, uterine size is typically larger during the second trimester than that expected for a singleton. In one study, fundal heights obtained between 20 and 30 weeks' gestation averaged 5 cm greater in twins than in singletons (Rouse, 1993).

Palpation of fetal parts to diagnose twins before the third trimester is difficult. Even then, obesity or hydramnios can hinder assessment. Palpating two fetal heads strongly supports the diagnosis. Moreover, a hand-held Doppler ultrasonic unit may isolate two fetal heartbeats if their rates are clearly distinct from each other and from the mother.

Overall, however, clinical criteria alone to diagnose multifetal gestations is unreliable. In the Routine Antenatal Diagnostic Imaging with Ultrasound (RADIUS) trial, for 37 percent of women who did not have a screening ultrasound examination, their twin pregnancy was not diagnosed until 26 weeks' gestation. In 13 percent of unscanned women, their multifetal gestation was identified only during their admission for delivery (LeFevre, 1993).

■ Sonography

Sonographic examination should detect practically all sets of twins. Further, it should aim to determine fetal number, estimated gestational age, chorionicity, and amnionicity. Importantly, the risk for many twin-specific complications varies in relation to these (Table 48-2) (Hack, 2008; Manning, 1995).

With sonography, separate gestational sacs, if present, can be identified early in twin pregnancy (Fig. 48-2). Subsequently, each fetal head should be seen in two perpendicular planes to avoid mistaking a fetal trunk for a second fetal head. Ideally, two fetal heads or two abdomens are seen in the same image plane to avoid scanning the same fetus twice and interpreting it as twins. Higher-order multifetal gestations are more challenging to evaluate. Even in the first trimester, identifying the actual number of fetuses and their position can be difficult. This determination is especially important if selective reduction is considered (p. 858).

In determining chorionicity, sonography's accuracy diminishes as gestational age advances. It has a 98-percent accuracy in the first trimester but may be incorrect in up to 10 percent of second-trimester examinations. Overall, chorionicity can be correctly determined with sonography before 24 weeks in approximately 95 percent of cases (Emery, 2015; Lee, 2006).

The sonographic features that are used to determine chorionicity vary according to gestational age. Early in the first trimester, the number of chorions equates to the number of

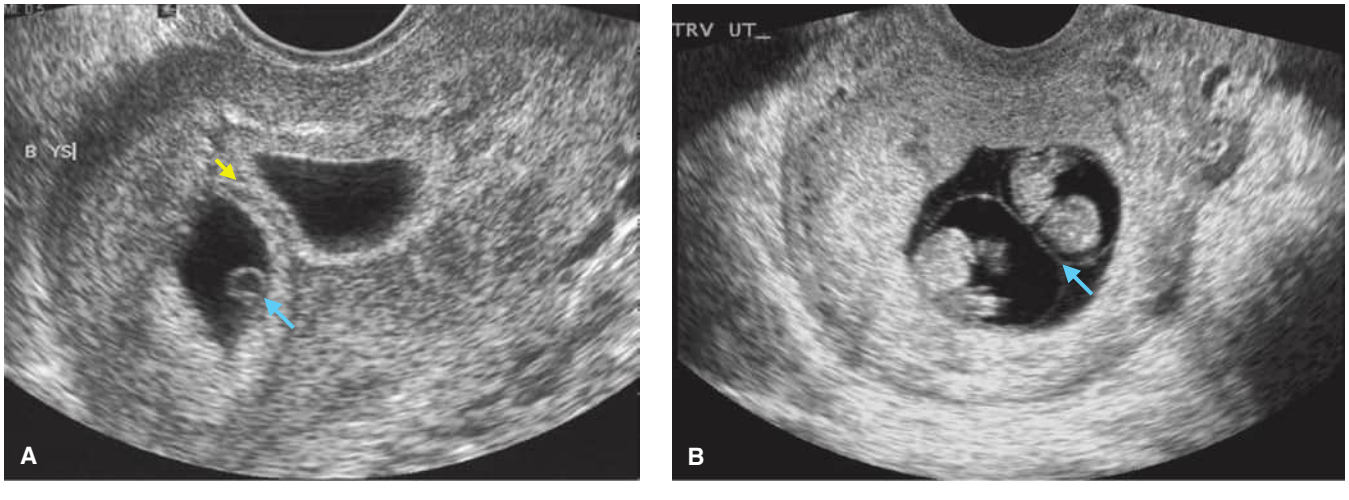


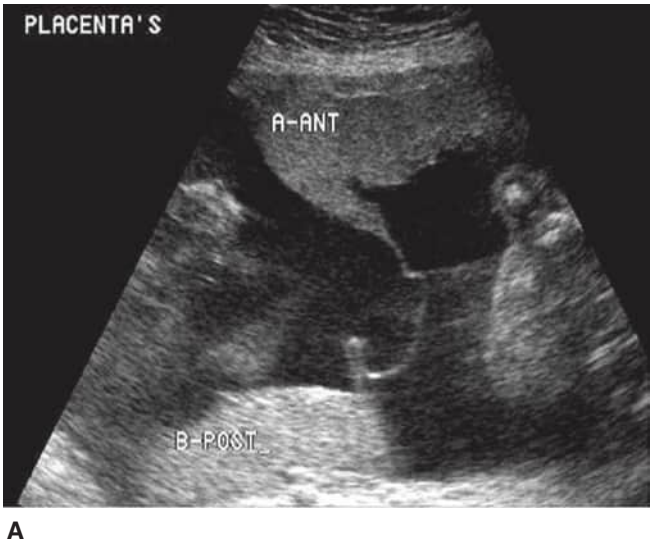
FIGURE 48-2 Sonograms of first-trimester twins. **A.** Dichorionic diamnionic twin pregnancy at 6 weeks' gestation. Note the thick dividing chorion (*yellow arrow*). One of the yolk sacs is indicated (*blue arrow*). **B.** Monochorionic diamnionic twin pregnancy at 8 weeks' gestation. Note the thin amnion encircling each embryo, resulting in a thin dividing membrane (*blue arrow*).

gestational sacs. A thick band of chorion that separates two gestational sacs signals a dichorionic pregnancy, whereas monochorionic twins have a single gestational sac. If the gestation is monochorionic diamnionic, it may be difficult to visualize the thin intervening amnion before 8 weeks' gestation. If the intervening membrane is difficult to visualize, the number of yolk sacs *usually* correlates with the number of amnions. However, the number of yolk sacs as a predictor of amnionicity may not always be accurate (Shen, 2006). Although uncommonly seen early, cord entanglement identifies a monoamnionic gestation.

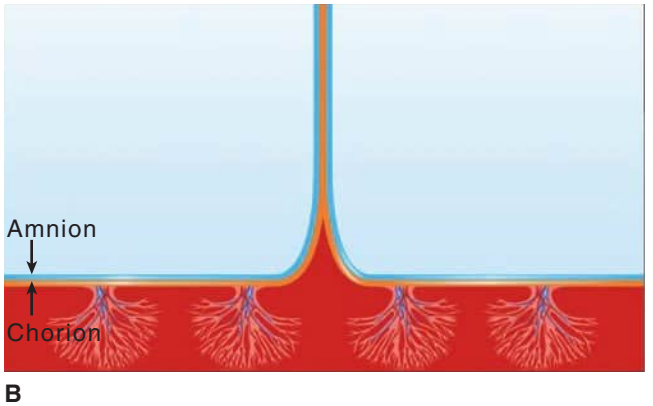
At 10 to 14 weeks' gestation, sonographic assessment of chorionicity may be determined using four features. These are the number of placental masses, presence of an intervening membrane dividing the sacs, thickness of that membrane, and fetal gender (Emery, 2015; Khalil, 2016). First, two separate placentas suggest dichorionicity. The converse is not necessarily true, such as cases with a single fused placental mass. Second, identification of a thick dividing membrane—generally ≥2 mm—supports a presumed diagnosis of dichorionicity. In a dichorionic pregnancy, this visualized membrane is composed of four layers—two amnions and two chorions. Also, the *twin peak sign*—also called *lambda* or *delta sign*—is seen by examining the point of origin of the dividing membrane on the placental surface. The peak appears as a triangular projection of placental tissue extending a short distance between the layers of the dividing membrane (Fig. 48-3).

In contrast, monochorionic pregnancies have a dividing membrane that is so thin (generally <2 mm) that it may not be seen until the second trimester. The relationship between the membranes and placenta without apparent extension of placenta between the dividing membranes is called the *T sign* (Fig. 48-4). Evaluation of the dividing membrane can establish chorionicity in more than 99 percent of pregnancies in the first trimester (Maruotti, 2016; Miller, 2012). Lack of a dividing membrane signals a monochorionic monoamnionic gestation.

Last, twins with differing gender indicates a dichorionic (and dizygotic) gestation. Rare exceptions were described earlier (p. 839).

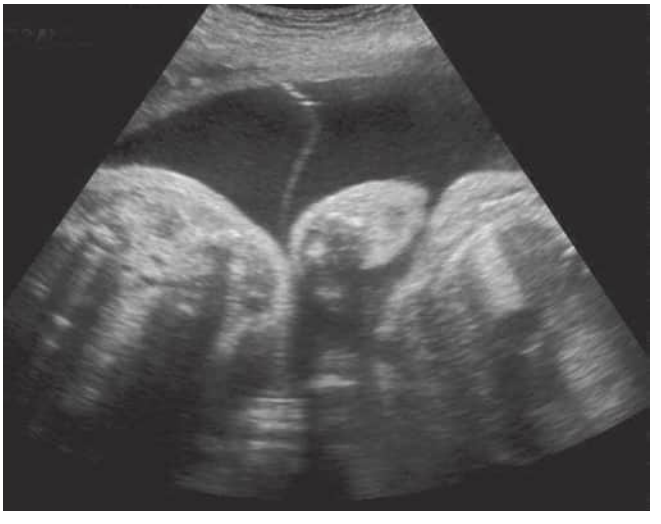


A



B

FIGURE 48-3 A. Sonographic image of the "twin-peak" sign, also termed the "lambda sign," in a 24-week gestation. At the top of this sonogram, tissue from the anterior placenta is seen extending downward between the amnion layers. This sign confirms dichorionic twinning. **B.** The "twin-peak" sign is seen at the bottom of this schematic diagram. The triangular portion of placenta insinuates between the amniochorion layers.



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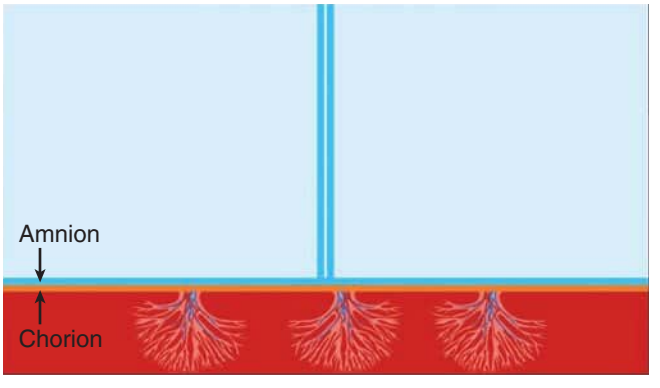


B

FIGURE 48-4 A. Sonographic image of the "T" sign in a monochorionic diamnionic gestation at 30 weeks. At the top of this sonogram, the two apposed amnion layers are seen as the thin line extending downward. **B.** Schematic diagram of the "T" sign. Twins are separated only by a membrane created by the juxtaposed amnion of each twin. A "T" is formed at the point at which amnions meet the placenta.

■ Other Diagnostic Aids

Magnetic resonance (MR) imaging may help delineate complications in monochorionic twins, including conjoined twins (Hu, 2006). Abdominal radiography can be used if fetal number in a higher-order multifetal gestation is uncertain. However, radiographs generally have limited utility and lead to an incorrect diagnosis if fetuses move during the exposure.

No biochemical test reliably identifies multifetal gestations. Serum levels of β-hCG and of maternal serum alpha-fetoprotein (MSAFP) are usually higher, but ranges may overlap with those of singletons.

■ Placental Examination

Careful visual examination of the placenta and membranes after delivery can establish zygosity and chorionicity in many cases. First, the placenta is gently delivered to preserve the attachment of the amnion and chorion. With one common amnionic sac or with juxtaposed amnions not separated by chorion, the fetuses are monozygotic (see Fig. 48-1). If adjacent amnions are separated by chorion, the fetuses could be either dizygotic or monozygotic, but dizygosity is more common (Fig. 48-5). If the neonates are of the same sex, blood typing of cord blood samples may be helpful. Different genders or blood types reflects dizygosity, although the same gender or blood type in each fetus does not confirm monozygosity. Postnatal zygosity genetic testing is available, and the benefits and ethics have been debated (Brown, 2015; Craig, 2015).

MATERNAL PHYSIOLOGICAL ADAPTATIONS

The physiological burdens of pregnancy and likelihood of serious maternal complications are typically greater with multifetal gestations than with singleton ones. In the first trimester and with its higher serum β-hCG levels, multifetal gestations often cause nausea and vomiting. In women carrying more than one fetus, blood volume expansion is greater and averages 50 to 60 percent compared with 40 to 50 percent in those with a singleton (Pritchard, 1965). This augmented hypervolemia teleologically offsets blood loss with vaginal delivery of twins, which is twice that with a single fetus. Although red cell mass also accrues, it does so proportionately less in twin pregnancies. Combined with greater iron and folate requirements, this predisposes to anemia.

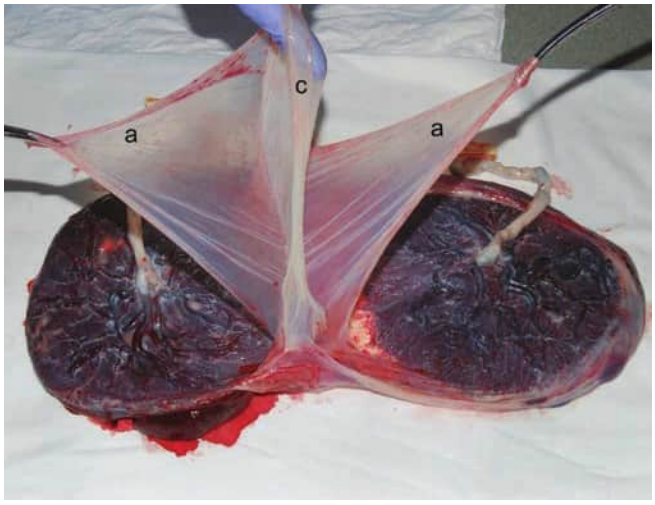


FIGURE 48-5 Dichorionic diamnionic twin placenta. The membrane partition that separated twin fetuses is elevated and consists of chorion (*c*) between two amnions (*a*).

Women carrying twins also have a typical pattern of blood pressure change. One study assessed serial blood pressures in more than 13,000 singleton and twin pregnancies (MacDonald-Wallis, 2012). As early as 8 weeks' gestation, the diastolic blood pressure in women with twins was lower than that with singleton pregnancies. It generally rose by a greater degree at term. An earlier study demonstrated that this later rise was at least 15 mm Hg in 95 percent of women with twins compared with only 54 percent of women with a singleton (Campbell, 1986).

Hypervolemia along with decreased vascular resistance has an impressive effect on cardiac function. In one study of 119 women with twins, cardiac output rose another 20 percent above that in women with a singleton (Kametas, 2003). Similarly, a study of serial maternal echocardiography examinations found a greater elevation in cardiac output in 20 women with uncomplicated twin pregnancies (Kuleva, 2011). Both studies found that the augmented cardiac output was predominantly due to greater stroke volume rather than higher heart rate. Vascular resistance was significantly lower in twin gestations throughout pregnancy compared with singleton ones. In a study of 30 uncomplicated twin pregnancies, this same group of investigators identified progressive diastolic dysfunction from the first to third trimester. The dysfunction subsequently normalized after delivery (Ghi, 2015).

Uterine growth in a multifetal gestation is substantively greater than in a singleton one. The uterus and its nonfetal contents may achieve a volume of 10 L or more and weigh in excess of 20 pounds. Especially with monozygotic twins, excessive amounts of amnionic fluid may rapidly accumulate. In these circumstances, maternal abdominal viscera and lungs can be appreciably compressed and displaced by the expanding uterus. As a result, the size and weight of the large uterus may preclude more than a sedentary existence for these women.

Rarely, maternal renal function can become seriously impaired, most likely as the consequence of obstructive uropathy (Jena, 1996). Hydramnios is a common associate, and therapeutic amniocentesis may provide relief for the mother, may improve obstructive uropathy, and possibly may lower rates of preterm labor or rupture of membranes. Unfortunately, hydramnios often develops remote from term and rapidly reaccumulates.

PREGNANCY COMPLICATIONS

Several complications, discussed next, complicate multifetal pregnancy. Others are preterm birth and discordant fetal growth, which are discussed in later sections.

■ Spontaneous Abortion and Vanishing Fetus

Among twins, monochorionic twins have significantly higher early fetal loss rates than dichorionic pairs (D'Antonio, 2013).

Twins achieved through ART may be at greater risk for abortion compared with those conceived spontaneously (Szymusik, 2012). However, among ART-conceived gestations, twins have lower miscarriage rates than singletons (Matias, 2007).

In some cases, only one fetus is spontaneously lost. As a result, the incidence of twins in the first trimester is much greater than the incidence of twins at birth. Estimates suggest that while 1 in 8 *pregnancies* begin multifetal, only 1 in 80 *births* are multifetal (Corsello, 2010). Sonography studies in the first trimester have shown that one twin dies and "vanishes" before the second trimester in 10 to 40 percent of all twin pregnancies (Brady, 2013; Harris, 2020). The incidence is higher following ART conception.

A vanishing fetus is more common in higher-order multiples. In one study of spontaneous reduction in 709 multifetal pregnancies before 12 weeks' gestation, one or more embryos died in 36 percent of twin pregnancies, in 53 percent of triplet pregnancies, and in 65 percent of quadruplet pregnancies (Dickey, 2002). Interestingly, in one study, ultimate pregnancy duration and birthweight were inversely related to initial gestational sac number regardless of the final number of fetuses at delivery (Seong, 2020). This effect was most pronounced in twins who started as quadruplets. Evidence for adverse immediate and long-term effects of twin spontaneous reduction on the remaining pregnancy is conflicting (Harris, 2020; McNamara, 2016).

Spontaneous reduction of a twin gestation may affect prenatal screening results. In one study of ART-conceived gestations, 56 twin pregnancies with a single early demise and 897 singleton gestations were compared (Gjerris, 2009). First-trimester serum marker concentrations did not differ between the groups if the embryonic loss was identified before 9 weeks' gestation. If diagnosed after 9 weeks, the marker levels were higher and less precise. With a vanishing twin, first-trimester maternal serum levels of the pregnancy-associated plasma protein A (PAPP-A) can be elevated. Second-trimester MSAFP and dimeric inhibin A levels also can be higher (Huang, 2015). Early loss of one twin may also affect noninvasive prenatal testing using cell-free DNA (cfDNA) (Chap. 17, p. 336). In one report, 15 percent of the false-positive results were attributed to this effect (Futch, 2013). The development of single-nucleotide polymorphism technology for cfDNA testing holds promise in better identifying these cases (Curnow, 2015). Thus, a spontaneously reduced abortus is ideally identified to help avoid confusion with results from aneuploidy and neural-tube defect screening.

Congenital Malformations

The incidence of these is appreciably higher in multifetal gestations compared with singleton ones. In one study, the congenital malformation rate was 406 per 10,000 twins compared with 238 per 10,000 singletons (Glinianaia, 2008). This rate in monochorionic twins was almost twice that of dichorionic twin gestations. One large study between 1998 and 2010 found that twins had a 73-percent greater risk of congenital heart disease than singletons. The occurrence risk and concordance were substantially higher among monochorionic twins (Best, 2015; Gijtenbeek, 2019).

From a 30-year European registry of multifetal births, structural anomaly rates rose steadily from 2.2 percent in 1987 to 3.3 percent in 2007 (Boyle, 2013). Yet, during this time, the proportion of dizygotic twins grew by 30 percent, whereas the proportion of monozygotic twins remained stable. This higher risk of congenital malformations in dizygotic twins over time correlated with increased availability of ART. An increase in birth defect rates related to ART has been reported (Wen, 2020). However, if data are adjusted for maternal age or duration of subfertility, the risk of congenital anomalies does not appear to be increased by ART (Zhu, 2006).

Low Birthweight

Multifetal gestations are more likely to be low birthweight than singleton pregnancies due to restricted fetal growth and preterm delivery. Birthweights in twins closely paralleled those of singletons until 28 to 30 weeks' gestation. Thereafter, twin birthweights progressively lagged (Fig. 48-6). Beginning at 35 to 36 weeks' gestation, twin birthweights clearly diverge from those of singletons. Thus, abnormal growth should be diagnosed only when fetal size is less than expected for *multifetal gestation*. Accordingly, twin and triplet growth curves have been developed (Kim, 2010; Odibo, 2013; Vora, 2006). To confirm suitable growth in dichorionic pairs, we perform sonography every 4 weeks, starting at 16 to 20 weeks. Monochorionic twins are imaged every 2 weeks for twin-twin transfusion syndrome (p. 848). To identify suspected fetal-growth restriction, we use the standards of birthweight for twin gestations stratified by placental chorionicity (Ananth, 1998).

Hypertension

Compared with mothers of singletons, those with multifetal gestations are more likely to develop a pregnancy-associated hypertensive disorder, and the incidence further rises with advancing fetal number (Day, 2005). In one analysis, 14 percent of parturients with twins developed a hypertensive disorder

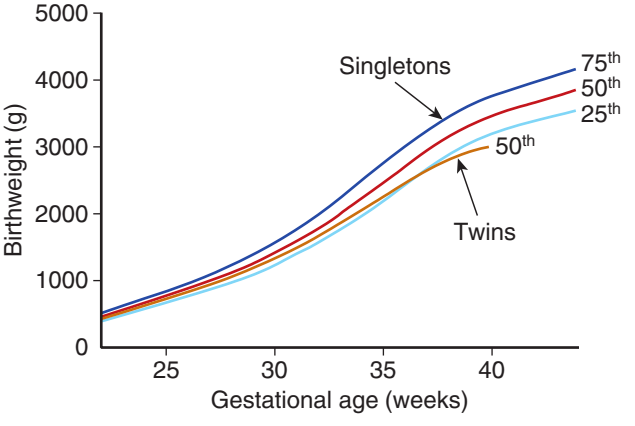


FIGURE 48-6 Birthweight percentiles (25th to 75th) for 357,205 singleton neonates compared with the 50th birthweight percentile for 3714 twins, Parkland Hospital 1988–2012. Infants with major malformations, pregnancies complicated by stillbirth, and twin gestations with >25 percent discordance also were excluded. (Data from Dr. Don McIntire.)

of pregnancy (Aviram, 2021). No specific zygosity confers a greater rate of these disorders (Lučovnik, 2016). However, with twins and gestational diabetes, the preeclampsia incidence is increased (Dave, 2021). Similar to singleton pregnancies with hypertensive disorders, fetal-growth restriction is a potential outcome (Proctor, 2019) (Chap. 40, p. 702).

Data suggest that rising fetal number and levels of antiangiogenic factor play roles in preeclampsia pathogenesis in multiples (Chap. 40, p. 694). Nonhypertensive women with twins compared with those with singletons have higher levels of the antiangiogenic factors *soluble fms-like tyrosine kinase 1 (sFlt-1)* and *soluble endoglin* and lower levels of proangiogenic *placental growth factor (PlGF)* (Faupel-Badger, 2015). In women with twins *and* preeclampsia in one study, both sFlt-1 levels and sFlt-1/PlGF ratios rose and PlGF concentrations declined compared with *normotensive* women with twins (Rana, 2012). Aspirin therapy is recommended to help prevent preeclampsia and is discussed with prenatal care (p. 853).

Long-term Infant Development

In cohort studies evaluating twin and singletons, academic performance is similar and is unaffected by ART-assisted conception (Christensen, 2006; Spangmose, 2017). For mono- or dichorionic pairs born preterm, neurodevelopment at 2 years was reported to be similar (Tosello, 2021).

However, among normal-birthweight neonates, the cerebral palsy (CP) risk is twofold higher among multifetal pregnancies compared with singletons. In term and preterm neonates from 12 large CP registries, the overall CP rate was 1.6 per 1000 singleton live births and 7 per 1000 live births from multifetal pregnancies (Perra, 2021). In this and another registry study, the higher CP rate in multifetal gestations was attributed mainly to prematurity (Sellier, 2021) (Chap. 34, p. 620). Fetal-growth restriction, congenital anomalies, twin-twin transfusion syndrome, and fetal demise of a co-twin are other potential contributors.

UNIQUE FETAL COMPLICATIONS

Several unique complications arise in multifetal pregnancies. These are described in twins but also can be found in higher-order multifetal gestations. Most fetal complications attributed to the twinning process itself are seen with monozygotic twins. Their pathogenesis is best understood after reviewing the possibilities shown in Figure 48-1.

Monoamnionic Twins

These twins make up less than 1 percent of all twin pregnancies and 4 percent of monochorionic pairs (Chitrit, 2021; Sebire, 2000). However, they have high rates of many significant complications.

Fetal loss rates in monoamnionic twins are substantial. Among fetuses alive before 16 weeks' gestation, less than half survive to the neonatal period. Fetal abnormalities and spontaneous miscarriage contribute to most losses (Prefumo, 2015). A high perinatal death rate is attributable to preterm birth, twin-twin transfusion syndrome, cord entanglement, birthweight discordance, and congenital anomalies (Buca, 2020; Saccone, 2020).

Congenital anomaly rates in monoamnionic twins reach 18 to 28 percent (Post, 2015). Concordance of anomalies is found in only approximately one quarter of cases. Because of the greater risk of cardiac anomalies, fetal echocardiography is indicated. Of note, monoamnionic twins are by definition monozygotic and thus presumed to be genetically identical, except in rare cases (Zwijnenburg, 2010). Interestingly, the risk for Down syndrome in each fetus of the monozygotic pair is similar to or lower than the risk in maternal age-matched singletons (Sparks, 2016).

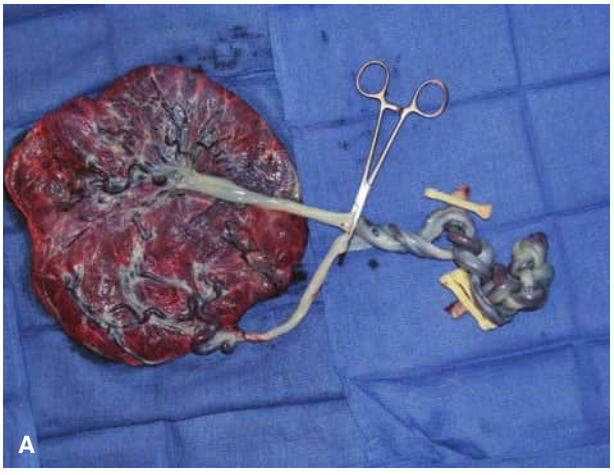
Twin-twin transfusion syndrome rates in monoamnionic twins are lower than in monochorionic diamnionic pregnancies (Murgano, 2020). This may be due to the near universal presence in monoamnionic twins of arterioarterial anastomoses, which are presumed to be protective (Hack, 2009). Nonetheless, twin-twin transfusion syndrome surveillance is recommended and described in that section.

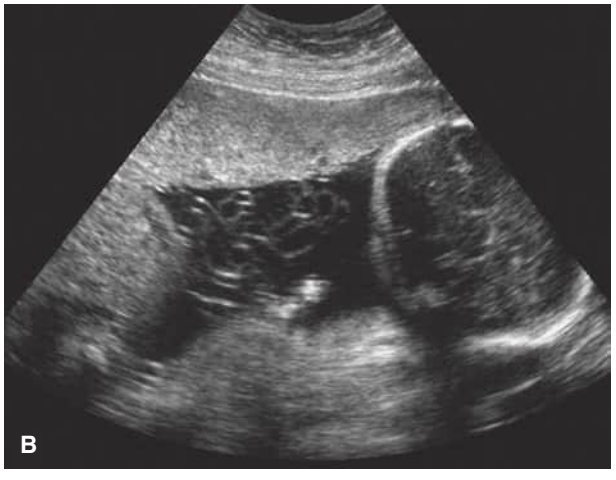
Umbilical cord entanglement is a frequent event (Fig. 48-7). Although color-flow Doppler sonography can help diagnose entanglement, factors that lead to pathological umbilical vessel constriction are unknown. Fetal death from cord entanglement is thus unpredictable, and monitoring for this is relatively ineffective. Moreover, studies of inpatient or outpatient fetal surveillance of monoamnionic twin pregnancies show conflicting data. Heyborne and coworkers (2005) reported no stillbirths in 43 women admitted at 26 to 27 weeks' gestation for daily fetal surveillance. Conversely, 13 fetuses died in 44 women managed as outpatients. In the MONOMONO Working Group (2019) study of 195 women with these twins, the fetal death rate was 3.3 percent in 75 mothers admitted at 24 to 29 weeks' gestation compared with 10.8 percent in the 120 gravidas monitored outpatient. Notably, no fetal deaths occurred after 32 weeks' gestation in either group. Last, Van Mieghem and associates (2014) found the risk of "potentially preventable death" was not significantly different in women with inpatient (2.1 percent) or outpatient (4.7 percent) fetal surveillance.

In the United States, mothers with monoamnionic twins are often admitted at 24 to 28 weeks' gestation to begin 1 hour of daily fetal heart rate monitoring (American College of Obstetricians and Gynecologists, 2021b). Optimal surveillance is unclear and may include nonstress testing or biophysical profile assessment (Chap. 20, p. 386). Betamethasone, discussed later, is considered to promote pulmonary maturation (p. 855). If fetal testing remains reassuring and no other intervening indications arise, cesarean delivery is performed at $32^{0/7}$ to $34^{0/7}$ weeks' gestation. To help manage these many care items, the Society for Maternal-Fetal Medicine (2020) offers a prenatal checklist.

Unique and Aberrant Twinning

Several aberrations in monozygotic twinning result in a spectrum of fetal malformations. These are traditionally ascribed to incomplete splitting of an embryo into two separate twins. However, they theoretically may result from early secondary





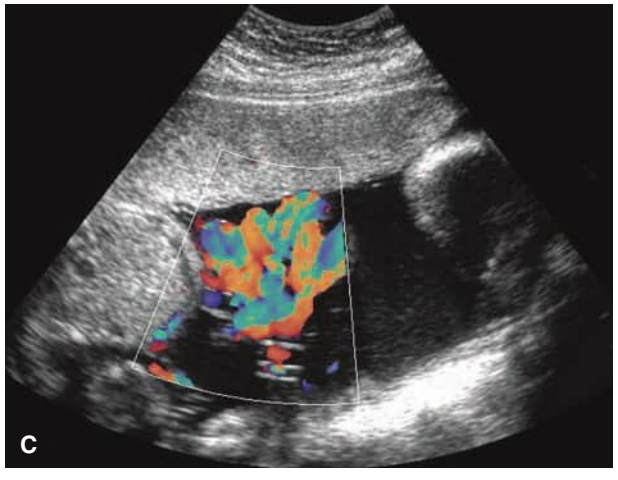


FIGURE 48-7 Monochorionic monoamnionic cord entanglement. **A.** Despite marked knotting of the cords, vigorous twins were delivered by cesarean. **B.** Preoperative sonogram of this pregnancy shows entwined cords. **C.** This finding is accentuated with application of color Doppler. (Reproduced with permission from Dr. Julie Lo.)

fusion of two separate embryos. These separated embryos are either symmetrical or asymmetrical. The spectrum of asymmetrical twinning includes external parasitic twins, fetus-in-fetu, and twin reversed-arterial-perfusion (TRAP) sequence, which is described later (p. 850).

Conjoined Twins

Joining of the twins may begin at either pole and produce characteristic forms depending on which body parts are joined or shared (Fig. 48-8) (Spencer, 2000). The frequency of conjoined twins has a prevalence of 1.5 in 100,000 births, and thoracopagus is the most common type (Mutchinick, 2011).

Conjoined twins can be identified using sonography in the first trimester (Chen, 2011). This provides an opportunity for parents to decide whether to continue the pregnancy. During sonographic interrogation, fetal poles are seen to be closely associated and do not change relative position from one another (Fig. 48-9). Other clues are more than three vessels in the umbilical cord, fewer limbs than expected, spine hyperflexion, bifid fetal pole, and increased nuchal thickness. Three-dimensional ultrasound, color Doppler, and MR imaging are valuable adjuncts to clarify shared organs (Baken, 2013).

Postnatal surgical separation may be successful if essential organs are not shared. Conjoined twins may have discordant structural anomalies that further complicate decisions about whether to continue the pregnancy. Consultation with a pediatric surgeon often assists with parental decisions.

Viable-aged conjoined twins should be delivered by cesarean. For pregnancy termination, however, vaginal delivery is possible because the union is often pliable. Still, dystocia is common, and vaginal delivery may be traumatic to the uterus or cervix.

External Parasitic Twins and Fetus-in-fetu

Attached to a relatively normal twin, an *external parasitic twin* is a grossly defective fetus or merely fetal parts. It usually consists of externally attached supernumerary limbs, often with some viscera. Classically, however, a functional heart or brain is absent. Parasitic twins are believed to derive from a dead defective twin, whose surviving tissue attaches to and receives vascular support from the normal co-twin (Spencer, 2001). In one study, parasitic twins accounted for 4 percent of all conjoined twins (Mutchinick, 2011).

With *fetus-in-fetu*, one embryo may enfold early within its co-twin and mainly intraabdominally. Normal development of this rare parasitic twin usually arrests in the first trimester. Thus, normal spatial arrangement and many organs are lacking. Classically, vertebral or axial bones are found in the fetiform mass, whereas a heart and brain are absent. These masses are thought to be a monozygotic, monochorionic diamnionic twin gestation and are typically supported by large parasitic vessels to the host (McNamara, 2016).

Monochorionic Twins and Vascular Anastomoses

All monochorionic placentas likely share some anastomotic connections. With rare exceptions, anastomoses between twins are unique to monochorionic twin placentas. However, the number, size, and direction of these seemingly haphazard connections vary markedly (Fig. 48-10). In one analysis of more than 200 monochorionic placentas, the median number of anastomoses was eight (Zhao, 2013).

Anastomoses may be artery-to-artery, vein-to-vein, or artery-to-vein communications and are located on the chorionic

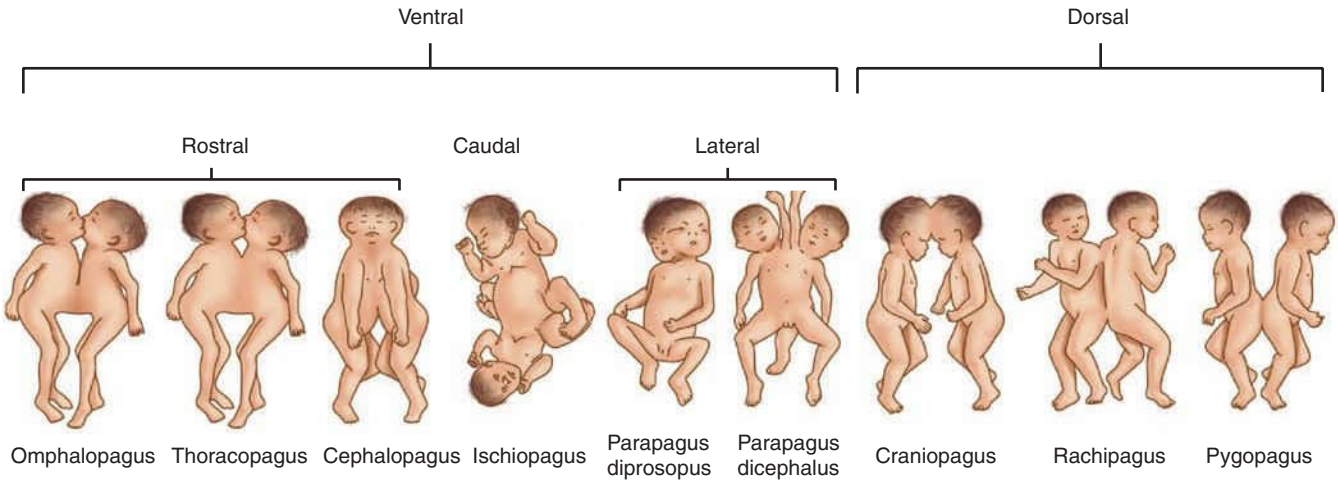


FIGURE 48-8 Types of conjoined twins.

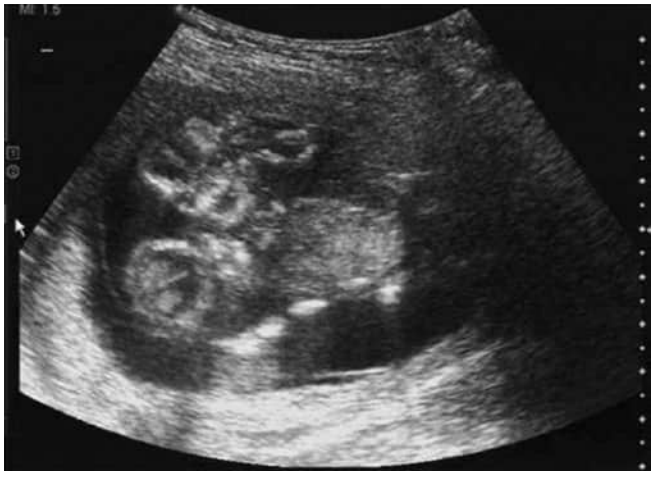


FIGURE 48-9 Sonogram of a conjoined twin pregnancy at 13 weeks' gestation. These thoracoomphalopagus twins have two heads but a shared chest and abdomen.

surface of the placenta. In contrast to these superficial connections, deep artery-to-vein communications can extend through the capillary bed of a given villus (Fig. 48-11). These deep arteriovenous anastomoses create a common villous compartment or "third circulation" that has been identified in approximately half of monochorionic twin placentas.

Whether these anastomoses are dangerous to either twin depends on the degree to which they are hemodynamically balanced. In those with significant pressure or flow gradients, a shunt will develop between fetuses. This chronic fetofetal transfusion may result in several clinical syndromes that include *twin-twin transfusion syndrome (TTTS), twin anemia–polycythemia sequence (TAPS),* and *twin reversed-arterial-perfusion (TRAP) sequence*.

Twin-Twin Transfusion Syndrome

In this syndrome, blood is transfused from a donor twin to its recipient sibling such that the donor may eventually become

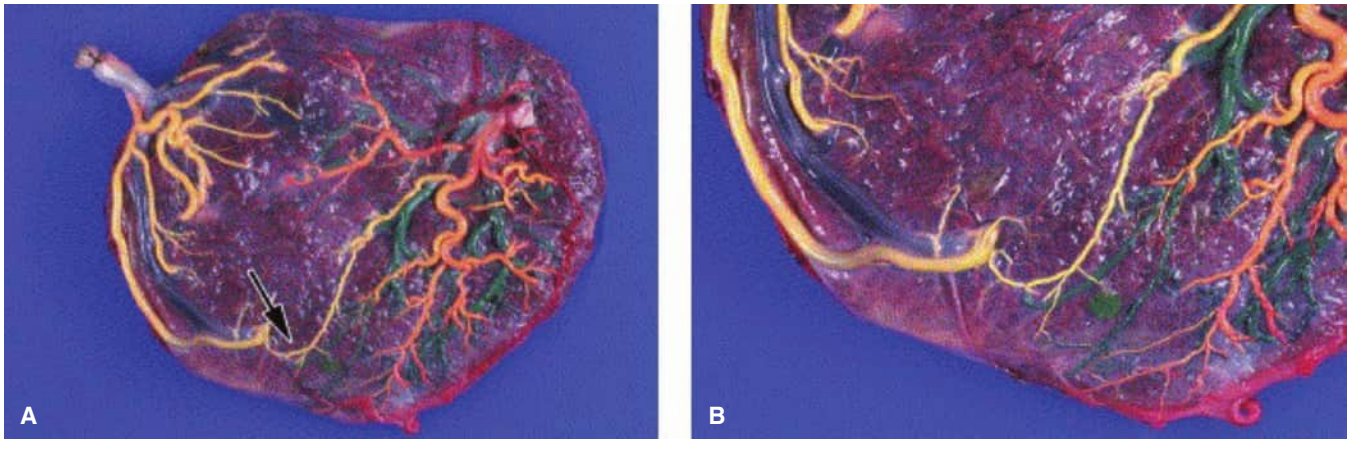


FIGURE 48-10 Shared placenta from pregnancy complicated by twin-twin transfusion syndrome. The following color code was applied for injection. Left twin: yellow = artery, blue = vein; right twin: red = artery, green = vein. **A.** Part of the arterial network of the right twin is filled with yellow dye, due to the presence of a small artery-to-artery anastomosis (*arrow*). **B.** Close-up of the lower portion of the placenta displays the yellow dye-filled anastomosis. (Reproduced with permission from De Paepe ME, DeKoninck P, Friedman RM: Vascular distribution patterns in monochorionic twin placentas, Placenta. 2005 Jul;26(6):471–475.)

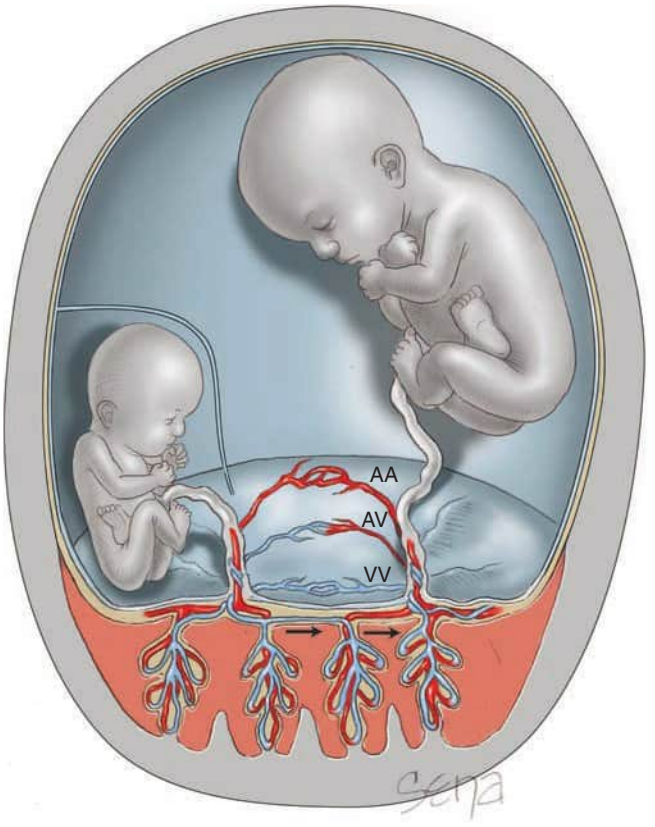


FIGURE 48-11 Anastomoses between twins may be artery-to-vein (AV), artery-to-artery (AA), or vein-to-vein (VV). Schematic representation of an AV anastomosis in twin-twin transfusion syndrome that forms a "common villous district" or "third circulation" deep within the villous tissue. Blood from a donor twin may be transferred to a recipient twin through this shared circulation. This transfer leads to a growth-restricted discordant donor twin (*left*) with markedly reduced amnionic fluid, causing it to be "stuck."

anemic and its growth may be restricted. In contrast, the recipient becomes polycythemic and may develop circulatory overload with heart failure manifest as hydrops. Classically, the donor twin is smaller and pale, and its recipient sibling is larger and has volume excess. As a result, the recipient neonate may suffer hyperviscosity and occlusive complications. Polycythemia in the recipient twin may also lead to severe hyperbilirubinemia and kernicterus (Chap. 33, p. 606). TTTS complicates 10 to 15 percent of monochorionic twins (Marwan, 2019).

Chronic TTTS results from unidirectional flow through deep arteriovenous anastomoses. Deoxygenated blood from a *donor* placental artery is pumped into a cotyledon shared by the recipient (see Fig. 48-11). Once oxygen exchange is completed in the chorionic villus, the oxygenated blood leaves the cotyledon via a placental vein of the *recipient* twin. Unless compensated—typically through superficial arterioarterial anastomoses—this unidirectional flow leads to volume depletion in the donor and volume excess in the recipient (Lewi, 2013).

TTTS typically presents in midpregnancy when the donor fetus becomes oliguric from hypovolemia and decreased renal perfusion (Society for Maternal-Fetal Medicine, 2013). This fetus develops oligohydramnios, and the recipient fetus develops severe hydramnios, presumably due to increased urine production from hypervolemia. Virtual absence of amnionic fluid in the donor sac prevents fetal motion, giving rise to the descriptive term *stuck twin* or *polyhydramnios–oligohydramnios syndrome—"poly–oli."* This amnionic fluid imbalance is associated with growth restriction, contractures, and pulmonary hypoplasia in the donor twin, and premature rupture of the membranes and heart failure in the recipient.

Fetal Brain Damage. Cerebral palsy, microcephaly, porencephaly, and multicystic encephalomalacia are serious complications associated with placental vascular anastomoses. The exact pathogenesis of neurological damage is not fully understood but is likely caused by ischemic necrosis leading to cavitary brain lesions. In the donor twin, ischemia results from hypotension, anemia, or both. In the recipient, ischemia develops from blood pressure instability and episodes of profound hypotension (Lopriore, 2011). Cerebral lesions may also be associated with preterm delivery (Chap. 34, p. 618). In one review of 315 liveborn fetuses from pregnancies with TTTS, cerebral abnormalities were found in 8 percent (Quarello, 2007).

If one twin of an affected pregnancy dies, blood is acutely transfused from high-pressure vessels of the living twin through anastomoses to low-resistance vessels of the dead twin. This leads rapidly to hypovolemia and possible ischemic antenatal brain damage in the survivor (Fusi, 1990, 1991). A less likely cause is emboli of thromboplastic material originating from the dead fetus.

The acuity of hypotension following the death of one twin with TTTS makes successful intervention for the survivor nearly impossible. Even with delivery immediately after a co-twin demise is recognized, the hypotension that occurs at the moment of death has likely already caused irreversible brain damage (Langer, 1997; Wada, 1998). As such, immediate delivery is not considered beneficial in the absence of another indication.

Diagnosis. TTTS is diagnosed based on two sonographic criteria (Society for Maternal-Fetal Medicine, 2013). First, a monochorionic pregnancy is identified. Second, hydramnios defined by a largest vertical pocket >8 cm in one sac and oligohydramnios defined by a largest vertical pocket <2 cm in the other twin is found. Growth discordance or growth restriction may be found with TTTS, but these per se are not considered diagnostic criteria.

Organizations that include the American College of Obstetricians and Gynecologists (2021b), Society for Maternal–Fetal Medicine (2013), and North American Fetal Therapy Network recommend sonographic surveillance of pregnancies at risk for TTTS (Emery, 2015). These examinations begin at approximately 16 weeks' gestation, and studies are performed every 2 weeks. In one study of 108 monochorionic twin pairs, a sonographic evaluation interval >2 weeks was associated with a higher Quintero stage at the time of TTTS diagnosis (Thorson, 2011).

Once identified, TTTS is typically classified by the Quintero (1999) staging system (Fig. 48-12):

- Stage I—discordant amnionic fluid volumes as described in the earlier paragraph, but urine is still visible sonographically within the bladder of the donor twin

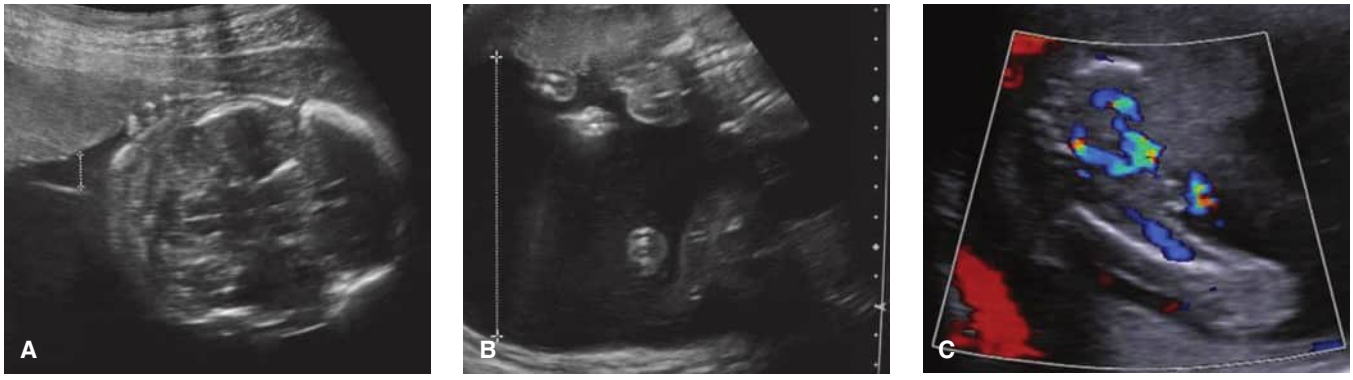


FIGURE 48-12 A. Sonogram of stage I TTTS at 19 weeks' gestation. Oligohydramnios in the donor twin sac causes the membrane to essentially wrap around the "stuck twin" and suspend it from the anterior uterine wall. **B.** In this same pregnancy, hydramnios is seen in the recipient twin sac. The measured pocket exceeds 10 cm. **C.** Stage II TTTS in a donor twin at 17 weeks' gestation. Color Doppler highlights the arteries that outline the fetal bladder, which contains no urine.

- Stage II—criteria of stage I, but urine is not visible within the donor bladder
- Stage III—criteria of stage II and abnormal Doppler studies of the umbilical artery, ductus venosus, or umbilical vein
- Stage IV—ascites or frank hydrops in either twin
- Stage V—demise of either fetus.

In addition to these criteria, cardiac function of the recipient twin also declines with TTTS (Wohlmuth, 2018). Although fetal echocardiographic findings are not part of the Quintero staging system, many centers routinely perform fetal echocardiography for TTTS. Theoretically, earlier diagnosis of fetal cardiomyopathy may identify pregnancies that would benefit from early intervention (Votava-Smith, 2015). One measure, the *myocardial performance index (MPI)*, is a Doppler index of each ventricle's function. Scoring systems that include cardiac function have been developed, but their usefulness to predict outcomes remains controversial (Miller, 2021b; Society for Maternal-Fetal Medicine, 2013).

Management and Prognosis. The prognosis for multifetal gestations complicated by TTTS is related to Quintero stage and gestational age at presentation. Some stage I cases remain stable or regress without intervention. However, 60 percent progress (Emery, 2016; Stirnemann, 2021). Conversely, outcomes in those identified at stage III or higher are much worse, and the perinatal loss rate is 70 to 100 percent without intervention (Miller, 2021b; Society for Maternal-Fetal Medicine, 2013).

Several therapies available for TTTS include laser ablation of vascular placental anastomoses, amnioreduction, and selective feticide. Similar to amniocentesis (Chap. 17, p. 344), amnioreduction is needle drainage of excess amnionic fluid.

These techniques have been evaluated in randomized trials. The Eurofetus trial included 142 women with severe TTTS diagnosed before 26 weeks' gestation. Participants were randomly assigned to laser ablation of vascular anastomoses or to serial amnioreduction (Senat, 2004). Laser ablation yielded a 76-percent rate of survival to age 6 months for at least one twin compared with a 51-percent rate with amnioreduction. Analyses of most randomized studies confirm better neonatal outcomes with laser therapy compared with selective amnioreduction (Marwan, 2019; Roberts, 2008; Rossi, 2008, 2009). However, evaluation of twins from the Eurofetus trial through 6 years of age did not demonstrate an additional survival benefit beyond 6 months or improved neurological outcomes in those treated with laser (Salomon, 2010). At this time, laser ablation of anastomoses is preferred for severe TTTS (stages II–IV). Optimal therapy for stage I disease is controversial, and laser ablation or expectant surveillance is an option (Emery, 2015; Stirnemann, 2021).

Of techniques, an ablation method may laser individual anastomoses or may ablate the entire vascular equator. This equator is the border between twin vasculature on the chorionic surface. Equatorial ablation, which is referred to as a *Solomon technique*, reduces the likelihood of TTTS recurrence. This method also lowers rates of TAPS, which can be a laser-therapy sequelae and described next (Slaghekke, 2014).

After laser therapy, close ongoing surveillance is necessary. Weekly ultrasound and Doppler studies are recommended (Marwan, 2019; Miller 2021b). These evaluations monitor fetal growth, amnionic fluid volumes, placental function, and anemia. Delivery timing is usually influenced by TTTS recurrence, fetal-growth restriction, or by abnormal Doppler velocimetry values, which reflect poor placental function (Chap. 47, p. 830).

Another treatment option, selective fetal reduction, has generally been considered if severe amnionic fluid and growth disturbances develop before 20 weeks. In such cases, both fetuses typically will die without intervention. Any substance injected into one twin may affect the other twin because of shared circulations. Thus, for the fetus chosen for reduction, feticidal methods aim to occlude the umbilical vein or umbilical cord. Radiofrequency ablation, fetoscopic ligation, or coagulation with laser, monopolar, or bipolar energy are options (Challis, 1999; Chang, 2009; Parra-Cordero, 2016). Even after these procedures, however, risks to the remaining fetus are still appreciable (Rossi, 2009). Early termination of the entire pregnancy is yet another option.

Twin Anemia–Polycythemia Sequence

Chronic fetofetal transfusion underlies this form, which is characterized by significant hemoglobin differences between donor and recipient twins. Similar to TTTS, the donor twin

in spontaneous TAPS is anemic and usually smaller than the recipient twin, which is polycythemic. However, TAPS lacks the discrepancies in amnionic fluid volumes typical of TTTS. *Spontaneous* TAPS can develop at any gestational age and complicates 1 to 6 percent of monochorionic twins (Marwan, 2019). *Iatrogenic* TAPS develops in up to 13 percent of pregnancies after laser ablation of the placenta and usually develops within 5 weeks of a procedure (Lewi, 2013; Tollenaar, 2021). In iatrogenic TAPS, the former TTTS recipient twin usually becomes anemic, whereas the former donor becomes polycythemic (Tollenaar, 2016).

Sonographically measuring blood flow velocity in the fetal middle cerebral artery (MCA) can accurately identify fetal anemia (Chap. 14, 262). Antenatally, TAPS is diagnosed by discordant MCA peak systolic velocity (PSV) values between twins. Specifically, an MCA-PSV value that is >1.5 multiples of the median (MoM) in the donor twin and <1.0 MoM in the recipient twin (Society for Maternal-Fetal Medicine, 2013). Others have suggested alternative threshold values (Khalil, 2020; Tollenaar, 2019).

A staging system for TAPS has been proposed, and higher stage is associated with increased perinatal mortality rate (Slaghekke, 2010; Tollenaar, 2021). Screening for *spontaneous* TAPS is controversial, as improvements in perinatal outcomes have not been demonstrated (Khalil, 2016; Society for Maternal-Fetal Medicine, 2013).

Management options include expectant care, delivery, laser surgery, intrauterine transfusion, selective feticide, and pregnancy termination. A clinical trial evaluating fetoscopic laser therapy for TAPS is currently ongoing. Antenatal surveillance mirrors that just described for TTTS. Again, delivery timing is usually influenced by worsening fetal growth or by abnormal Doppler velocimetry values. Postnatal treatment often requires blood transfusion for the donor twin and partial exchange transfusion of the recipient twin.

Twin Reversed-arterial-perfusion Sequence

Also known as *acardiac twinning*, this rare, serious complication of monochorionic multifetal gestation has an estimated incidence of 1 case in 35,000 births. With classic TRAP sequence, the twin pair is a normally formed donor twin that shows features of heart failure and a grossly malformed recipient twin that lacks a heart (acardius) and other structures. In one theory, the TRAP sequence is caused by a large artery-to-artery placental shunt, often also accompanied by a vein-to-vein shunt (Fig. 48-13). Within the single, shared placenta, arterial perfusion pressure of the donor twin exceeds that in the recipient twin. The recipient thus receives reversed blood flow containing deoxygenated arterial blood from its co-twin (Lewi, 2013). This "used" arterial blood reaches the recipient twin through its umbilical arteries and preferentially goes to its iliac vessels. Thus, only the lower body is perfused, and disrupted growth and development of the upper body follows. In these cases, failed head growth is called *acardius acephalus*; a partially developed head with identifiable limbs is called *acardius myelacephalus*; and failure of any recognizable structure to form is *acardius amorphous,* which is shown in Figure 48-14. Because of this vascular connection, the normal donor twin must not

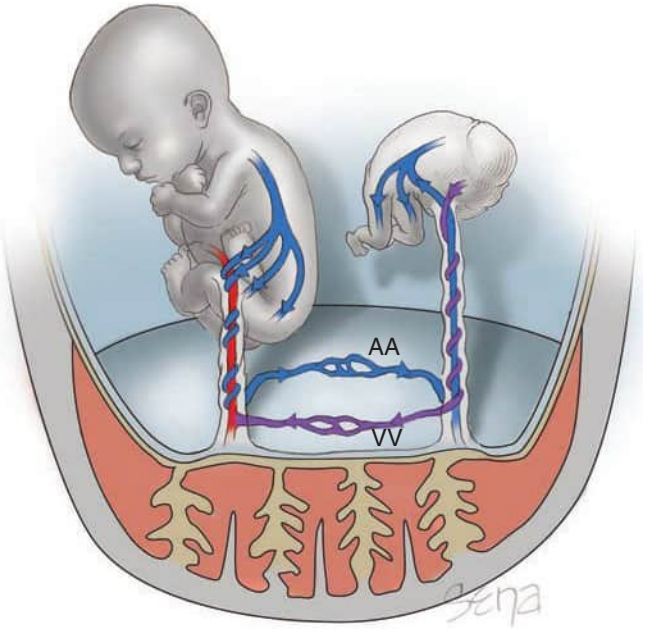


FIGURE 48-13 Twin reversed-arterial-perfusion sequence. In the TRAP sequence, there is usually a normally formed donor twin that has features of heart failure, and a recipient twin that lacks a heart. It is hypothesized that the TRAP sequence follows a large artery-to-artery placental shunt, often also accompanied by a vein-to-vein shunt. Within the single, shared placenta, perfusion pressure of the donor twin overpowers that in the recipient twin, who thus receives reverse blood flow from its twin sibling. The "used" arterial blood that reaches the recipient twin preferentially goes to its iliac vessels and thus perfuses only the lower body. This disrupts growth and development of the upper body.

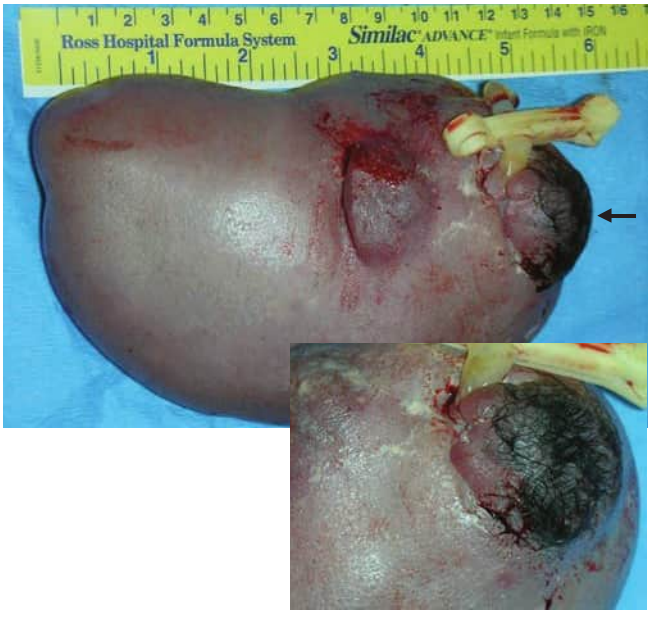


FIGURE 48-14 Photograph of an acardiac twin weighing 475 grams. The underdeveloped head is indicated by the black arrow, and its details are shown in the inset. A yellow clamp is seen on its umbilical cord. Its viable donor co-twin was delivered vaginally at 36 weeks and weighed 2325 grams. (Reproduced with permission from Dr. Michael D. Hnat.)

only support its own circulation but also must pump blood to and through the underdeveloped acardiac recipient. This may lead to cardiomegaly and high-output heart failure in the donor twin (Fox, 2007; Marwan, 2019).

In the past, the donor-twin mortality rate exceeded 50 percent. This stemmed largely from complications of prematurity or from a prolonged high-output state leading to cardiac failure (Dashe, 2001). Risk is directly related to size of the acardiac twin. When the acardiac twin is large, treatment is generally offered. Radiofrequency ablation (RFA) is the preferred modality of therapy, and contemporary reports now suggest improved perinatal outcomes. The North American Fetal Therapy Network reviewed their experiences with 98 cases from 1998 to 2008 in which RFA of the umbilical cord was performed. Median gestational age at delivery was 37 weeks' gestation, and 80 percent of donor neonates survived (Lee, 2013).

Hydatidiform Mole with Coexisting Normal Fetus

This rare gestation contains one normal fetus, and its co-twin is a complete molar pregnancy. It must be differentiated from a partial molar pregnancy, which is a singleton, triploid fetus and its placenta composed of molar tissue (Fig. 13-4, p. 238).

Diagnosis in the first half of pregnancy is common. Sonographically, a normal-appearing twin is accompanied by its co-twin, which is a large placenta containing multiple small anechoic cysts. Often, these pregnancies are terminated, but pregnancy continuation is increasingly adopted. The live birth rate from one review was 50 percent (Zilberman, 2020). The risk of gestational trophoblastic neoplasia (GTN), which is a malignant sequelae of hydatidiform mole, is similar whether the pregnancy is terminated or not (Massardier, 2009; Sebire, 2002). Given the limited number of cases, robust data for firm recommendations are lacking. Discussed in Chapter 13 (p. 237), complications of expectant management include vaginal bleeding, hyperemesis gravidarum, thyrotoxicosis, and early-onset preeclampsia. Many of these complications result in preterm birth with its attendant adverse perinatal outcomes. Logically, close antepartum and postpartum surveillance is needed for those continuing the pregnancy. Postpartum GTN surveillance is essential and described in Chapter 13 (p. 240).

DISCORDANT GROWTH

Fetal size inequality develops in approximately 15 percent of twin gestations (Miller, 2012). Generally, as the weight difference within a twin pair grows, the perinatal mortality rate rises proportionately. Earlier discordancy and monochorionicity pose increased mortality risks for the smaller twin. Specifically, with discordant growth identified at or before 20 weeks' gestation in studies, 8 to 15 percent of the growth-restricted fetuses die (Couck, 2020; Curado, 2020; D'Antonio, 2018).

Pathogenesis

The etiology of growth discordance in monochorionic twins likely differs from that in dichorionic twins. First, in monochorionic twins, the single placenta is not always equally shared, and this leads to higher discordant growth rates than in dichorionic pairs (Fig. 48-15). In cases with TTTS, discordancy in monochorionic twins is usually attributed to placental anastomoses that cause a perfusion imbalance between twins. Reduced perfusion of the donor twin can diminish placental and fetal growth (Lewi, 2013). Last, monochorionic twins at times can be discordant in size because they are discordant for structural anomalies.

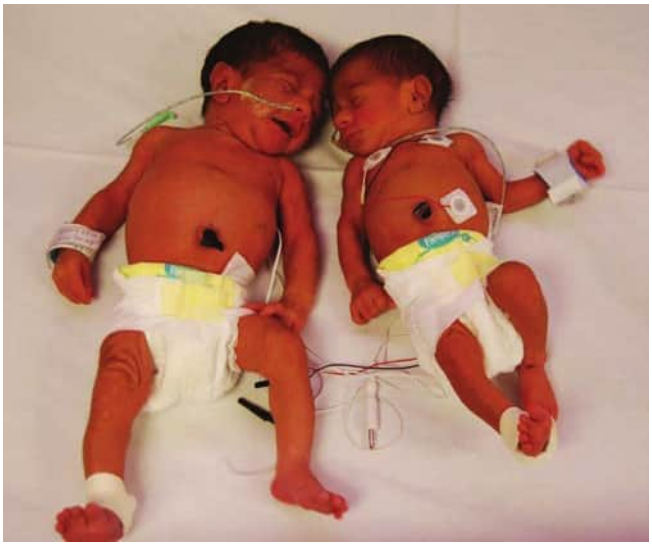


FIGURE 48-15 Marked growth discordance in monochorionic twins. (Reproduced with permission from Dr. Laura Greer.)

In dichorionic twins, discordancy may result from various factors. Dizygotic fetuses may have different genetic growth potential, especially if they are of opposite genders. Second, because the placentas are separate and require more implantation space, one placenta might have a suboptimal implantation site. Additionally, umbilical cord abnormalities such as velamentous insertion, marginal insertion, or vasa previa may play a role (Chap. 6, p. 114). One study showed that the incidence of severe discordancy is twice as great in triplets as it is in twins (Bagchi, 2006). This supports the view that in-utero crowding promotes multifetal growth restriction. Placental pathology may be contributory. In one study of 668 twin placentas, a strong relationship between histological placental abnormalities and birthweight discordancy was observed in dichorionic but not monochorionic twin pregnancies (Kent, 2012).

Diagnosis

Antenatal size discordancy between twins can be best determined sonographically. Crown-rump length differences are not reliable predictors for birthweight discordance (Miller, 2012). Thus, most discordancy surveillance begins after the first trimester. One common method uses sonographic fetal biometry to compute an estimated weight for each twin (Chap. 15, p. 274). Percent discordancy is then calculated as the weight of the larger twin minus the weight of the smaller twin, divided by the weight of the larger twin. The American College of Obstetricians and Gynecologists (2021b) defines discordance as an estimated fetal weight difference >20 percent.

Management

The risk for adverse perinatal outcomes in the setting of growth discordance remains controversial. Some suggest that twin gestations with discordant growth between two fetuses that are appropriately grown for gestational age are not at increased risk for adverse outcomes (American College of Obstetricians and Gynecologists, 2021b; Appleton, 2007). Others have shown an increased risk for adverse fetal outcomes but not for poor neonatal outcomes (Amaru, 2004; D'Antonio, 2018). However, accumulated data suggest that weight discordancy exceeding 25 to 30 percent most accurately predicts an adverse perinatal outcome (Cohen, 2001; Chen, 2019). At Parkland Hospital, twin weight-discordancy values from 1370 delivered twin pairs were stratified by percentage increments (Hollier, 1999). The incidence of respiratory distress syndrome, intraventricular hemorrhage, seizures, periventricular leukomalacia, sepsis, and necrotizing enterocolitis rose directly with the percentage of weight discordancy. Rates of these conditions grew substantially if discordancy exceeded 25 percent. The relative risk of fetal death increased significantly to 5.6 if weight discordancy was >30 percent and rose to 18.9 if >40 percent.

Nonstress testing and biophysical profile assessment have all been recommended in management of twin growth discordancy. If significant discordancy is identified in a monochorionic twin pair, umbilical artery Doppler studies in the smaller fetus may help guide management (Gratacós, 2007). Data are limited to establish the optimal timing of delivery of twins with size discordancy alone. At advanced gestational ages, delivery can be pursued.

Selective Fetal-growth Restriction

Restricted growth of one twin fetus is termed *selective fetal-growth restriction (sFGR)* and usually develops late in the second and early third trimester. Some diagnose sFGR if the abdominal circumference (AC) measurement difference exceeds 20 mm or if fetal-growth discordance is >20 percent (Khalil, 2019). If sFGR is diagnosed, weekly testing of fetal well-being, evaluation of amnionic fluid volume, and umbilical artery Doppler velocimetry are undertaken. Investigators have correlated Doppler results with placental findings and with the degree of sFGR to predict fetal outcome (Gratacós, 2012). These correlations have yielded categories of sFGR.

- Type I shows positive end-diastolic flow, a smaller degree of weight discordance, and a relatively benign clinical course.
- Type II displays persistently absent end-diastolic flow in the smaller twin and carries a high risk of deterioration and demise.
- Type III has intermittently absent or reversed end-diastolic flow. Because of large artery-to-artery anastomoses associated with the placentas in this last category, type III is associated with a lower risk of deterioration than type II. In all evaluated cases, unequally shared placenta was noted to some degree.

Serial evaluation of fetal growth is performed every 3 weeks (Chap 47, p. 829). At Parkland Hospital, daily inpatient surveillance is undertaken in women with fetal-growth restriction in one twin or with twin discordancy exceeding 25 percent in the setting of a twin with restricted growth.

FETAL DEMISE

At any time during multifetal pregnancy, one or more fetuses may die, either simultaneously or sequentially. Most causes stem from complications of fetal anomaly or chorionicity. Related to the latter, compared with dichorionic twins, monochorionic pairs suffer higher rates of sFGR, TTTS, or TAPS from unequal vascular anastomoses, and monoamnionic pairs can die from cord entanglement.

When death is early, it may manifest as a vanishing twin (p. 843). For the survivor, the risk of death after the first trimester is not increased, and the pregnancy requires no additional surveillance for this specific indication. In a slightly more advanced gestation, the dead fetus may be compressed appreciably—*fetus compressus,* or it may be flattened remarkably through desiccation—*fetus papyraceus* (Fig. 48-16).

In gestations past 20 weeks, the stillbirth rate in twins in the United States was 1.4 percent of live births and exceeded the 0.6-percent rate in singletons (MacDorman, 2015). After a *single intrauterine fetal demise (sIUFD)* in these later gestations, risks to the remaining co-twin include death, preterm birth, and neurological injury (D'Antonio, 2017; Mackie, 2019). With the last, acute hypovolemia from volume shifts within placental anastomoses occurs immediately, and neurological injury is not preventable.

Related to co-twin death, monochorionic diamnionic twins with an sIUFD were 16 times more likely to experience death of the co-twin than were dichorionic twins with an sIUFD in one large series (Morikawa, 2012). In most studies, the rate of co-twin demise after sIUFD declines after 26 to 28 weeks' gestation and with advancing gestational age (Mackie, 2019; McPherson, 2012; Southwest Thames Obstetric Research Collaborative, 2012; Wood, 2014).

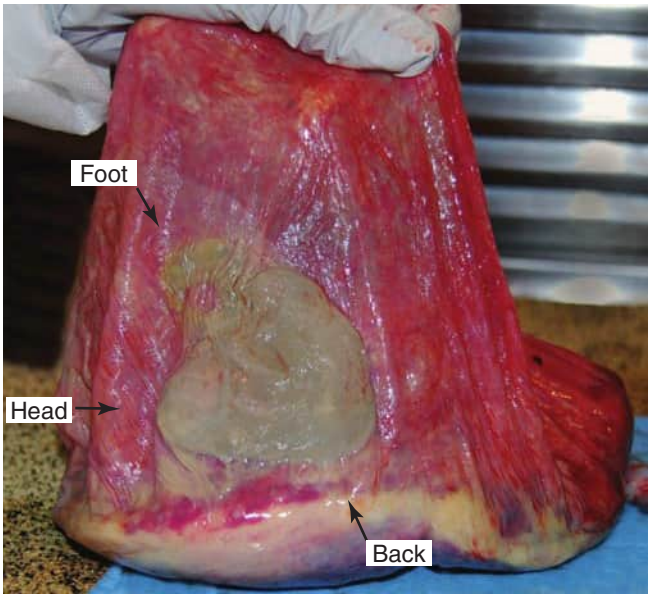


FIGURE 48-16 This fetus papyraceus is a tan ovoid mass compressed against the fetal membranes. Anatomical parts can be identified as marked. Demise of this twin had been noted during sonographic examination performed at 17 weeks' gestation. Its viable co-twin delivered at 40 weeks. (Reproduced with permission from Dr. Michael V. Zaretsky.)

The rate of preterm birth following sIUFD is increased but is similar between mono- and dichorionic twins. Advancing rates are seen at later gestational ages (D'Antonio, 2017; Ong, 2006).

The neurological prognosis for a surviving co-twin is influenced by chorionicity. In one review of diamnionic twin pregnancies complicated by sIUFD *before* 34 weeks, neurodevelopmental morbidity was 29 percent in monochorionic twins and was threefold higher than in dichorionic gestations (Mackie, 2019). In other series with sIUFD *after* 34 weeks, the likelihood of neurological deficits was essentially the same between monochorionic and dichorionic twin pregnancies (Hillman, 2011).

Because of this significant neurological risk, if one fetus of a monochorionic twin gestation dies after the first trimester but before viability, pregnancy termination can be considered (Blickstein, 2013). After viability, ultimate delivery timing balances the risk of prematurity against co-twin demise. Early management emphasizes maternal and co-twin safety and gestation prolongation (American College of Obstetricians and Gynecologists, 2021b). Antenatal corticosteroids for survivor lung maturity can be considered. For sIUFD occurring after 34 weeks' gestation, delivery is reasonable (Spong, 2011).

Last, the death of one fetus could theoretically trigger coagulation defects in the mother. Only a few cases of maternal coagulopathy after a single fetal death in a twin pregnancy have been reported. This is probably because the surviving twin is usually delivered within a few weeks of the demise (Eddib, 2006).

PRENATAL CARE

At Parkland Hospital clinics, women with multifetal gestations are seen every 2 weeks beginning at 22 weeks' gestation. One imperative is preterm delivery prevention, and a digital cervical examination is performed at each visit to screen for cervical shortening or dilation.

The maternal diet should provide additional requirements for calories, protein, minerals, vitamins, and essential fatty acids. The Institute of Medicine (IOM) (2009) recommends a 37- to 54-lb weight gain for women with twins and a normal body mass index. The daily recommended augmented caloric intake for women with twins is 40 to 45 kcal/kg/d. Diets contain 20 percent protein, 40 percent carbohydrate, and 40 percent fat divided into three meals and three snacks daily. Based on upper-intake levels from the Food and Nutrition Board of the IOM, one review endorsed supplementation of calcium, magnesium, zinc, and vitamins C, D, and E (Goodnight, 2009).

Discussed in Chapter 40 (p. 705), low-dose aspirin prophylaxis is recommended in women at high risk of preeclampsia, which includes those with a multifetal pregnancy (LeFevre, 2014). An 81-mg oral daily dose is initiated between 12 and 28 weeks' gestation and is continued until delivery (American College of Obstetricians and Gynecologists, 2020b).

Prenatal screening for fetal aneuploidy is carried out as described in Chapter 17 (p. 334). Thus, the combined test or secondary screening is done and interpreted with value thresholds set for multifetal pregnancies. Noninvasive prenatal screening with cfDNA also is acceptable (American College of Obstetricians and Gynecologists, 2020d; Judah, 2021; Khalil, 2021). Interpretation caveats for those with a vanishing twin were described earlier (p. 844).

To screen for structural anomalies, a midpregnancy anatomic sonography survey is performed. In addition, monochorionic twins undergo echocardiography because of an increased risk for cardiac anomalies (Bahtiyar, 2007). As noted earlier (p. 844), fetal growth is assessed with sonography. Amnionic fluid volume is quantified using the deepest vertical pocket in each sac. A measurement <2 cm is considered oligohydramnios, and a measurement >8 cm is considered hydramnios (Duryea, 2017; Hernandez, 2012).

Twin pregnancies are at increased risk for stillbirth compared to singleton gestations. The intrauterine fetal death rate is two- to threefold higher in monochorionic pregnancies compared with dichorionic gestations (Lee, 2008; Morikawa, 2012). Cheong-See and colleagues (2016) reported a higher stillbirth rate in monochorionic gestations compared with dichorionic gestations beyond 34 weeks' gestation. Outpatient weekly nonstress test or biophysical profile may help lower the rate of intrauterine death in twin gestations (Booker, 2015; Burgess, 2014). Weekly antenatal surveillance is undertaken at 36 weeks' gestation for uncomplicated dichorionic pregnancies and at 32 weeks' gestation or uncomplicated monochorionic gestations (American College of Obstetricians and Gynecologists, 2021a). However, all antenatal testing schemes have high false-positive rates. In cases of abnormal testing in one twin and normal results in another, iatrogenic preterm delivery remains a major concern. Therefore, patients are carefully counseled prior to initiating antenatal testing in twins.

PRETERM BIRTH

Gestational length shortens and preterm birth risk rises with accruing fetal number. In 2019 in the United States, the preterm birth rate in twins and triplets was 60 and 98 percent, respectively (Martin, 2021). One review showed that approximately 60 percent of preterm births in twins are indicated, a third result from spontaneous labor, and 10 percent follow preterm prelabor rupture of membranes (PPROM) (Chauhan, 2010).

Of risks, preterm birth rates vary with chorionicity and are higher with monochorionic compared with dichorionic twins. Other implicated factors are prior preterm birth, adolescence, nulliparity, obesity, and diabetes (Marleen, 2018, 2021).

Prediction

One goal of multifetal prenatal care is to identify women likely to experience preterm delivery. To and associates (2006) sonographically measured cervical length in 1163 twin pregnancies at 22 to 24 weeks' gestation. Rates of preterm delivery before 32 weeks were 66 percent in those with cervical lengths of 10 mm; 24 percent for lengths of 20 mm; and only 1 percent for lengths of 40 mm. In one review, a cervical length <20 mm was most accurate for predicting birth before 34 weeks' gestation. The specificity was 97 percent, and positive likelihood ratio was 9.0 (Conde-Agudelo, 2010). Notably, a closed

internal os by digital examination predicted postponed delivery equally well as the combination of a normal sonographically measured cervical length and negative fetal fibronectin test result (McMahon, 2002).

Unfortunately, cervical length assessment in twin pregnancies has not led to improved outcomes (Gordon, 2016). The Society for Maternal–Fetal Medicine (2016) recommends against routine cervical length screening in multifetal gestations.

Fetal fibronectin levels also may predict preterm birth (Marleen, 2020). Again, neonatal outcomes are not improved in twins, and this screening tool is not recommended (American College of Obstetricians and Gynecologists, 2021b).

Prevention

Bed Rest

In general, most strategies for preterm birth prevention are ineffective for singleton and multifetal pregnancies (American College of Obstetricians and Gynecologists, 2021b). Of options, bed rest with or without hospitalization does not prolong multifetal pregnancy. In one metaanalysis, the practice did not reduce the risk of preterm birth (da Silva Lopes, 2017). At Parkland Hospital, elective hospitalization was compared with outpatient management, and no advantages were found (Andrews, 1991). Importantly, however, almost half of women managed as outpatients required admission for specific indications such as hypertension or threatened preterm delivery.

Limited physical activity, early work leave, more frequent health-care visits, serial sonographic examinations, and structured maternal education regarding preterm delivery risks have been advocated to reduce preterm birth rates in women with multiple fetuses. However, little evidence suggests that these practices substantially change this outcome.

Prophylactic Tocolysis

This has not been studied extensively in multifetal pregnancies. In one review of prophylactic oral beta-mimetic therapy that included 374 twin pregnancies, treatment did not reduce the rate of twins delivering before 37 or before 34 weeks' gestation (Yamasmit, 2015). In light of the Food and Drug Administration warning against the use of oral terbutaline because of maternal side effects, the prophylactic use of beta-mimetic drugs in multifetal gestations seems unwarranted.

Progesterone Therapy

17-alpha-hydroxyprogesterone caproate (17-OHPC) injections are not effective for multifetal gestations (Caritis, 2009; Combs, 2011; Rouse, 2007). Moreover, women carrying twins and having a cervical length <36 mm or a length <25 mm did not benefit despite their greater risk for preterm birth (Durnwald, 2010; Senat, 2013).

Vaginal micronized progesterone in various formulations in randomized studies has also proved ineffective for preterm birth prevention before 34 weeks in a general twin population (Norman, 2009; Rode, 2011). For women with a short cervix, subgroup analysis and a metaanalysis show conflicting results regarding benefits (D'Antonio, 2021; Klein, 2011; Rehal, 2021). At Parkland Hospital, current management of multifetal gestations does not typically include any progesterone therapy.

Cervical Cerclage

Prophylactic cerclage does not improve perinatal outcome in women with twin pregnancies. Studies have included women with and without a short cervix (D'Antonio, 2021; Jarde, 2017; Newman, 2002). *Physical examination–indicated cerclage* in women with a second-trimester twin gestation and a dilated cervix may be beneficial. Roman and coworkers (2016, 2020) reported that women undergoing rescue cerclage plus prophylactic antibiotic and indomethacin administration before 24 weeks' gestation had lower preterm birth and perinatal mortality rates than those without a cerclage.

Pessary

The silicone Arabin vaginal pessary encircles and theoretically compresses the cervix, alters the inclination of the cervical canal, and relieves direct pressure on the internal cervical os. In a study of its use in women with a short cervix between 18 and 22 weeks' gestation, a subgroup analysis of 23 women with twins showed a significant reduction in the delivery rate before 32 weeks compared with the rate in 23 control pregnancies (Arabin, 2003). In another randomized trial of twins, women treated with a cervical pessary had significantly fewer births before 34 weeks (Goya, 2016).

Other randomized studies comparing pessary against expectant care are less favorable. In one trial with 1180 uncomplicated twin pregnancies, pessary use failed to alter the preterm birth rate (Nicolaides, 2016). Another trial of 813 unselected women had similar findings. However, delivery rates before 32 weeks were lower—29 versus 14 percent—in a subset of women with a cervical length <38 mm (Liem, 2013). Instead, other trials show no benefit from pessary use in this subgroup (Nicolaides, 2016; Norman, 2021). At this time, pessary use is not recommended by the American College of Obstetricians and Gynecologists (2021b).

Treatment

Tocolytic therapy to help halt preterm labor in multifetal pregnancy does not measurably improve neonatal outcomes (Canadian Preterm Labor Investigators Group, 1992; Yamasmit, 2015). Moreover, tocolytic therapy in women with a multifetal pregnancy entails higher maternal risk than in singleton pregnancy. This stems in part from augmented pregnancy-induced hypervolemia, which raises cardiac demands and increases the susceptibility to iatrogenic pulmonary edema (Chap. 50, p. 883). In one study, all women with a multifetal gestation treated with a beta-mimetic drug for preterm labor had more cardiovascular complications—43 versus 4 percent—than women with singletons (Gabriel, 1994). In a retrospective analysis, nifedipine tocolysis in 58 singleton and 32 twin pregnancies led to higher incidences of side effects such as maternal tachycardia in women with twins—19 versus 9 percent (Derbent, 2011).

Antenatal corticosteroids for fetal lung maturation have not been well studied in multifetal gestations. Of studies, many compare outcomes among singletons and twins whose

mothers either did or did not receive this therapy. In one large retrospective study evaluating betamethasone, neonatal morbidity rates were reduced in both twin and singleton treated groups (Melamed, 2016). Another similar comparison found reduced rates of periventricular hemorrhage rates in treated groups but not improved respiratory distress syndrome (RDS) rates (Gonçalves-Ferri, 2021). Similarly, in another study, short-term neurological outcome was better in treated twin and singletons, but rates of mortality, RDS, and cerebral palsy were not reduced (Ushida, 2020). However, in one study solely with twins, the rate of RDS or of composite neonatal morbidity was not lower with corticosteroid therapy (Viteri, 2016). These authors posited pharmacokinetics in twin gestation as a potential explanation. Currently, recommended use of agents is the same for multifetal and singleton gestations (American College of Obstetricians and Gynecologists, 2021b). This therapy is described fully in Chapter 45 (p. 802).

Preterm Prelabor Membrane Rupture

The frequency of PPROM rises with increasing plurality. In a population-based study of more than 290,000 live births, the proportion of preterm birth complicated by PPROM was 13 percent in singletons. This rate was 17, 20, 20, and 100 percent in twins, triplets, quadruplets, and higher-order multiples, respectively (Pakrashi, 2013). For both twin and singleton pregnancies, most studies show comparable neonatal risk with expectant management, which is outlined in Chapter 45 (p. 798) (Kibel, 2017). However, the time between births, often termed *latency*, is shorter with twins. With PPROM after 24 weeks' gestation, the median number of days to subsequent delivery was 4 days for twins compared with 7 days for singletons in one study (Madden, 2021). After 30 weeks' gestation, this latency for twins is significantly shortened (Mercer, 1993).

Delayed Delivery of Second Twin

Rarely, after preterm birth of one fetus, it may be advantageous for undelivered fetus(es) to remain in utero. This may be especially so at periviable gestational ages. However, this advantage must be balanced against substantial maternal risk. In one systematic review, nearly 40 percent of mothers suffered complications with delayed delivery (Cheung, 2020). These include infection, postpartum hemorrhage, and placental abruption.

From population-based data of delayed deliveries, the median latency duration was 6 days (range 6 to 107 days) in 200 twin pregnancies (Zhang, 2004). In all studies, retained fetuses had better overall survival rates than the first-born neonate. In one series of 38 twins, the mean latency was 19 days. Of first-born twins born at <25 weeks' gestation, none survived, but 50 percent of their co-twins did. Beyond 25 weeks, survival rates were 65 for first-born and 95 percent for second-born twins (Arabin, 2009). In their series of 28 twin pairs, cerclage, antibiotic therapy, and tocolysis did not improve outcomes (Fayad 2003).

If delayed delivery is attempted, counseling should include the potential for serious maternal complications. The range of gestational age for which benefits outweigh the risks for delayed delivery is likely narrow, and gestations of 22 to 24 weeks would seem the most probable to benefit (Oyelese, 2005). In our experience, good candidates for delayed delivery are rare.

LABOR AND DELIVERY

Delivery Timing

Several factors affect this timing and include gestational age, fetal growth, maternal complications, lung maturity, and stillbirth risk. The substantially greater stillbirth rate in monochorionic monoamnionic twins was discussed earlier (p. 845). In dichorionic diamnionic twins, stillbirth rates rose to 10.6 deaths per 1000 pregnancies at $38^{6/7}$ weeks' gestation in a systematic review of more than 30,000 twin pairs. The peak rate in monochorionic diamnionic twins was 9.6 deaths per 1000 pregnancies at $37^{6/7}$ weeks (Cheong-See, 2016).

In uncomplicated twins, stillbirth risk is balanced against the morbidity of prematurity. Pulmonary maturation is usually synchronous in twins and occurs several weeks earlier than in singletons (Leveno, 1984). However, in some cases, pulmonary function may differ. With sFGR, the smaller, stressed twin has lower rates of RDS but higher rates of bronchopulmonary dysplasia (Groene, 2021).

The American College of Obstetricians and Gynecologists (2021b) recommends delivery at $38^{0/7}$ to $38^{6/7}$ weeks' gestation for uncomplicated dichorionic diamnionic twin pregnancies. Uncomplicated monochorionic diamnionic twin pregnancies can be delivered between $34^{0/7}$ and $37^{6/7}$ weeks. For monochorionic monoamnionic twin pregnancies, delivery is recommended at $32^{0/7}$ to $34^{0/7}$ weeks. At Parkland Hospital, we generally follow these recommendations and do not routinely deliver monochorionic diamnionic twin pregnancies before 37 weeks unless another obstetrical indication develops.

Preparations

A litany of complications may be encountered during labor and delivery of multiple fetuses. Rates of uterine contractile dysfunction, abnormal fetal presentation, umbilical cord prolapse, placenta previa, placental abruption, emergent operative delivery, and postpartum hemorrhage rates from uterine atony are higher. Moreover, second twins at term have worse composite neonatal outcomes compared with outcomes of their co-twin regardless of delivery method (Smith, 2007; Thorngren-Jerneck, 2001). All of these must be anticipated, and thus certain precautions and special arrangements are prudent. These include the following:

1. An appropriately trained obstetrical attendant should remain with the mother throughout labor. Continuous electronic monitoring is preferable. If membranes are ruptured and the cervix dilated, the presenting fetus is monitored internally.

2. An intravenous infusion system capable of delivering fluid rapidly is established. In the absence of hemorrhage, lactated Ringer or an aqueous dextrose solution is infused at a rate of 60 to 125 mL/hr.
3. Blood for transfusion is readily available if needed.
4. An obstetrician skilled in intrauterine identification of fetal parts and in intrauterine manipulation of a fetus should be present.
5. A sonography machine is readily available to evaluate the presentation and position of the fetuses during labor and to image the remaining fetus after delivery of the first.
6. An anesthesia team is immediately available in the event that emergent cesarean delivery is necessary or that intrauterine manipulation is required for vaginal delivery.
7. For each fetus, at least one attendant who is skilled in resuscitation and care of newborns and who has been appropriately informed of the case should be immediately available.
8. The delivery area should provide adequate space for the nursing, obstetrical, anesthesia, and pediatric team members to work effectively. Equipment must be on site to provide emergent anesthesia, operative intervention, and maternal and neonatal resuscitation.

Analgesia and Anesthesia

For multifetal pregnancies, decisions regarding analgesia and anesthesia must factor planned route of delivery. Other potential problems may stem from preterm labor, preeclampsia, desultory labor, need for intrauterine manipulation, and postpartum uterine atony and hemorrhage.

Labor epidural analgesia is ideal because it provides excellent pain relief and can be rapidly extended cephalad if internal podalic version or cesarean delivery is required. If general anesthesia becomes necessary for intrauterine manipulation during vaginal birth, uterine relaxation can be accomplished rapidly with a halogenated inhalation agent (Chap. 25, p. 481). Some clinicians use intravenous or sublingual nitroglycerin or intravenous terbutaline to achieve uterine relaxation. If used, these agents are usually best administered by the anesthesia team.

Fetal Presentation

For labor and delivery, the fetal presentations are best determined sonographically. If active labor is confirmed, the decision for vaginal or cesarean delivery is reached, and fetal presentation is a major factor. Among the possible presentation combinations, those most common at admission for delivery are cephalic-cephalic, cephalic-breech, and cephalic-transverse. At Parkland Hospital between 2008 and 2013, 71 percent of twin pregnancies had a cephalic presentation of the first fetus at the time of labor and delivery admission. During parturition, fetal presentation of a second twin can be unstable. For them, compound or footling breech presentations and face or brow attitudes are relatively common and even more so if fetuses are small or numerous, amnionic fluid is excessive, or maternal parity is high. Cord prolapse also is frequent in these circumstances.

Delivery Route

Cephalic First Twin

With *cephalic–cephalic presentation*, general consensus supports consideration of vaginal birth in a laboring woman near term (American College of Obstetricians and Gynecologists, 2021b; D'Alton, 2010). From studies, planned cesarean delivery does not improve neonatal outcome when both twins are cephalic (de Castro, 2016; Schmitz, 2017). With trials of labor, vaginal delivery rates approximate 80 percent.

With *cephalic–noncephalic* presentation, the optimal delivery route remains controversial. Patient selection and provider expertise with vaginal breech delivery is crucial and described in Chapter 28 (p. 527). As a result, one common option is cesarean delivery of both twins. Less often, after spontaneous vaginal delivery of a first twin, intrapartum external cephalic version of the second twin can be performed. In case series, this practice, compared with internal podalic version, was associated with higher rates of intrapartum cesarean delivery and fetal distress (Gocke, 1989; Smith 1997). With internal podalic version, a hand placed into the uterus grasps fetal feet to deliver the fetus by breech extraction (Fig. 48-17). Last and least desirable is vaginal delivery of the first but cesarean delivery of the second twin due to intrapartum complications. These are umbilical cord prolapse, placental abruption, contracting cervix, or nonreassuring fetal heart rate. Most but not all studies report the worst composite fetal outcomes for this scenario (Alexander, 2008; Rossi, 2011).

For cephalic–noncephalic twins, each with birthweights >1500 g and gestational ages >32 weeks, several reports attest to the safety of vaginal delivery. In one study of 5915 pregnancies with a cephalic first twin and either cephalic or noncephalic second twin, 25 percent planned for cesarean delivery (Schmitz, 2017). The other 75 percent planned a trial of vaginal delivery, which was successful in 80 percent. Interestingly, perinatal mortality and morbidity rates were significantly higher in the planned cesarean delivery group delivered at <37 weeks—5.2 versus 3.0 percent, respectively. Additionally, for those delivered vaginally, neonatal outcomes were similar for second

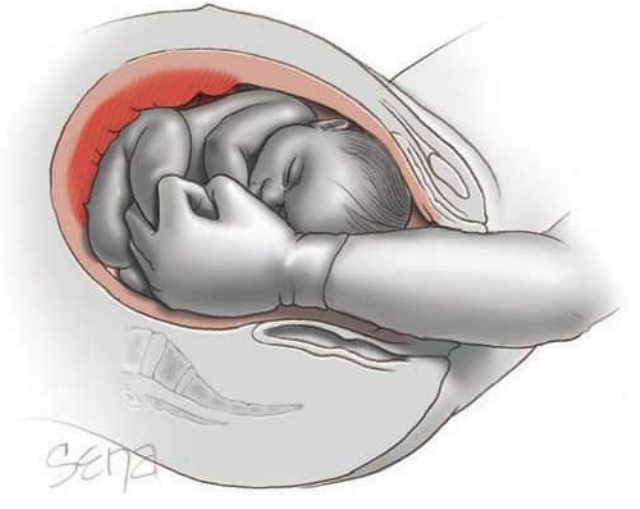


FIGURE 48-17 Internal podalic version. Upward pressure on the head by an abdominal hand is applied (not shown) as downward traction is exerted on the feet.

twins that were cephalic or noncephalic (Schmitz, 2018). The Twin Birth Study had similar inclusion criteria and randomly assigned women to planned vaginal or planned cesarean delivery. Perinatal outcomes were similar in both groups. For those delivered vaginally, neonatal outcomes were similar for second twins that were cephalic or noncephalic (Barrett, 2013).

For neonates weighing <1500 g compared with those weighing more, comparable or even better fetal outcomes with vaginal delivery compared with cesarean delivery have been reported (Mol, 2020; Sentilhes, 2015). However, rates of urgent operations for the second twin may be higher (Hiersch, 2021).

Other investigators advocate cesarean delivery for both fetuses of a cephalic–noncephalic twin pair (Armson, 2006; Hoffmann, 2012). Yang and coworkers (2005a,b) studied 15,185 cephalic–noncephalic pairs. The risks of asphyxia-related neonatal deaths and morbidity were higher in the group in which both twins were delivered vaginally compared with the group in which both twins were delivered surgically.

Breech First Twin

Problems with the first twin presenting as a breech are similar to those encountered with a singleton breech fetus. First, the fetal body can be small, and delivery of the extremities and trunk through an inadequately effaced and dilated cervix can leave the relatively larger head trapped above the cervix. This is more likely when disproportion between the head and body is significant. Examples are preterm or growth-restricted fetuses or those with macrocephaly from hydrocephaly. Second, umbilical cord prolapse is an ever-present risk. Last, twin fetuses may become locked together during delivery if the first presents breech and the second cephalic. As the breech of the first twin descends through the birth canal, the chin locks between the neck and chin of the second cephalic-presenting co-twin. This phenomenon is rare, and Cohen and coworkers (1965) described it only once in 817 twin gestations.

If these problems are anticipated or identified, cesarean delivery is often preferred with a viable-sized fetus. Even without these problems, many obstetricians perform cesarean delivery if the first twin presents as breech, and this is our practice. However, data support the safety of vaginal delivery for twins older than 32 weeks and weighing >1500 g (Blickstein, 2000). In one study, cesarean delivery was planned in 1169 such pairs. Vaginal delivery was planned in 298 pairs and was successful in 64 percent. Cesarean delivery of the second twin was done in 1 percent. Neonatal mortality or morbidity measures did not differ between delivery groups (Korb, 2020).

Labor Augmentation or Induction

In general, active labor with twins progresses more slowly in both nulliparas and multiparas compared with that in singletons (Hochler, 2021). Second-stage labor of the first twin also is longer (Levin, 2021).

In women with twins who meet all criteria for oxytocin administration, *labor augmentation* is suitable (Chap. 26, p. 492). For *labor induction*, studies have found that oxytocin alone or in combination with cervical ripening can safely be used in twin gestations (Hamou, 2016; Ko, 2014). Compared with prelabor cesarean delivery, others have found higher maternal morbidity rates with labor induction, and ultimate cesarean delivery rates approximate 40 percent (Dougan, 2020; Grossman, 2021). In an analysis of twin births in the United States, induction rates of twin pregnancies have declined from nearly 14 percent in 1999 to 10 percent in 2008 (Lee, 2011). Generally, at Parkland Hospital we do not augment or induce labor in women with a multifetal gestation. Concerns include risks for uterine rupture from an overdistended uterus and postpartum hemorrhage. In suitable candidates with a strong desire for vaginal birth, amniotomy induction has been one option.

Vaginal Delivery

After delivery of the firstborn, one clamp is placed near the neonate, and another is placed nearer the placenta. Until the last fetus is delivered, each cord must remain clamped to prevent fetal hypovolemia and anemia caused by blood leaving the placenta via anastomoses and then through an unclamped cord. Cord blood is generally not collected until after delivery of all fetuses. After the second neonate is delivered, *two* plastic clamps are placed on the placenta's cord to differentiate it from the first. In higher-order deliveries, color-tagged or alphabetically labeled clamps can be simpler than adding additional clamps. This same practice holds for cesarean delivery. At this time, evidence is insufficient to recommend for or against delayed umbilical cord clamping in multifetal gestations (American College of Obstetricians and Gynecologists, 2020a).

Following vaginal delivery of the first twin, the presenting part of the second twin, its size, and its relationship to the birth canal should be quickly ascertained by combined abdominal, vaginal, and, at times, intrauterine examination. Sonography is a valuable aid. If the fetal head or the breech is fixed in the birth canal, moderate fundal pressure is applied and membranes are ruptured. Immediately afterward, digital examination of the cervix is repeated to exclude cord prolapse. Labor is allowed to resume. If contractions do not begin within approximately 10 minutes, dilute oxytocin may be used to stimulate contractions.

The preferred interval between delivery of the first and second twins is frequently cited as <30 minutes. In some studies, longer intertwin intervals are associated with poorer outcome of the second twin (Leung, 2002; Stein, 2008). Others have correlated fetal heart rate tracing abnormalities during the intertwin interval rather than its length with poorer outcome (Algeri, 2019).

If the occiput or breech presents immediately over the pelvic inlet, but is not fixed in the birth canal, the presenting part can often be guided into the pelvis by one hand in the vagina, while a second hand on the uterine fundus exerts moderate pressure caudally. A presenting shoulder may be gently converted into a cephalic presentation. Alternatively, with abdominal manipulation, an assistant can guide the presenting part into the pelvis. Sonography can aid guidance and allow heart rate monitoring.

If the occiput or breech is not over the pelvic inlet and cannot be so positioned by gentle pressure or if appreciable uterine bleeding develops, delivery of the second twin can be problematic. To obtain a favorable outcome, an obstetrician skilled in intrauterine fetal manipulation and anesthesia personnel skilled

in providing anesthesia to effectively relax the uterus for vaginal delivery of a noncephalic second twin are essential (American College of Obstetricians and Gynecologists, 2021b). To take maximum advantage of the dilated cervix before the uterus contracts and the cervix retracts, delay should be avoided. Prompt cesarean delivery of the second fetus is preferred if no one present is skilled in the performance of internal podalic version or if anesthesia that will provide effective uterine relaxation is not immediately available.

Trial of Labor after Cesarean Delivery

The main concern with trial of labor after cesarean delivery (TOLAC) is uterine rupture from a distended uterus. One metaanalysis found rates of rupture and of successful vaginal birth were comparable with those for TOLAC in singleton gestations (Kabiri, 2019). Other studies also support the safety of TOLAC for selected women with twins (Cahill, 2005; Ford, 2006). In one assessment of 186 women undergoing TOLAC, two thirds delivered both twins vaginally. Of failed attempts, 45 percent underwent cesarean for delivery of the second twin (Varner, 2005). According to the American College of Obstetricians and Gynecologists (2019), evidence currently does not suggest an increased risk of uterine rupture, and women with twins and one previous cesarean delivery with a low transverse incision may be considered TOLAC candidates. At Parkland Hospital, we recommend repeat cesarean delivery.

Cesarean Delivery Technique

Several unusual intraoperative problems can arise during cesarean delivery of twins or higher-order multiples. Supine hypotension is common, and thus gravidas are positioned in a left lateral tilt to deflect uterine weight off the aorta. A low transverse hysterotomy is preferable if the incision can be made large enough to allow atraumatic delivery of all fetuses. Piper forceps can be used if a second twin is presenting breech. In some cases, a vertical hysterotomy beginning as low as possible in the lower uterine segment may be advantageous. For example, if a fetus is transverse with its back down and the arms are inadvertently delivered first, it is much easier and safer to extend a vertical uterine incision upward than to extend a transverse incision laterally or to make a "T" incision vertically.

Triplet or Higher-order Gestation

Fetal heart rate monitoring during labor with triplet pregnancies is challenging. A scalp electrode can be attached to the presenting fetus, but it is difficult to ensure that the other two fetuses are each being monitored separately. With vaginal delivery, the first neonate is usually born with little or no manipulation. Subsequent fetuses, however, are delivered according to the presenting part. This often requires complicated obstetrical maneuvers such as total breech extraction with or without internal podalic version or even cesarean delivery. Associated with malposition of fetuses is an increased incidence of cord prolapse. Moreover, reduced placental perfusion and hemorrhage from separating placentas are more likely during delivery.

Data from the Consortium on Safe Labor found that only 17 percent of women with triplet gestation attempting vaginal birth were actually delivered vaginally. In these births, composite neonatal morbidity rates were increased (Lappen, 2016). In 7000 triplet pregnancies, vaginal delivery also was associated with a higher perinatal mortality rate (Vintzeleos, 2005). For all these reasons, we deliver most pregnancies complicated by three or more fetuses by cesarean delivery. Vaginal delivery is reserved for those circumstances in which survival is not expected because fetuses are markedly immature or abnormal or maternal complications make cesarean delivery hazardous to the mother. Centers for Disease Control and Prevention (2009) national data show that 94 percent of triplets are delivered by cesarean.

Other cases series describe more positive outcomes (Grobman, 1998; Peress, 2019). In sum, the American College of Obstetricians and Gynecologists (2021b) notes vaginal birth may be considered for uncomplicated triplet pregnancies, if the first fetus is cephalic and attendants are experienced with multifetal vaginal birth. As with twins, candidate fetuses should weigh >1500 g.

REDUCING FETAL NUMBER

For multifetal gestations, *multifetal pregnancy reduction (MPR)* aims to lower fetal number to improve survival rates of the remaining fetuses. Instead, with *selective reduction*, early pregnancy intervention focuses on a fetus with an anomaly or serious health risk. With *selective termination*, the indications are analogous to those for selective reduction, but interventions are performed at a later gestational age (American College of Obstetricians and Gynecologists, 2020c).

Selective reduction or MPR is typically done in the late first trimester. This gestational age is chosen because most spontaneous abortions have already occurred, the remaining fetuses are large enough to be evaluated sonographically, the amount of devitalized fetal tissue remaining after the procedure is small, and the risk of aborting the entire pregnancy as a result of the procedure is low.

Skill in sonographically guiding needles through the mother's abdomen and uterus is required. For reductions of fetuses with their own chorion, potassium chloride is used and is injected into the fetal heart or thorax. Entering or traversing the sacs of fetuses picked for retention is avoided. For monochorionic fetuses and potentially shared vasculature, cord-occlusion is used, and with radiofrequency ablation (RFA), the needle is inserted into the intrafetal portion of the umbilical cord.

Before reduction procedures, discussion should include the morbidity and mortality rates associated with expectant care, entire pregnancy termination, or selective fetal reduction (American College of Obstetricians and Gynecologists, 2020c). With these options, specific risks include (1) loss of all remaining fetuses, (2) abortion or retention of the wrong fetus, (3) damage without death to a fetus, (4) preterm labor, (5) fetuses with discordant or growth restriction, and (6) maternal complications. With reduction procedures, uncommon potential complications are infection, hemorrhage, or disseminated intravascular coagulopathy because of retained products of conception.

Multifetal Pregnancy Reduction

In most cases of MPR, higher-order gestations are reduced by one or more fetuses. With triplets, reduction to twins or a singleton lowers the rate of preterm birth before 34 weeks compared with expectant management. Miscarriage rates are not higher (Anthoulakis, 2017; Morlando, 2015). With even higher-order multiples, spontaneous loss and preterm birth rates also decline after MPR (Evans, 2014; Liu, 2020).

Twin gestations also may be reduced to a singleton pregnancy. Maternal comorbidities or concerns for monochorionic twin complications, described earlier, are frequent indications (Rao, 2021; Vieira, 2019).

Selective Reduction or Selective Termination

If multiple fetuses are discordant for anatomical or genetic anomalies, elimination of the abnormal fetus is an option. Other indications are severe TTTS, TAPS, TRAP, or sFGR. Because abnormalities are often not fully delineated until the second trimester, selective termination is performed later in gestation than selective reduction and entails greater risk. This procedure is therefore usually not performed unless the abnormality is severe but not lethal. In some cases, termination is considered because the abnormal fetus may jeopardize the normal one.

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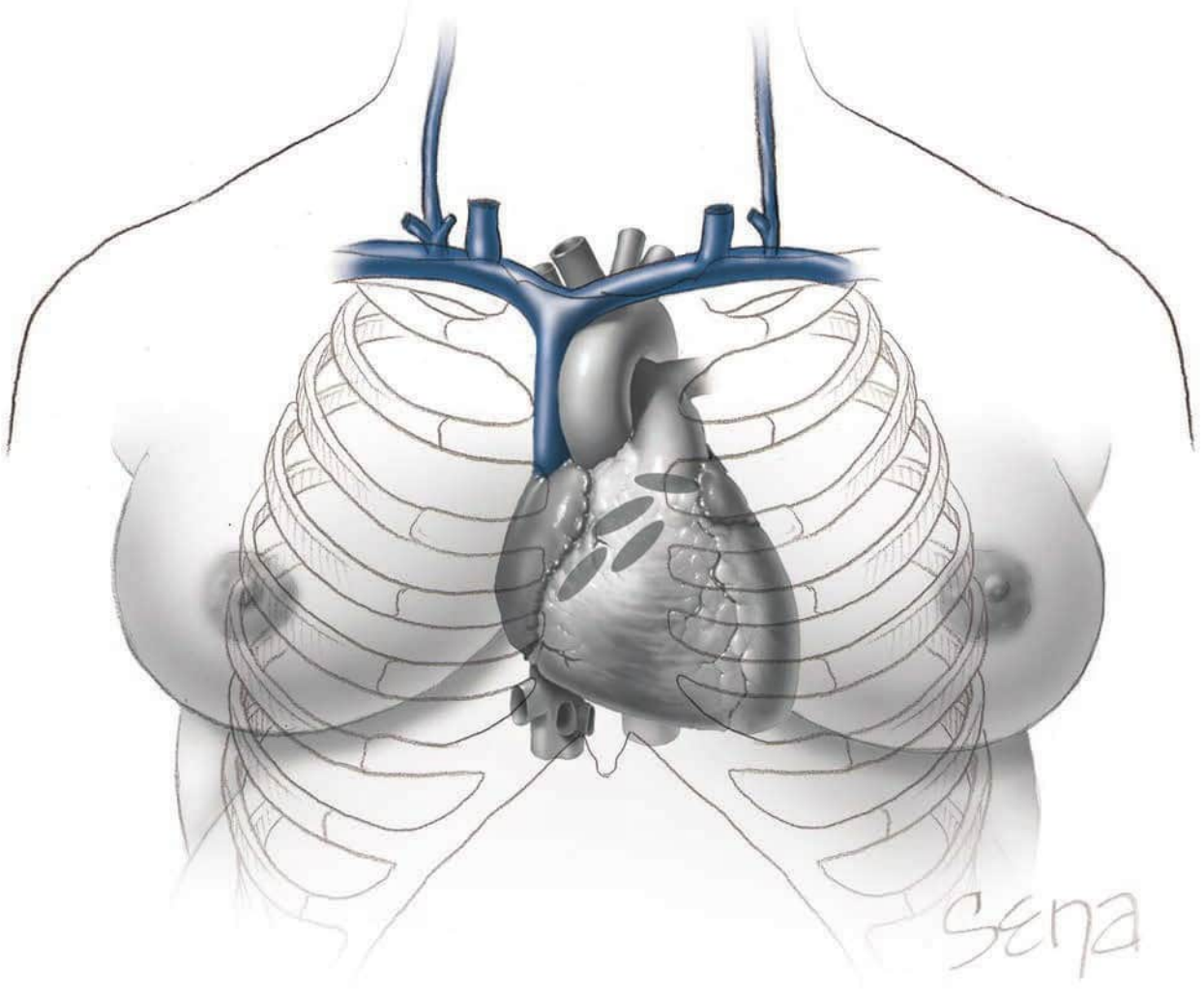
SECTION 12

MEDICAL AND SURGICAL COMPLICATIONS



CHAPTER 49

General Considerations and Maternal Evaluation

Pregnant women are susceptible to any medical and surgical disorder that can affect women of childbearing age. Chronic illnesses often precede pregnancy, and an acute condition can complicate an otherwise normal pregnancy. Both chronic and acute disorders raise the risk for antepartum hospitalization. Approximately 10 per 100 pregnant women incur an antepartum admission, and one third are for nonobstetrical conditions that include renal, pulmonary, and infectious diseases (Gazmararian, 2002). The hospitalization rate due to trauma approximates 4 admissions per 1000 deliveries (Kuo, 2007). Those with intellectual and developmental disabilities have a higher incidence of hospitalization (Mitra, 2018). Last, 1 to 2 percent of pregnant women will undergo a nonobstetrical surgical procedure (Tolcher, 2018).

Obstetricians should have a working knowledge of the wide-ranging medical disorders common to childbearing-aged women. Many of these are within the purview of the general obstetrician. Other disorders, however, will warrant consultation with specialists in maternal-fetal medicine, and still others require a multidisciplinary team. The latter may include internists and medical subspecialists, surgeons, and anesthesiologists (Levine, 2016). The Society for Maternal-Fetal Medicine (2014) has redefined aspects of maternal care and proposed conditions requiring specialized care.

Treatment should never be withheld because a woman is pregnant. To ensure this and allow for individualized care, several questions must be addressed:

- What management would be recommended if the woman were not pregnant?
- If the proposed management is different because the woman is pregnant, can this be justified?
- What are the risks and benefits to the mother and her fetus, and are they counter to each other?
- Can an individualized management plan be devised that balances risks versus benefits?

MATERNAL PHYSIOLOGY AND LABORATORY VALUES

Pregnancy induces physiological changes in virtually all organ systems. Many of these are discussed in Chapter 4 and in the subsequent chapters in this section. In turn, numerous laboratory test results also are normally altered. Some values would be considered abnormal in the nonpregnant woman. Conversely, some may appear to be within a normal range but are decidedly abnormal for the gravida. These changes may complicate the evaluation of coexisting conditions. To aid interpretation, normal laboratory values in pregnancy are listed in the Appendix (p. 1227).

MEDICATIONS

Fortunately, most medications needed to treat frequently encountered illnesses in pregnancy can be given with relative safety (Briggs, 2017). That said, notable exceptions are

considered in Chapter 8 and throughout this text. The risks and benefits of medication use during pregnancy and lactation are outlined in drug labels using the Pregnancy and Lactation Labeling Rule (PLLR) requirement from the U.S. Food and Drug Administration (FDA).

NONOBSTETRICAL SURGERY

The chances of adverse maternal and perinatal outcomes following nonobstetrical surgery during pregnancy are relatively low and cannot be separated from risks of the underlying condition (Balinskaite, 2017). However, risks are likely greater with complications. Compared with simple appendicitis, perforated appendicitis with feculent peritonitis has significantly higher maternal and perinatal morbidity and mortality rates even if surgical and anesthetic techniques are flawless. Moreover, procedure-related complications may adversely affect outcomes. For example, a woman who has uncomplicated removal of an inflamed appendix may suffer aspiration of acidic gastric contents during tracheal intubation or extubation.

Maternal Morbidity

The most frequent nonobstetrical surgical procedures performed during pregnancy are appendectomy, cholecystectomy, and adnexal surgery (Vujic, 2019; Yu, 2018). Postoperative complications in nonpregnant patients can similarly harm gravid women. However, data comparing these complications in these two groups are conflicting. The National Surgical Quality Improvement Program showed that morbidity and mortality rates from nonobstetrical surgery did not differ between pregnant and nonpregnant women (Moore, 2015). In a Taiwanese cohort of nearly 5600 gravidas, the infectious postoperative complication rate was slightly higher and the mortality rate was fourfold greater than those rates in nonpregnant women (Huang, 2016).

The reported postoperative complication rate in gravidas approximates 5 percent, and the maternal mortality rate in these cases is <1 percent (Huang, 2016; Vujic, 2019). Moreover, preoperative infection, specifically sepsis, is associated with a higher risk of maternal death (Erekson, 2012).

Perinatal Morbidity

Excessive perinatal morbidity associated with nonobstetrical surgery is also attributable in many cases to the disease itself rather than to surgery and anesthesia. Two- to threefold elevated risks for spontaneous abortion, preterm delivery, preeclampsia, and cesarean delivery have been reported (Yu, 2018). Balinskaite and associates (2017) identified a greater risk of fetal death, preterm birth, fetal-growth restriction, and cesarean delivery in 47,628 women undergoing nonobstetrical surgery. Most of these complications developed in cases performed emergently (Vujic, 2019). The Swedish Birth Registry provides valuable data comparing perinatal outcomes in women undergoing surgery with those of the general obstetrical population (Table 49-1) (Mazze, 1989). The incidences of congenital malformations and stillbirth were not significantly different from those of nonexposed newborns. However, incidences of low birthweight, preterm birth, and neonatal death were significantly higher. Increased neonatal death rates were largely due to prematurity.

TABLE 49-1. Birth Outcomes in 5405 Pregnant Women Undergoing Nonobstetrical Surgery

Outcome	Rate	*p* value[a]
Stillbirth	0.7%	NS
Major malformation	1.9%	NS
Preterm <37 wk	7.5%	<0.05
Birthweight <1500 g	1.2%	<0.05
Birthweight <2500 g	6.6%	<0.05
Neonatal death by 7 days	1.1%	<0.05

[a]Compared with 720,000 pregnancies in women without surgery.
NS = not significant.

Fetal abnormality rates are not associated with maternal surgery in early pregnancy. Källén and Mazze (1990) reported a *nonsignificant* relationship between elevated neural-tube defect rates and operations performed at 4 to 5 weeks' gestation. A large database study found no evidence that anesthetic agents were teratogenic (Czeizel, 1998). According to Briggs and coworkers (2017), most inhalation anesthetic agents appear safe.

More recently, concerns of neurodevelopmental harm with the use of anesthetics for obstetrical or fetal surgery have been raised. In 2016, the FDA issued a warning regarding impaired brain development in children following in utero exposure to inhaled isoflurane, sevoflurane, and desflurane as well as intravenous propofol and midazolam. Such risks appear to accrue after 3 hours or more of exposure (Olutoye, 2018).

LAPAROSCOPIC SURGERY

In the first trimester, laparoscopy is the most common procedure used for diagnosis and management of several surgical disorders. In 2017, the Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) updated its recommendations concerning laparoscopy use in pregnant women (Table 49-2) (Pearl, 2017).

For pregnancy in general, laparotomy also is common. One 5-year study of almost 1300 pregnant women reported that open appendectomy was performed in 36 percent of 857 gravidas compared with only 17 percent of nonpregnant patients. Of those undergoing cholecystectomy, an open approach was used in 10 percent of 436 pregnant women compared with 5 percent of nonpregnant women (Silvestri, 2011). In a study from Japan, Shigemi and colleagues (2019) described 6018 pregnant women undergoing abdominal surgery—4047 by laparotomy and 1971 by laparoscopy. Operative times, hospital stay lengths, and rates of adverse fetal events and blood transfusion were all greater in the laparotomy group (Table 49-3). Others instead report equally satisfactory outcomes with either approach (Cox, 2016; Lee, 2019). Randomized

TABLE 49-2. Some Guidelines from the Society of American Gastrointestinal Endoscopic Surgeons (SAGES) for Laparoscopic Surgery in Pregnant Women

Indications—same as for nonpregnant women
Investigation of acute abdominal processes
Excision of an adnexal mass
Appendectomy, cholecystectomy, nephrectomy, adrenalectomy, splenectomy

Technique
Position: lateral recumbent
Entry: open Hasson technique, careful Veress needle, or optical trocar; fundal height may alter insertion site selection
Secondary trocars: direct visualization for placement; gravid uterus may alter insertion site selection
CO_2 insufflation pressures: 10–15 mm Hg
Monitoring: capnography intraoperatively, FHR assessment pre- and postoperatively
Perioperative pneumatic compression devices and early postoperative ambulation

CO_2 = carbon dioxide; FHR = fetal heart rate.

trials to compare benefits and risks of laparoscopy versus laparotomy during pregnancy are needed, but implementation seems unfeasible (Bunyavejchevin, 2013; Lee, 2019).

For adnexal mass surgery in pregnancy, laparoscopy is preferred, and several studies confirm its relative safety (Daykan, 2016; Webb, 2015). In addition, laparoscopic splenectomy, adrenalectomy, and nephrectomy also have been described in pregnant women (Asizare, 2014; Dong, 2014; Miller, 2012).

When first used, 26 to 28 weeks became the upper gestational-age limit recommended. However, as experience has accrued, many now describe laparoscopic surgery performed in the third trimester (Shigemi, 2019). In one report, a third of gravidas undergoing laparoscopic cholecystectomy or appendectomy were >26 weeks' gestation (Rollins, 2004). No serious adverse sequelae are linked to these procedures, and laparoscopy can safely be performed in all trimesters.

Hemodynamic Effects

Precise effects of laparoscopy in the human fetus are unknown, but animal investigations are informative. During laparoscopy, required abdominal insufflation causes hemodynamic changes that are summarized in Table 49-4. Reedy and associates (1995) studied baboons at the human equivalent of 22 to 26 weeks' gestation. No substantive physiological changes were found with insufflation pressures of 10 mm Hg, but 20 mm Hg caused significant maternal cardiovascular and respiratory changes after 20 minutes. These included faster respiratory rate, respiratory acidosis, diminished cardiac output, and increased pulmonary artery and capillary wedge pressures. In pregnant ewes, uteroplacental blood flow declines when intraperitoneal insufflation pressure exceeded 15 mm Hg (Barnard, 1995; Hunter, 1995). This stemmed from decreased perfusion pressure and elevated placental vessel resistance (see Table 49-4).

In women, cardiorespiratory changes are generally not severe if insufflation pressures remain <15 mm Hg. Despite maintaining these low insufflation pressures in women at midpregnancy, the cardiac index dropped 26 percent after 5 minutes of insufflation and 21 percent after 15 minutes (Steinbrook, 2001). Even so, mean arterial pressures, systemic vascular resistance, and heart rate did not change significantly.

TABLE 49-3. Comparative Outcomes in Pregnant Women Undergoing Abdominal Surgery

Factor	Open	LSC	*p* value
Primary outcome[a]	1.3%	0.36%	<0.05
Transfusion rate	2.3%	0.41%	0.002
Operative time	115 min	95 min	<0.001
Hospital stay	9.2 d	5.9 d	<0.001

[a]Includes miscarriage, stillbirth, or preterm delivery.
LSC = laparoscopically.

Technique

The following is an overview of laparoscopic technique in pregnancy. For a detailed description and illustrations refer to Chapter 15 in *Cunningham and Gilstrap's Operative Obstetrics,* 3rd edition (Kho, 2017).

Preparation for laparoscopy differs little from that used for laparotomy. Bowel cleansing is not needed but may aid visualization and manipulations by emptying the colon. Nasogastric or orogastric decompression reduces the risk of stomach trocar puncture and aspiration. Aortocaval compression is avoided by a left-lateral tilt of the patient's body. Positioning of the lower extremities in boot-type stirrups maintains access to the vagina for fetal sonographic assessment or *manual* uterine displacement. Intrauterine manipulators are logically avoided. Pregnancy-related hypercoagulability combined with pneumoperitoneum-associated, lower-extremity venous stasis raises venous thromboembolism risks. Prophylactic pneumatic compression devices are wrapped around the calves during patient positioning.

Most reports describe the use of general endotracheal anesthesia with monitoring of end-tidal carbon dioxide—$EtCO_2$ (Hong, 2006; Ribic-Pucelj, 2007). With controlled ventilation, $EtCO_2$ is maintained between 30 and 35 mm Hg.

Beyond the first trimester, technical modifications of standard pelvic laparoscopic entry are required to avoid uterine

TABLE 49-4. Physiological Effects of CO_2 Insufflation of the Peritoneal Cavity

System	Effects[a]	Mechanisms	Possible Maternal-Fetal Effects
Respiratory	Increased $Paco_2$; decreased pH	CO_2 absorption	Hypercarbia, acidosis
Cardiovascular	Increased: heart rate; systemic vascular resistance; pulmonary, central venous, and mean arterial pressures	Hypercarbia and increased intraabdominal pressure	Uteroplacental hypoperfusion—possible fetal hypoxia, acidosis, and hypoperfusion[b]
	Decreased cardiac output	Decreased venous return	
Blood flow	Decreased splanchnic flow with hypoperfusion of liver, kidneys, and gastrointestinal organs	Increased intraabdominal pressure	As above
	Decreased venous return from lower extremities	Increased intraabdominal pressure	As above
	Increased cerebral blood flow	Hypercarbia possibly from shunting due to splanchnic tamponade	Increased CSF pressure[b]

[a]Effects intensified when insufflation pressure >20 mm Hg in baboons (Reedy, 1995).
[b]Data primarily from animal studies.
CO_2 = carbon dioxide; CSF = cerebrospinal fluid; $Paco_2$ = partial pressure of CO_2.
Data from O'Rourke, 2006; Reynolds, 2003.

puncture or laceration (Fig. 49-1). Many recommend open entry techniques to avoid perforations of the uterus, pelvic vessels, and adnexa. With the method described by Hasson (1971, 1974), the abdomen is incised at or above the umbilicus, and the peritoneal cavity entered under direct visualization (Fig. 49-2). At this point, the cannula is connected to the insufflation system, and a 12–mm Hg pneumoperitoneum is created. The initial insufflation should be conducted slowly to allow for prompt assessment and reversal of any untoward pressure-related effects. Gas leakage around the cannula is managed by tightening the surrounding skin with a towel clamp. Insertion of secondary trocars into the abdomen is most safely performed under direct laparoscopic viewing. Single-port surgery also has been described (Dursun, 2013).

In more advanced pregnancies, direct entry through a left upper quadrant port in the midclavicular line, 2 cm beneath the costal margin, may better avoid the fundus (Donkervoort, 2011; Stepp, 2004). Known as the *Palmer point*, this entry site is also used in gynecological laparoscopy because visceroparietal adhesions infrequently form here (Vilos, 2007).

Gasless laparoscopy is a less commonly selected alternative approach that uses a rod with intraabdominal fan-blade-shaped

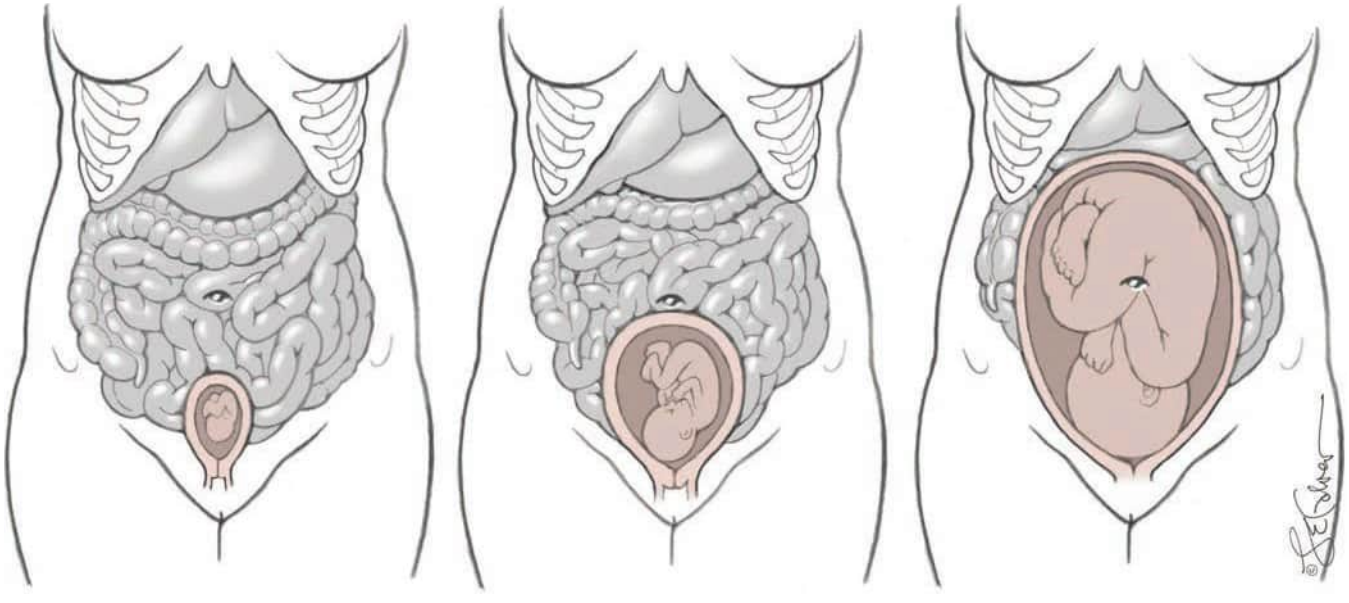


FIGURE 49-1 Pregnant uterus at 10, 20, and 36 weeks' gestation depicting distortion of other intraperitoneal organs. (Reproduced with permission from Kho KA: Diagnostic and operative laparoscopy. In Yeomans ER, Hoffman BL, Gilstrap LC III, et al (eds): Cunningham and Gilstrap's Operative Obstetrics, 3rd ed. New York, NY: McGraw Hill; 2017.)

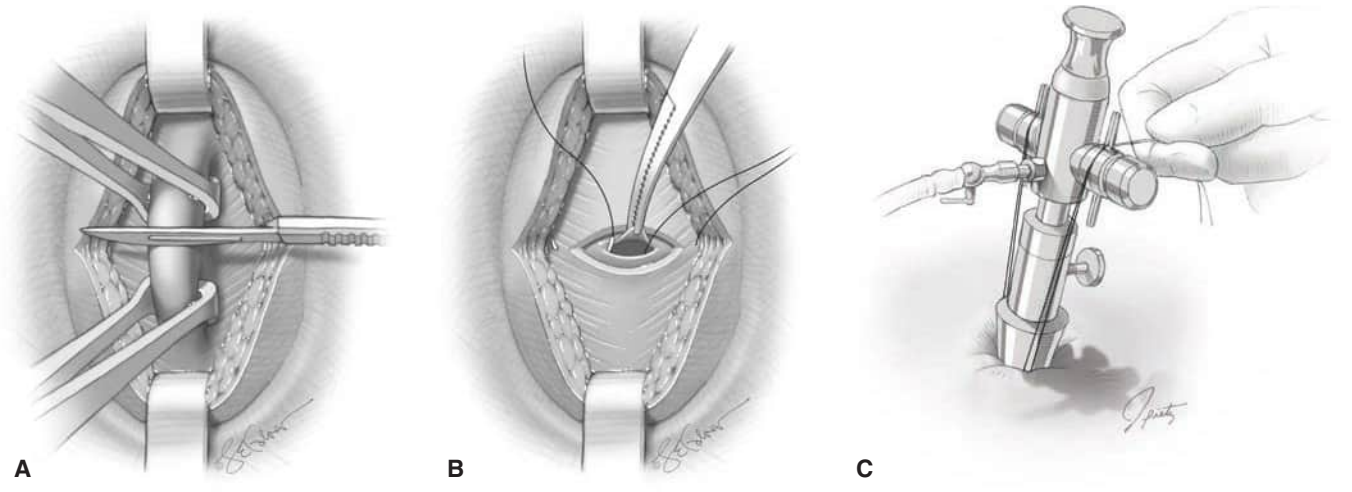


FIGURE 49-2 Hasson open entry technique for laparoscopic instrument placement. **A.** Fascia grasped with two Allis clamps and elevated prior to sharp incision. **B.** Two fascial stitches incorporate the peritoneum and fascia. **C.** These fascial sutures are wrapped around holders of the Hasson cannula to anchor it in place. (Reproduced with permission from Kho KA: Diagnostic and operative laparoscopy. In Yeomans ER, Hoffman BL, Gilstrap LC III, et al (eds): Cunningham and Gilstrap's Operative Obstetrics, 3rd ed. New York, NY: McGraw Hill; 2017.)

retractors. When opened, these allow the abdominal wall to be lifted upward. It avoids the typical laparoscopic cardiovascular changes because abdominal wall elevation is created by retraction rather than insufflation (Phupong, 2007).

■ Complications

Risks inherent to any abdominal endoscopic procedure are probably slightly greater during pregnancy. The obvious unique one is perforation of the pregnant uterus with a trocar or Veress needle (Kizer, 2011; Mala, 2014). That said, reported complications are infrequent (Choi, 2021; Koo, 2012; Post, 2019).

■ Perinatal Outcomes

Perinatal outcomes in women are limited to observational studies. Reedy and colleagues (1997) used the updated Swedish Birth Registry database to analyze a 20-year period with more than 2 million deliveries. Of 2181 laparoscopic procedures, most were performed during the first trimester. Perinatal outcomes for these women were compared with those of all women in the database and those undergoing open surgical procedures. These investigators confirmed the earlier findings of an increased risk of low birthweight, preterm delivery, and fetal-growth restriction with surgery during pregnancy. Differences were not found, however, in outcomes of women undergoing laparoscopy versus laparotomy. An observational study of 262 women undergoing surgery for an adnexal mass noted similar findings (Koo, 2012). Although the abortion and stillbirth rates are low with abdominal surgery, laparotomy has more adverse outcomes compared with laparoscopy (see Table 49-3).

RADIOGRAPHY

Imaging modalities are used as adjuncts for diagnosis and therapy during pregnancy. Options include sonography, radiography, computed tomography (CT), and magnetic resonance (MR) imaging. Of these, radiography is the most problematic. Inevitably, some radiographic procedures are performed before recognition of early pregnancy, usually because of trauma or serious illness (Herfel, 2018). Fortunately, most diagnostic radiographic procedures are associated with minimal fetal risks. However, as with medications, these procedures may lead to a needless therapeutic abortion because of patient or physician anxiety or to litigation if pregnancy outcome is adverse.

The American College of Radiology (ACR) has addressed the growing concern of collective radiation doses in all fields of medicine (Amis, 2007). More recent publications have been in support of FDA efforts to decrease radiation exposure and to reduce the number of unnecessary examinations. Recommendations also include considerations for radiosensitive populations, such as children and pregnant or potentially pregnant women. At our institutions, special recommendations are made for gravidas. Radiation exposure values and duration are recorded and monitored in high-exposure areas such as CT and fluoroscopy units. Last, consultation with the radiologist is advised (Chansakul, 2017).

■ Ionizing Radiation

The term *radiation* refers to energy transmission and thus is applied to x-rays and also to microwaves, ultrasound, diathermy, and radio waves. Of these, x-rays and gamma rays have short wavelengths with very high energy and are ionizing radiation forms. The other four energy forms have rather long wavelengths and low energy (Brent, 2009).

Ionizing radiation can directly damage DNA or can create free hydroxyl radicals that in turn damage DNA (Hall, 1991; National Research Council, 1990). Methods of measuring the effects of x-rays are summarized in Table 49-5. The standard terms used are *exposure* (in air), *dose* (to tissue), and *relative effective dose* (to tissue accounting for biological effects). In the range of

TABLE 49-5. Some Measures of Ionizing Radiation

Exposure	Number of ions produced by x-rays per kg of air Unit: roentgen (R)
Dose	Amount of energy deposited per kg of tissue Modern unit: gray (Gy) (1 Gy = 100 rad) (1000 mGy = 1 Gy) Traditional unit: rad
Relative effective dose	Amount of energy deposited per kg of tissue normalized for biological effectiveness (1000 mSv = 1 Sv) Modern unit: sievert (Sv) (1 Sv = 100 rem) Traditional unit: rem

energies for diagnostic x-rays, the dose is now expressed in grays (Gy), and the relative effective dose is expressed in sieverts (Sv). These can be used interchangeably. For consistency, all doses discussed subsequently are expressed in currently used units of gray (1 Gy = 100 rad) or sievert (1 Sv = 100 rem). To convert, 1 Sv = 100 rem = 100 rad.

As noted, x- and gamma-radiation at high doses can damage DNA, and this yields two biological effects in the fetus (Brent, 2009). These are *deterministic effects* and *stochastic effects*.

Deterministic Effects

One potential harm of radiation exposure is deterministic, which may result in abortion, growth restriction, congenital malformations, or intellectual disability. These deterministic effects are threshold effects, and the threshold level is the *NOAEL—no observed adverse effect level* (Brent, 2009). Although controversial, the NOAEL concept supports that there is no risk below the threshold dose of 0.05 Gy or 5 rad. It also suggests that the threshold for gross fetal malformations is more likely to be 0.2 Gy (20 rad) (Lowe, 2020).

The deterministic effects of ionizing radiation have been extensively studied for cell damage that leads to disordered embryogenesis. These have been assessed in animal models as well as in Japanese atomic bomb survivors and the Oxford Survey of Childhood Cancers (Sorahan, 1995). Other sources have confirmed prior observations and provide additional information (Groen, 2012).

Animal Studies

In the mouse model, the lethality risk is highest during the preimplantation period, which extends up to 10 days postconception (Kanter, 2014). Blastomere destruction caused by chromosomal damage is the likely cause (Hall, 1991).

During organogenesis, high-dose radiation—1 Gy or 100 rad—is more likely to cause malformations and growth restriction and less likely to be lethal. Studies of brain development suggest effects on neuronal development and a window of cortical sensitivity in early and midfetal periods. Instead, acute low-dose ionizing radiation appears to have no deleterious effects (Howell, 2013).

Human Data

Data on adverse human effects of high-dose ionizing radiation mostly derive from the atomic bomb survivors of Hiroshima and Nagasaki (Greskovich, 2000; Otake, 1987). The International Commission on Radiological Protection (2003) confirmed initial studies showing that the risk of severe intellectual disability was greatest between 8 and 15 weeks' gestation (Table 49-6) (American College of Radiology, 2018). The mean decrease in intelligence quotient (IQ) scores was 25 points per Gy or 100 rad. The dose response appears linear, but it is unclear whether there is a threshold dose. At <8 weeks' or >25 weeks' gestation, a higher risk of intellectual disability in humans has not been documented, even with doses exceeding 0.5 Gy or 50 rad (International Commission on Radiological Protection, 2003). Most estimates err on the conservative side by assuming a linear nonthreshold hypothesis. In a study of fetuses exposed to a low radiation dose in the first trimester, Guilbaud and colleagues

TABLE 49-6. Deterministic Effects of Ionizing Radiation in Pregnancy

GA (wks)	CA (wks)	<50 mGy (<5 rad)	50–100 mGy (5–10 rad)	>100 mGy (>10 rad)
0–2	—	None	None	None
3–4	1–2	None	Probably none	Low risk of spontaneous abortion
5–10	3–8	None	Potential uncertain and probably too subtle to be clinically detectable	Possible malformations increasing in likelihood as dose increases
11–17	9–15	None	Potential uncertain and probably too subtle to be clinically detectable	Risk of decreased IQ or of mental retardation, increasing in frequency and severity with increasing dose
18–27	16–25	None	None	IQ deficits not detectable at diagnostic doses
>27	>25	None	None	None applicable to diagnostic exposures

CA = conceptional age; GA = gestational age; IQ = intelligence quotient.

(2019) did not find an increased risk for miscarriage, congenital anomalies, or fetal-growth restriction.

Reports have described high-dose radiation used to treat women for malignancy, menorrhagia, and uterine myomas. Dekaban (1968) described 22 infants with microcephaly, intellectual disability, or both following exposure in the first half of pregnancy to an estimated 2.5 Gy or 250 rad for *therapeutic* radiation. These doses are also carcinogenic for the fetus (Brent, 2015).

Summary of Fetal Radiation Exposure

From 8 to 15 weeks' gestation, the fetus is most susceptible to radiation-induced intellectual disability (see Table 49-6). Whether this is a threshold or nonthreshold linear function of dose is unresolved. The Committee on Biological Effects (1990) estimates the risk of severe intellectual disability to be as low as 4 percent for 0.1 Gy (10 rad) and as high as 60 percent for 1.5 Gy (150 rad). Recall that these doses are 2 to 100 times higher than those considered maximal from diagnostic radiation. Importantly, cumulative doses from multiple procedures may reach the harmful range, especially at 8 to 15 weeks' gestation. At 16 to 25 weeks' gestation, the risk is less, and there is no proven risk before 8 weeks or after 25 weeks (American College of Obstetricians and Gynecologists, 2017).

Embryofetal risks from low-dose diagnostic radiation appear to be minimal. Current evidence suggests that risks for malformations, growth restriction, or spontaneous abortion are not increased from a radiation dose of less than 0.05 Gy (5 rad). Brent (2009) concluded that gross congenital malformation rates would not be greater with exposure to less than 0.2 Gy (20 rad). Diagnostic radiographs seldom exceed 0.1 Gy (10 rad) and thus, these procedures are unlikely to cause deterministic effects (Strzelczyk, 2007). As emphasized by Groen and coworkers (2012), 0.1 Gy is the radiation equivalent to that from more than 1000 chest x-rays.

Stochastic Effects

These effects refer to random, presumably unpredictable oncogenic or mutagenic effects of radiation exposure. Stochastic effects concern associations between fetal diagnostic radiation exposure and increased risk of childhood cancers or genetic diseases. Excess cancers can result from in utero exposure to doses as low as 0.01 Sv or 1 rad (Doll, 1997; National Research Council, 2006). The estimated risk of childhood cancer following fetal exposure to 0.03 Gy or 3 rad doubles the background risk of 1 cancer in 600 exposed fetuses to that of 2 in 600 (Hurwitz, 2006).

In one report, in utero radiation exposure was linked to 10 solid cancers in adults from age 17 to 45 years. There was a dose-response relationship as previously noted at the 0.1 Sv or 10 rem threshold. These cancers likely are associated with a complex series of interactions between DNA and ionizing radiation. These interactions make it more problematic to predict cancer risk from low-dose radiation of less than 10 rem. Importantly, below doses of 0.1 to 0.2 Sv, evidence of a carcinogenic effect is not convincing (Brent, 2009, 2014; Preston, 2008; Strzelczyk, 2007).

X-Ray Dosimetry

Estimates of dose to the uterus and embryo for various frequently used radiographic examinations are summarized in Table 49-7. Imaging of maternal body parts farthest from the uterus results in a very small dose of radiation scatter to the embryo or fetus. The size of the woman, radiographic technique, and equipment performance are other variables (Wagner, 1997). Thus, data in the table serve only as guidelines. When the radiation dose for a specific individual is required, a medical physicist should be consulted. The Health Physics Society lists answers to questions commonly asked by patients (Health Physics Society, 2020).

TABLE 49-7. Dose to the Uterus for Common Radiologic Procedures

Study	View	Dose[a] per View (mGy)	No. Films[b]	Dose (mGy)
Skull[c]	AP, PA, Lat	<0.0001	4.1	<0.0005
Chest	AP, PA[c], Lat[d]	<0.0001–0.0008	1.5	0.0002–0.0007
Mammogram[d]	CC, Lat	<0.0003–0.0005	4.0	0.0007–0.002
Lumbosacral spine[e]	AP, Lat	1.14–2.2	3.4	1.76–3.6
Abdomen[e]	AP		1.0	0.8–1.63
Intravenous pyelogram[e]	3 views		5.5	6.9–14
Hip[b] (single)	AP	0.7–1.4	2.0	1–2
	Lat	0.18–0.51		

[a]Calculated for x-ray beams with half-value layers ranging from 2 to 4 mm aluminum equivalent.
[b]Based on data and methods reported by Laws, 1978.
[c]Entrance exposure data from Conway, 1989.
[d]Estimates based on compilation of above data.
[e]Based on NEXT data reported in National Council on Radiation Protection and Measurements, 1989.
AP = anterior-posterior; CC = cranial-caudal; Lat = lateral; PA = posterior-anterior.

Therapeutic Radiation

The Radiation Therapy Committee Task Group of the American Association of Physics in Medicine emphasizes careful individualization of cancer radiotherapy for the pregnant woman (Stovall, 1995). In some cases, shielding of the fetus and other safeguards can be employed (Fenig, 2001; Nuyttens, 2002). However, in other instances, the fetus will be exposed to dangerous radiation doses, and a carefully designed plan must be improvised (Prado, 2000). Models that estimate the fetal dose given during maternal brain radiotherapy or tangential breast irradiation have been developed (Mazonakis, 2017). The adverse pregnancy outcomes that occur years after abdominopelvic radiotherapy are detailed in Chapter 66 (p. 1164). (Brent, 2015; Wo, 2009).

Diagnostic Radiation

Radiographs

To estimate fetal risk, approximate x-ray dosimetry must be known. According to the American College of Radiology, no single diagnostic procedure results in a radiation dose significant enough to threaten embryo-fetal well-being (Hall, 1991).

For standard radiographs, dosimetry is presented in Table 49-7. In pregnancy, the anterior-posterior-view chest radiograph is the most common study, and fetal exposure is exceptionally small—0.0007 Gy or 70 mrad. The dose with one abdominal radiograph is higher—0.001 Gy or 100 mrad—because the embryo or fetus lies directly in the x-ray beam path. The standard intravenous pyelogram may exceed 0.005 Gy or 500 mrad because of several exposures. The one-shot pyelogram described in Chapter 56 (p. 999) is useful when urolithiasis or other causes of urinary tract obstruction are unproven by sonography. Mammography and most "trauma series" radiographs of an extremity, skull, or rib deliver low doses because of distance from the fetus (Cepeda-Martins, 2021; Shakerian, 2015).

Fluoroscopy and Angiography

Dosimetry calculations are much more difficult with these procedures because of variations in the number of radiographs obtained, total fluoroscopy time, and fluoroscopy time during which the fetus lies in the radiation field. As shown in Table 49-8, the range varies. Although the FDA limits the exposure rate for conventional fluoroscopy such as barium studies, special-purpose systems such as angiography units have the potential for much higher exposure.

Angiography and vascular embolization may occasionally be necessary for trauma and for serious maternal disorders. As before, a greater distance from the embryo or fetus lowers the exposure and risk.

Computed Tomography

In a recent report describing nearly 3.5 million pregnancies, the use of CT imaging from 1996 to 2016 increased fivefold (Kwan, 2019). These studies are usually performed by obtaining a spiral of 360-degree images that are postprocessed in multiple planes. Of these, the axial image remains the most frequently obtained. Multidetector CT (MDCT) images are now standard for common clinical indications. The most recent detectors have more channels, and these multidetector protocols may result in higher dosimetry compared with prior CT imaging techniques. Several imaging parameters have an effect on exposure (Brenner, 2007). These include pitch, kilovoltage, tube current, collimation, slice number, tube rotation, and total acquisition time. If a study is performed with and without contrast, the dose is doubled because twice as many images are obtained. Fetal exposure also varies with maternal size and fetal size and position. As with plain radiography, the closer the target area is to the fetus, the greater the delivered dose.

Cranial CT imaging for evaluation of neurological disorders and eclampsia is the most frequently performed CT study in gravidas (Chaps. 41, p. 718 and 63, p. 1126). Nonenhanced CT scanning is often used to detect acute hemorrhage within the epidural, subdural, or subarachnoid spaces (Fig. 49-3). Radiation dosage is negligible because of distance from the fetus (Goldberg-Stein, 2012).

Abdominal procedures are more problematic. Hurwitz and associates (2006) employed a 16-channel multidetector scanner to calculate fetal exposure at 0 and 3 months' gestation using a phantom model. Calculations were made for three commonly requested procedures in pregnant women (Table 49-9). The study showed their pulmonary embolism protocol has the same dosimetry exposure as the ventilation-perfusion (V/Q) lung scan discussed subsequently. Although the appendicitis protocol has the highest radiation exposure, it is very useful clinically when MR imaging is not available. Using a greater pitch markedly decreases the dosimetry and yields a sensitivity of 92 percent, a specificity of 99 percent, and a negative-predictive value of 99 percent (Lazarus, 2007). This is discussed further in Chapter 55 (p. 987).

TABLE 49-8. Estimated X-Ray Doses to the Uterus/Embryo from Common Fluoroscopic Procedures

Procedure	Dose to Uterus (mGy)	Fluoroscopic Exposure in Seconds (SD)
Cerebral angiography[a]	<0.1	—
Cardiac angiography[b,c]	0.65	223 (± 118)
Single-vessel PTCA[b,c]	0.60	1023 (± 952)
Double-vessel PTCA[b,c]	0.90	1186 (± 593)
Upper gastrointestinal series[d]	0.56	136
Barium swallow[b,e]	0.06	192
Barium enema[b,f,g]	20–40	289–311

[a]Wagner, 1997.
[b]Calculations based on data of Gorson, 1984.
[c]Finci, 1987.
[d]Suleiman, 1991.
[e]Based on female data from Rowley, 1987.
[f]Assumes embryo in radiation field for entire examination.
[g]Bednarek, 1983.
PTCA = percutaneous transluminal coronary angioplasty; SD = standard deviation.

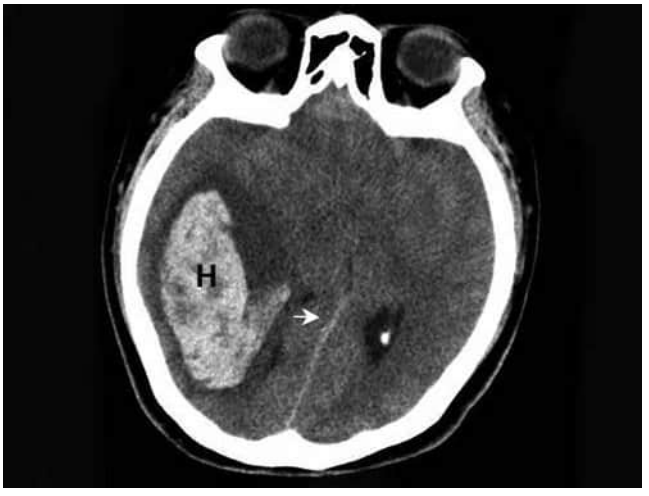


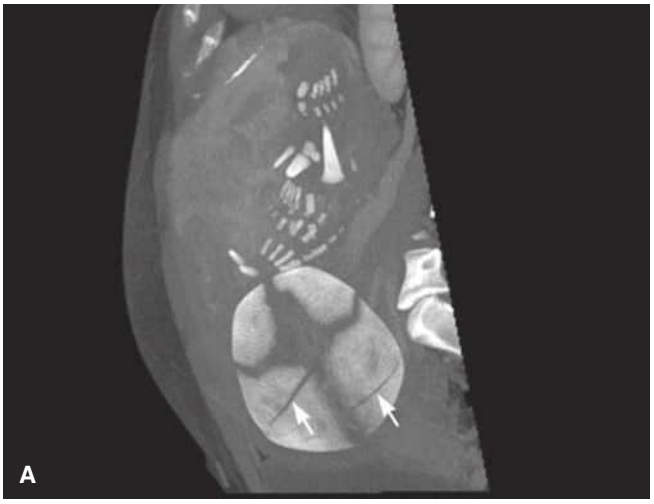
FIGURE 49-3 An image from a noncontrast computed tomography head study demonstrates a large right-sided frontoparietal temporal intraparenchymal hematoma (*H*). The midline (*arrow*) is shifted to the left due to mass effect from the hematoma. (Reproduced with permission from Dr. Amanda Zofkie.)

For suspected urolithiasis, the multidetector-scan protocol is used if sonography is nondiagnostic. White and coworkers (2007) identified urolithiasis in 13 of 20 women with gestations aged an average of 26 weeks. Last, as shown in Figure 49-4, abdominal tomography is performed if indicated in the pregnant woman with severe trauma (Herfel, 2018; Shakerian, 2015).

Most experience with chest CT imaging is with cases of suspected pulmonary embolism. Historically, pulmonary scintigraphy—the V/Q scan—was recommended for pregnant women by 70 percent of radiologists and chest CT angiography by 30 percent (Stein, 2007). However, most currently agree that multidetector-CT pulmonary angiography (CTPA) has improved accuracy because of increasingly faster acquisition times (Brown, 2014). Despite advances in technology, scintigraphy is still recommended by the American Thoracic Society for gravidas with a normal chest x-ray (Leung, 2012). A higher use rate for CTPA has been reported, and dosimetry similar to that with V/Q scintigraphy has been emphasized (Brenner, 2007; Greer, 2015; Tromeur, 2019). The rapid turnaround time with current CTPA protocols at most hospitals has advanced its selection as the preferred modality (Sheen, 2018). The algorithm in the YEARS study describes

TABLE 49-9. Estimated Radiation Dosimetry with 16-Channel Multidetector Computed-Tomographic (MDCT) Imaging Protocols

	Dosimetry (mGy)	
Protocol	Preimplantation	3 Months' Gestation
Pulmonary embolism	0.20–0.47	0.61–0.66
Renal stone	8–12	4–7
Appendix	15–17	20–40



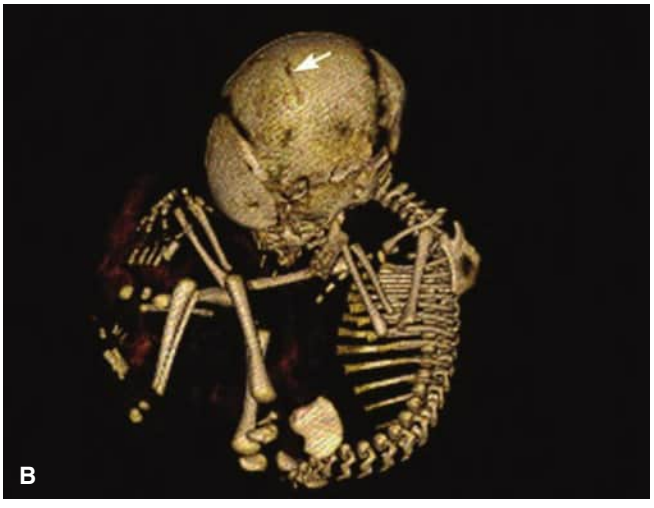


FIGURE 49-4 This woman in her third trimester was involved in a high-speed motor vehicle accident. **A.** Maximum intensity projection acquired for maternal indications readily identifies fetal skull fractures (*arrows*). **B.** 3-D reformatted CT image in a bone algorithm demonstrates the fetal skeleton from data acquired during the maternal examination. Again, the arrow marks one fracture site. (Reproduced with permission from Bailey AA, Twickler DM: Perioperative imaging. In Yeomans ER, Hoffman BL, Gilstrap LC III, et al (eds): Cunningham and Gilstrap's Operative Obstetrics, 3rd ed. New York, NY: McGraw Hill; 2017. Photo contributor: Dr. Travis Browning.)

the use of D-dimer values and clinical criteria to define a subgroup of gravidas warranting further imaging. Thus, the number of indicated CTPA studies resulting from this algorithm is markedly reduced (van der Pol, 2019). In pregnancy, although a negative D-dimer test is helpful, these levels may be normally elevated with increasing gestation and certain maternal complications (Chap. 55, p. 982).

Of other aspects in study selection, the fetal radiation doses are lower with CT pulmonary angiography (CTPA) compared with the V/Q scan. However, maternal chest radiation doses are substantially higher with CTPA (van Mens, 2017). The most recent ongoing Optimised Computed Tomography Pulmonary Angiography in Pregnancy Quality and Safety (OPTICA) study is a prospective trial

using a uniform low-dose CTPA protocol to enable definitive recommendations. Until results are known, our reduced-exposure CTPA protocol is recommended as the initial preferred imaging modality in suspected pulmonary embolism (Chap. 55, p. 987).

CT pelvimetry is used by some before attempting breech vaginal delivery (Chap. 28, p. 522). The fetal dose approaches 0.015 Gy or 1.5 rad, but use of a low-exposure technique may reduce this to 0.0025 Gy or 0.25 rad.

Radiographic Contrast Agents

These can be given intravenously or taken orally. Intravenous contrast agents are considered category B by the FDA. These agents are iodinated and of low osmolality, and thus they cross the placenta to the fetus. With water-soluble iodinated contrast, no cases of neonatal hypothyroidism or other adverse effects have been documented (American College of Obstetrics and Gynecology, 2017). Oral contrast preparations, typically containing iodine or barium, have minimal systemic absorption, and are unlikely to affect the fetus.

Nuclear Medicine Studies

These studies are performed by "tagging" a radioactive element to a carrier that can be injected, inhaled, or swallowed. For example, the radioisotope technetium-99m (Tc-99m) may be tagged to red blood cells, sulfur colloid, or pertechnetate. The method used to tag the agent determines fetal radiation exposure. The amount of placental transfer is obviously important, but maternal renal clearance is also factored because of fetal proximity to her bladder. Measurement of radioactive technetium is based on its decay, and the units used are the curie (Ci) or the Becquerel (Bq). Dosimetry is usually expressed in millicuries (mCi). The effective tissue dose is expressed in sievert units (Sv) with conversion of 1 Sv = 100 rem = 100 rad (see Table 49-5).

Depending on the physical and biochemical properties of a radioisotope, an average fetal exposure can be calculated (Wagner, 1997; Zanzonico, 2000). Commonly used radiopharmaceuticals and estimated absorbed fetal doses are given in Table 49-10. The radionuclide dose should be kept as low as possible (Zanotti-Fregonara, 2017). Exposures vary with gestational age and are greatest earlier in pregnancy for most radiopharmaceuticals. One exception is the later effect of iodine-131 on the fetal thyroid (Wagner, 1997).

In a V/Q scan, perfusion is measured with injected Tc-99m macroaggregated albumin, and ventilation is measured with inhaled xenon-127 or xenon-133. Fetal exposure with either is negligible (Chan, 2002; Mountford, 1997).

Thyroid scanning with iodine-123 or iodine-131 seldom is indicated in pregnancy. However, with the trace diagnostic doses used, fetal risk is minimal. In contrast, therapeutic doses of radioiodine to treat maternal Graves disease or thyroid cancer may cause fetal thyroid ablation and cretinism.

The sentinel lymphoscintigram is a commonly used preoperative study in nonpregnant women to detect the axillary lymph node most likely to have metastases from breast cancer. Tc-99m–sulfur colloid is used in this diagnostic study (Newman, 2007; Spanheimer, 2009). The calculated dose approximates 0.014 mSv or 1.4 mrad, which should not preclude its safe use during pregnancy.

SONOGRAPHY

The development of sonography for study of the fetus and mother is one of the greater achievements in obstetrics. The technique has become virtually indispensable in everyday practice. Its wide-ranging clinical uses are further discussed in Chapters 14 and 15 and in other sections of this book.

MAGNETIC RESONANCE IMAGING

Magnetic resonance technology does not use ionizing radiation, and its use in pregnancy is constantly evolving (Gopireddy, 2021; Mervak, 2019). Advantages include sharp resolution at soft-tissue interfaces, ability to characterize tissue composition, and acquisition of images in any plane—particularly axial, sagittal, and coronal. A portion of Chapter 14 (p. 263) is devoted to mechanisms that generate MR images, and imaging examples are provided throughout this book.

■ Safety

The update of the expert panel on MR safety of the ACR was summarized by Kanal and colleagues (2013). The panel concluded that no harmful human effects are reported from MR imaging. Similar conclusions were reached by the International Society for Ultrasound in Obstetrics and Gynecology (2017).

When operated within standardized limits, maternal and fetal imaging can be safely performed at clinical magnet strengths—3 tesla (T) and below. MR imaging can be used regardless of trimester: (1) if the information cannot be obtained with another nonionizing modality, namely sonography; (2) if the study results will guide maternal or fetal management during pregnancy; and (3) if the imaging cannot be delayed until the woman is no longer pregnant. The decision to use a magnetic field strength >1.5 T may be made for specific maternal indications. Early work also suggests imaging at 3 T is safe and it improves fetal assessment (Chartier, 2019; Victoria, 2016). No demonstrable fetal heart rate pattern changes occur during MR imaging of gravidas (Vadeyar, 2000). Last, studies evaluating children exposed in utero have shown no deleterious effects (Kok, 2004; Reeves, 2010).

Contraindications to MR imaging include internal cardiac pacemakers, neurostimulators, implanted defibrillators and infusion pumps, cochlear implants, shrapnel or other metal in biologically sensitive areas, some intracranial aneurysm clips, and any metallic foreign body in the eye. Of more than 51,000 nonpregnant patients scheduled for MR imaging, one study found that only 0.4 percent had an absolute contraindication to the procedure (Dewey, 2007).

TABLE 49-10. Radiopharmaceuticals Used in Nuclear Medicine Studies

Study	Estimated Activity Administered per Examination (mCi)[a]	Weeks' Gestation[b]	Dose to Uterus/ Embryo (mSv)[c]
Brain	20 mCi ^{99m}Tc DTPA	<12	8.8
		12	7[c]
Hepatobiliary	5 mCi ^{99m}Tc sulfur colloid	12	0.45
	5 mCi ^{99m}Tc HIDA		1.5
Bone	20 mCi ^{99m}Tc phosphate	<12	4.6
Pulmonary			
Perfusion	3 mCi ^{99m}Tc-macroaggregated albumin	Any	0.45–0.57 (combined)
Ventilation	10 mCi ^{133}Xe gas		
Renal	20 mCi ^{99m}Tc DTPA	<12	8.8
Abscess or tumor	3 mCi ^{67}Ga citrate	<12	7.5
Cardiovascular	20 mCi ^{99m}Tc-labeled red blood cells	<12	5
	3 mCi ^{210}Tl chloride	<12	11
		12	6.4
		24	5.2
		36	3
Thyroid	5 mCi $^{99m}TcO_4$	<8	2.4
	0.3 mCi ^{123}I (whole body)[d]	1.5–6	0.10
	0.1 mCi ^{131}I		
	Whole body	2–6	0.15
	Whole body	7–9	0.88
	Whole body	12–13	1.6
	Whole body	20	3
	Thyroid-fetal	11	720
	Thyroid-fetal	12–13	1300
	Thyroid-fetal	20	5900
Sentinel lymphoscintigram	5 mCi ^{99m}Tc sulfur colloid (1–3 mCi)		5

[a]mCi = millicuries. To convert to mrad, multiply by 100.
[b]Exposures are generally greater prior to 12 weeks compared with increasing gestational ages.
[c]Some measurements account for placental transfer.
[d]The uptake and exposure of ^{131}I increases with gestational age.
DPTA = diethylenetriaminepentaacetic acid; Ga = gallium; HIDA = hepatobiliary iminodiacetic acid; I = iodine; mCi = millicurie; mSv = millisievert; Tc = technetium; TcO_4 = pertechnetate; Tl = thallium.
Data from Adelstein, 1999; Bailey, 2017; Schwartz, 2003; Stather, 2002; Wagner, 1997; Zanzonico, 2000.

■ Contrast Agents

Several different elemental *gadolinium chelates* are used to create paramagnetic contrast. These cross the placenta and are found in the fetus and placenta and are concentrated in amnionic fluid (Oh, 2015). In doses approximately 10 times the normal human dose, a gadolinium-based contrast agent caused slight developmental delay in rabbit fetuses. Inadvertant fetal exposure usually occurs in early pregnancy (Bird, 2019). The American College of Radiology cites a study of 26 women given a gadolinium derivative in the first trimester without adverse fetal effects (Kanal, 2013). Despite this, routine use of gadolinium is not recommended unless potential benefits outweigh fetal risks (American College of Obstetricians and Gynecologists, 2017; American College of Radiology, 2020; Briggs, 2017). This recommendation stems from a possible dissociation of the toxic gadolinium ion from its ligand within amnionic fluid and thus potential prolonged exposure of the fetus.

■ Maternal Indications

In some cases, MR imaging may complement CT, and in others, MR imaging is preferable (Mervak, 2019). MR imaging

is also a superb tool to evaluate the maternal abdomen and retroperitoneal space. One example is evaluation of right lower quadrant pain in pregnancy, specifically with suspected appendicitis (Aguilera, 2018; Tsai, 2017). It can aid detection and localization of adrenal, renal, and gastrointestinal lesions as well as pelvic masses in pregnancy (Boyd, 2012; Raj, 2020; Tica, 2013).

Maternal central nervous system abnormalities, such as brain tumors or spinal trauma, are more clearly seen with MR imaging. This makes it invaluable in the diagnosis of neurological emergencies (Edlow, 2013). Other modalities include MR urography for renal urolithiasis and cardiac MR for investigating normal physiology, complex defects, and cardiomyopathies (Mullins, 2012; Nelson, 2015; Stewart, 2016). The application of cardiovascular MR imaging in pregnant women is expanding (Ducas, 2019).

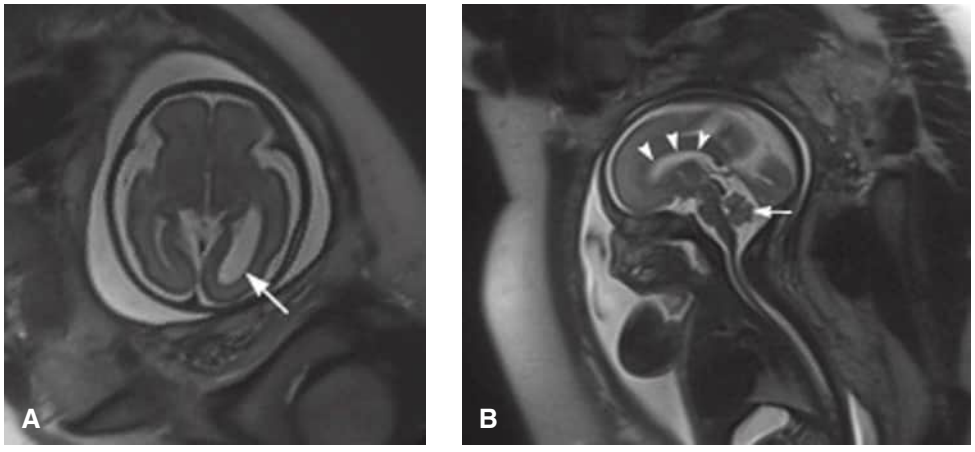


FIGURE 49-5 Nullipara with a 27 weeks' gestation. **A.** Axial T2-weighted MR image shows mild fetal unilateral ventriculomegaly involving the left lateral ventricle (*arrow*). **B.** Sagittal T2-weighted MR image demonstrates normal development of the corpus callosum (*arrowheads*) and vermis (*arrow*).

MR imaging helps also evaluate many pregnancy-specific disorders. It is chosen by many to determine the degree and extent of invasion in placenta accreta spectrum (Chap. 43, p. 762). As discussed in Chapter 40 (p. 701), MR imaging has provided important insights into the pathophysiology of preeclampsia (Nelander, 2018; Zeeman, 2014). As discussed in Chapter 37 (p. 656), CT and MR imaging are useful for puerperal infection evaluation, but MR imaging provides better visualization of the bladder flap area following cesarean delivery (Brown, 1999; Twickler, 1997). Last, preliminary studies of placental function with MR imaging are promising (Hutter, 2019).

■ Fetal Indications

Fetal MR imaging provides a complement to sonography (Laifer-Narin, 2007; Sandrasegaran, 2006). According to Zaretsky and associates (2003a), MR imaging can be used to display almost all elements of the standard fetal anatomical survey. Moreover, the quality of three-dimensional anatomical reconstruction with MR fetal imaging is superb (Werner, 2019). The most frequent fetal indications are evaluation of complex abnormalities of the brain, chest, and genitourinary systems (Williams, 2017). Reichel (2003) and Twickler (2002) and their colleagues have validated its use for fetal central nervous system anomalies and biometry (Fig. 49-5). Others have described MR imaging of fetuses with suprarenal masses or with renal anomalies and oligohydramnios (Castro, 2019; Hawkins, 2008). Fetal weight estimation may be more accurate with MR imaging than with sonography (Kadji, 2019; Zaretsky, 2003b). And MR imaging has been shown to accurately identify fetal anemia requiring transfusions (Jørgensen, 2019).

Fetal movement is problematic for MR imaging, but faster acquisitions eliminate the problem. Morphology is primarily assessed with fast T2-weighted sequences such as half-Fourier acquisition single shot turbo spin echo (HASTE) or single shot fast spin echo (SSFSE). Fetal indications and findings of MR imaging are discussed more extensively in Chapter 14 (p. 266) and throughout this book.

IMAGING DURING PREGNANCY

The American College of Obstetricians and Gynecologists (2017) has reviewed the effects of radiographic, sonographic, and magnetic-resonance exposure during pregnancy. Its suggested guidelines are shown in Table 49-11.

TABLE 49-11. Guidelines for Diagnostic Imaging During Pregnancy and Lactation

Sonography and magnetic resonance (MR) imaging are not associated with fetal risk and are preferred options for imaging in pregnancy
In general, radiation exposure during radiography, computed tomography (CT), or nuclear medicine imaging delivers a dose much lower than that associated with fetal harm. If needed to supplement sonography or MR imaging or if more readily available, these should not be withheld
With MR imaging, gadolinium contrast use should be restricted unless it significantly improves diagnostic accuracy to benefit fetal or maternal outcome
Breastfeeding should not be interrupted after gadolinium administration

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CHAPTER 50

Critical Care and Trauma

Treatment of the critically ill pregnant woman has improved over the past three decades with advances in intensive care capabilities. To achieve optimal outcomes, severe medical, surgical, and obstetrical disorders complicating pregnancy are frequently managed by a multidisciplinary team. Importantly, obstetricians and these other health-care team members must have a working knowledge of the unique considerations for pregnancy (Padilla, 2021). Some discussed in Chapter 49 include pregnancy-induced physiological changes, alterations in normal laboratory values, and consideration for the second patient—the fetus. Because critically ill women are usually young and healthy, their prognosis is generally good (Gaffney, 2014).

CRITICAL CARE

Despite noted gains, evidence suggests that severe morbidity rates are increasing (Friedman, 2016). In the United States, 1 to 3 percent of pregnant women require critical care services each year. The risk of death during such admissions ranges from 2 to 11 percent (American College of Obstetricians and Gynecologists, 2019a). Black women and Medicaid recipients are disparately affected (Wen, 2020).

Those with pregnancy-associated complications—especially hemorrhage, sepsis, and hypertension—have the greatest need for intensive care (Chantry, 2015; Guntupalli, 2015a,b). That said, many antepartum admissions are for nonobstetrical reasons, and these include diabetes, pneumonia or asthma, heart disease, chronic hypertension, pyelonephritis, and thyrotoxicosis (Guntupalli, 2015b; Zeeman, 2006). Cardiac disease is the leading non-obstetrical indication for intensive care unit (ICU) admission (Small, 2012). In instances of life-threatening hemorrhage, surgical procedures may be necessary, and close proximity to an operating room is paramount. For women who are undelivered, fetal well-being also is better served by this close proximity, especially because many are delivered preterm (Kilpatrick, 2016).

Organization of Critical Care

The concept and development of critical care for all aspects of medicine and surgery began in the 1960s. As a part of this effort, the National Institutes of Health held a Consensus Conference (1983) and the Society of Critical Care Medicine (1988, 1999) established guidelines for ICUs. Especially pertinent to obstetrics, these costly units prompted the evolution of a step-down *intermediate care unit*. These latter units were designed for patients who did not require intensive care but who needed a higher level of treatment than that provided on a general ward. The American College of Critical Care Medicine and the Society of Critical Care Medicine (1998) have published guidelines for these units (Table 50-1).

Obstetrical Critical Care

Although critical care for obstetrical patients has generally evolved along the path described in the last section, no detailed guidelines

TABLE 50-1. Guidelines for Conditions That Could Qualify for Intermediate Care

Cardiac: evaluation for possible infarction, stable infarction, stable arrhythmias, mild to moderate congestive heart failure, hypertensive urgency without end-organ damage
Pulmonary: stable patients for weaning and chronic ventilation, patients with potential for respiratory failure who are otherwise stable
Neurological: stable central nervous system, neuromuscular, or neurosurgical conditions that require close monitoring
Drug overdose: hemodynamically stable
Gastrointestinal: stable bleeding, liver failure with stable vital signs
Endocrinological: diabetic ketoacidosis, thyrotoxicosis that requires frequent monitoring
Surgical: postoperative from major procedures or complications that require close monitoring
Miscellaneous: early sepsis, patients who require closely titrated intravenous fluids, pregnant women with severe preeclampsia or other medical problems

From the American College of Critical Care Medicine, 1998; Nasraway, 1998.

direct this care. Most hospitals employ a blend of these concepts, and in general, units can be divided into three types.

First, medical and surgical ICUs in most hospitals care for severely ill obstetrical patients. These are staffed by specialists often certified in critical care medicine. Admissions or transfers to these units are situation-specific and based on the acuity of care needed and on the ability of the facility to provide it. For example, pregnant women who require ventilatory support, invasive monitoring, or pharmacological support of circulation are typically transferred to an ICU (Chantry, 2015). In an earlier review of more than 25 tertiary-care referral institutions, approximately 0.5 percent of obstetrical patients were transferred to these ICU types (Zeeman, 2006).

A second option is the obstetrical *intermediate care unit*. Sometimes referred to as a *high-dependency care unit*, this type is found at Parkland Hospital. Located within the labor and delivery unit, it has designated rooms staffed by experienced personnel. This two-tiered system incorporates the guidelines for intermediate and intensive care. Care is provided by maternal-fetal medicine specialists, obstetricians, and nurses with experience in critical care obstetrics. As needed, this team is expanded to include other obstetricians and anesthesiologists, hospitalists, gynecological oncologists, pulmonologists, cardiologists, surgeons, and other medical and surgical subspecialists (Stevens, 2015). Many tertiary-care centers have developed similar intermediate care units and use selected triage to ICUs.

Last, a few services have a full-care ICU as described first. However, it is distinctly operated by obstetrical and anesthesia personnel near the labor and delivery unit (Zeeman, 2003, 2006).

The American College of Obstetricians and Gynecologists (2019a) has summarized critical obstetrical care implementation depending on hospital size and technical facilities. For intrahospital transfers, the federal Emergency Medical Treatment and Labor Act (EMTALA) guidelines must be followed. Moreover, according to the American Academy of Pediatrics and the American College of Obstetricians and Gynecologists (2017), the minimal monitoring required for a critically ill patient during transport includes continuous pulse oximetry, electrocardiography, and regular assessment of vital signs. Patients must have secure venous access, and those who are mechanically ventilated must have endotracheal tube position confirmed and secured. Left uterine displacement and supplemental oxygen is applied routinely during transport of antepartum patients. Continuous fetal heart rate or tocodynamic monitoring is individualized.

Severe Maternal Morbidity

Childbirth can result in significant morbidity for the pregnant woman. To help address this, *severe maternal morbidity (SMM)* was developed as a population-based monitoring standard for the most common of these complications (Callaghan, 2012). An overall SMM rate is derived from 18 SMM indicators, which are abstracted from International Classification of Diseases-10 (ICD-10) codes in administrative databases. SMM rates for an individual indicator also may be informative. Some indicators are found in Table 50-1, and the full list is available at www.cdc.gov/reproductivehealth/maternalinfanthealth/smm/severe-morbidity-ICD.htm. Several of these are included in this chapter, whereas others are addressed in specific chapters on their topic.

The goal of SMM monitoring is to identify opportunities for intervention and prevention. Despite its promise, limitations should be recognized. First, the rate does not factor underlying patient comorbidities and obstetrical risks. Thus, a tertiary-care center that serves as a referral center for women with placenta accreta spectrum will understandably have higher blood transfusion rates. Second, the ICD-10 indicators for existing SMM events are not comprehensive. For example, only codes for *total* abdominal hysterectomy are currently included in the SMM rate, whereas *supracervical* hysterectomy is not. With these limitations in mind, caution should be exercised when using SMM as a quality metric to compare hospitals (Callaghan, 2012).

Hemodynamic Changes in Pregnancy

Data obtained during pregnancy with pulmonary artery catheterization (PAC) have contributed immensely to the understanding of normal pregnancy hemodynamics and pathophysiology of common obstetrical conditions. Clark and coworkers (1989) used PAC to obtain cardiovascular measurements in healthy

TABLE 50-2. Formulas for Deriving Various Cardiopulmonary Parameters

Mean arterial pressure (MAP) (mm Hg) = [SBP + 2 (DBP)] ÷ 3
Cardiac output (CO) (L/min) = heart rate × stroke volume
Stroke volume (SV) (mL/beat) = CO/HR
Stroke index (SI) (mL/beat/m^2) = stroke volume/BSA
Cardiac index (CI) (L/min/m^2) = CO/BSA
Systemic vascular resistance (SVR) (dyn × s × cm^{-5}) = [(MAP − CVP)/CO] × 80
Pulmonary vascular resistance (PVR) (dyn × s × cm^{-5}) = [(MPAP − PCWP)/CO] × 80

BSA = body surface area (m^2); CVP = central venous pressure (mm Hg); DBP = diastolic blood pressure; HR = heart rate (beats/min); MAP = mean systemic arterial pressure (mm Hg); MPAP = mean pulmonary artery pressure (mm Hg); PCWP = pulmonary capillary wedge pressure (mm Hg); SBP = systolic blood pressure.

pregnant women and again in these same women when nonpregnant (Chap. 4, p. 64). Other evaluated conditions include preeclampsia-eclampsia, acute respiratory distress syndrome, and amnionic-fluid embolism (Clark, 1997; Cunningham, 1987; Hankins, 1985). Because of these studies, most have concluded that such monitoring is seldom necessary (American College of Obstetricians and Gynecologists, 2013, 2019a, 2020; Magder, 2015).

Formulas for deriving some hemodynamic parameters are shown in Table 50-2. These measurements can be indexed for body size by dividing by body surface area. Normal values for nonpregnant adults are used, but with the caveat that these may not necessarily reflect changes induced by the low-resistance uteroplacental circulation.

Cardiac complications are a common indication for ICU admission of pregnant women (Guntupalli, 2015b). Evaluation of cardiac function is frequently performed using echocardiography. This technology is indispensable in interrogating cardiac anatomy and especially right-ventricular function (Krishnan, 2015; Thiele, 2015). It is considered in more detail in Chapter 52 (p. 918), and some normal values are listed in the Appendix (p. 1233).

Given the association of cardiac dysfunction with maternal morbidity and mortality, efforts have strived to expand cardiac monitoring by including noninvasive cardiac output monitoring (NICOM). With this tool, a small electrical current is applied to the chest, and voltage signals are captured by four skin sensors arranged in a box on the chest. Compared with Doppler echocardiography, NICOM significantly overestimates stroke volume and cardiac output (McLaughlin, 2017). This modality has not yet been widely adopted for use in the obstetrical population.

ACUTE PULMONARY EDEMA

The incidence of pulmonary edema complicating pregnancy averages 1 in 500 deliveries at tertiary referral centers. Of the two general etiologies, *cardiogenic*, namely, *hydrostatic edema* is caused by high pulmonary capillary hydraulic pressures. The other is *noncardiogenic*, that is, *permeability edema* caused by capillary endothelial and alveolar epithelial damage. In pregnancy, noncardiogenic pulmonary edema is more common. More than half of pregnant women who develop pulmonary edema have some degree of sepsis in conjunction with tocolysis, severe preeclampsia, or obstetrical hemorrhage combined with vigorous fluid therapy (O'Dwyer, 2015; Pordeus, 2018).

In one study, the etiologies of pulmonary edema were hypertension, cardiogenic, or both, and iatrogenic fluid overload (Pordeus, 2018). In another study of 53 cases, 83 percent were caused by hypertensive disorders; 11 percent, cardiac events; and 6 percent, sepsis (O'Dwyer, 2015). Although used less commonly today, tocolytic therapy with β-mimetic drugs was the cause of up to 40 percent of pulmonary edema cases (Gandhi, 2014; Jenkins, 2003).

■ Noncardiogenic Permeability Edema

Endotheliopathy is the common denominator that is associated with preeclampsia, sepsis, and acute hemorrhage—or frequently combinations thereof—and they are the most common predisposing factors to pulmonary edema (Table 50-3). These clinical scenarios are often associated with corticosteroids given to induce fetal lung maturation along with vigorous fluid replacement and tocolytic therapy (Thornton, 2011). Parenteral β-agonists are indisputedly linked to pulmonary edema. Some studies have also associated magnesium sulfate given for preeclampsia (Gandhi, 2014; Wilson, 2014; Xiao, 2014). Combined therapy is causative.

■ Cardiogenic Hydrostatic Edema

Ventricular failure causing pulmonary edema in pregnancy is usually associated with some form of hypertension, hemorrhage and anemia, and sepsis (Cunningham, 2019; Vaught, 2018).

TABLE 50-3. Some Causes and Associated Factors for Pulmonary Edema in Pregnancy

Noncardiogenic permeability edema: endotheliopathy with capillary-alveolar leakage
Preeclampsia syndrome
Acute hemorrhage
Sepsis: pyelonephritis, metritis
Tocolytic therapy: β-mimetics, $MgSO_4$
Aspiration pneumonitis
Vigorous intravenous fluid therapy
Pancreatitis
Cardiogenic pulmonary edema: myocardial failure with hydrostatic edema from excessive pulmonary capillary pressure
Hypertensive cardiomyopathy
Obesity: adipositas cordis
Left-sided valvular disease
Vigorous intravenous fluid therapy
Pulmonary hypertension

Although it can be due to congenital or acquired anatomical defects, diastolic dysfunction is frequently from chronic hypertension, obesity, or both (Jessup, 2003; Kenchaiah, 2002). In these women, acute systolic hypertension exacerbates diastolic dysfunction and causes pulmonary edema (Dennis, 2012; Vaught, 2018). In two studies of pregnant women with preeclampsia and pulmonary edema, half of them were undelivered (Gandhi, 2014; Pordeus, 2018).

Diagnosis

Clinical examination is confirmed by chest radiographs. Bedside lung sonography may be helpful to detect fluid in the interstitial space and alveoli (Pachtman, 2017). In many cases, when echocardiography is done later, systolic function is normal as measured by ejection fraction.

In addition, ventricular myocytes and fibroblasts secrete *brain natriuretic peptide (BNP)* and *atrial natriuretic peptide (ANP)* with the distention seen in heart failure. In nonpregnant patients, concentrations <100 pg/mL have an excellent negative predictive value, and levels >500 pg/mL have an excellent positive predictive value. It is problematic that levels frequently are 100 to 500 pg/mL and thus are nondiagnostic. Moreover, concentrations of N-terminal BNP and ANP are both elevated with preeclampsia (Szabo, 2014; Tihtonen, 2007). Normal values are discussed in Chapter 4 (p. 65), and those for normal pregnancy are given in the Appendix (p. 1231).

Management

Acute pulmonary edema requires emergency care. Oxygen therapy is initiated and furosemide is given in periodic 20- to 40-mg intravenous doses as needed. For oxygen delivery, nasal cannula, simple masks, and nonrebreathing masks are first-line systems. Both nasal cannula and simple mask allow mixing of supplemental oxygen with room air. Consequently, oxygen administration is imprecise (Bateman, 1998). A nonrebreathing mask has valves that limit the mixing of exhaled gas and room air with the oxygen supply. Flow rates up to 10 to 15 L/min may be achieved, and oxygen concentrations approach 95 percent (Boumphrey, 2003). As a treatment goal, a pulse oximetry reading >92 percent reflects adequate oxygenation.

Further treatment depends on whether a woman is ante- or postpartum. A live fetus prohibits the use of cardioactive drugs that might rapidly lower peripheral resistance and in turn severely diminish uteroplacental circulation. The cause of cardiogenic failure is determined by echocardiography, which will help direct further therapy. *Importantly, acute pulmonary edema is not an indication for emergency cesarean delivery*.

ACUTE RESPIRATORY DISTRESS SYNDROME

Acute lung injury that causes a form of severe permeability pulmonary edema and respiratory failure is termed *acute respiratory distress syndrome (ARDS)*. This is a pathophysiological continuum from mild pulmonary insufficiency to dependence on high inspired oxygen concentrations and mechanical ventilation. Uniform criteria for its diagnosis are lacking, and thus the incidence is variably reported for pregnancy. Rush and colleagues (2017) queried the nationwide inpatient samples of more than 5.4 million pregnancies and cited an incidence of 60 ventilated cases per 100,000 births. They found an overall mortality rate of 9 percent. This rate is much higher if caused or complicated by sepsis. Last, if ARDS develops antepartum, the perinatal mortality rate is correspondingly high.

Definitions

Physiological criteria required for diagnosis of acute lung injury are study dependent. In general, less precise terms are used for clinical care. Clinical findings include dyspnea, tachypnea, and oxygen desaturation. Most investigators define ARDS as radiographically documented pulmonary infiltrates, a ratio of arterial oxygen tension to the fraction of inspired oxygen (Pao_2:Fio_2) <200, and no evidence of heart failure (Baron, 2018). Revised by international consensus, the *Berlin Definition* includes categories of mild, moderate, and severe (Fan, 2018).

Etiopathogenesis

ARDS begins with an acute lung injury from various causes (Table 50-4). More than half of pregnant women with ARDS have some combination of sepsis, hemorrhage, shock, and fluid overload. Diffuse infectious pneumonia and sepsis are two of the most frequent single-agent causes. Because it is common, influenza pneumonitis often is a cause. Other etiologies such as pneumococcal, metapneumovirus, and Legionnaire disease also are encountered (Close, 2016; Fuchs, 2017). Of sepsis causes, pyelonephritis, puerperal pelvic infection, and chorioamnionitis are the most frequent. The contribution of *transfusion-related acute lung injury (TRALI)* is unclear (Chap. 44, p. 774).

TABLE 50-4. Some Causes of Acute Lung Injury and Respiratory Failure

Pneumonia: bacterial, viral, aspiration
Sepsis: chorioamnionitis, pyelonephritis, puerperal infection, septic abortion
Hemorrhage: shock, massive transfusion, transfusion-related acute lung injury (TRALI)
Preeclampsia syndrome
Tocolytic therapy
Embolism: amnionic fluid, trophoblastic disease, air, fat
Connective tissue disease
Substance abuse
Irritant inhalation and burns
Pancreatitis
Drug overdose
Fetal surgery
Trauma
Sickle-cell disease
Miliary tuberculosis
Cerebral hemorrhage

From Baron, 2018; Duarte, 2014; Lapinsky, 2015; Sibai, 2014; Snyder, 2013; Zeeman, 2006.

Endothelial injury in the lung capillaries releases cytokines that recruit neutrophils to the inflammation site. Here, they elaborate more cytokines to worsen tissue injury. Three stages describe ARDS development (Baron, 2018). First, the *exudative phase* follows widespread injury to the alveolar epithelium and to the microvascular endothelium, including the pulmonary vasculature. This endotheliopathy results in increased pulmonary capillary permeability, surfactant loss or inactivation, diminished lung volume, and vascular shunting that creates arterial hypoxemia. Next, the *proliferative phase* usually begins approximately 7 days later and lasts up to 21 days. Most patients recover during this phase. Last, the *fibrotic phase* results from healing. Despite these insults, the long-term prognosis for pulmonary function is surprisingly good (Baron, 2018; Herridge, 2003).

Clinical Course

With pulmonary injury, the clinical condition depends largely on the insult magnitude, the ability to compensate for it, and the disease stage. At first, physical examination findings are absent, except perhaps hyperventilation, and arterial oxygenation usually is adequate. With worsening, clinical and radiological evidence for pulmonary edema, decreased lung compliance, and increased intrapulmonary blood shunting become apparent. Progressive alveolar and interstitial edema develops, and inflammatory cells and erythrocytes extravasate. Ideally, pulmonary injury is identified at this early stage, and specific therapy is directed at the underlying insult.

Further progression to acute respiratory failure is characterized by marked dyspnea, tachypnea, and hypoxemia. Additional functional lung volume loss results in worsening of pulmonary compliance and greater shunting. Diffuse abnormalities are heard by auscultation, and a chest radiograph characteristically demonstrates bilateral lung involvement (Fig. 50-1). At this phase, the injury ordinarily would be lethal without ventilatory support. When shunting exceeds 30 percent, severe refractory hypoxemia develops. Comorbid metabolic and respiratory acidosis can result in myocardial irritability, dysfunction, and cardiac arrest.

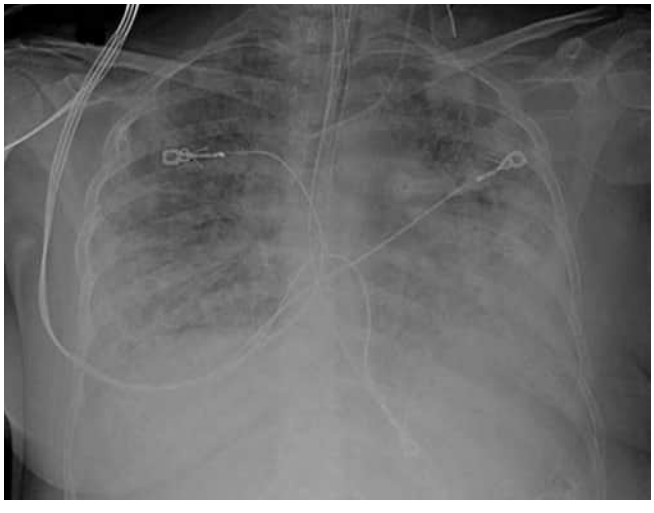

FIGURE 50-1 Anteroposterior chest radiograph of a second-trimester pregnant woman with marked bilateral parenchymal and pleural opacification secondary to acute respiratory distress syndrome (ARDS).

Management

ARDS mortality rates have declined because of advances in critical care medicine (Baron, 2018; Fan, 2018). Management requires close attention to recognizing and treating underlying medical and surgical disorders. In cases of severe acute lung injury, providing adequate oxygenation of peripheral tissues is balanced against ventilatory maneuvers that further aggravate lung injury. At least intuitively, increasing oxygen delivery should produce a corresponding rise in tissue uptake, but this is difficult to measure. Support of systemic perfusion with intravenous crystalloid and blood is imperative. Because sepsis is commonplace in lung injury, aggressive antimicrobial therapy is given for infection, and any necrotic tissues are debrided. Oxygen delivery can be greatly improved by correcting anemia. Specifically, each gram of hemoglobin carries 1.25 mL of oxygen when 90-percent saturated. By comparison, raising the arterial Pao_2 from 100 to 200 mm Hg results in the transport of only 0.1 mL of additional oxygen for each 100 mL of blood.

Reasonable goals in caring for the woman with severe lung injury are a Pao_2 of 60 mm Hg or 90-percent oxygen saturation using an inspired oxygen content <50 percent and positive end-expiratory pressures <15 mm Hg. With regard to the pregnancy, it remains controversial whether delivery of the fetus improves maternal oxygenation (Mallampalli, 2010). In a study of 29 women undergoing mechanical ventilation, 10 were delivered while intubated (Lapinsky, 2015). Respiratory function modestly improved in half, but no factors were identified that predicted a better outcome.

Mechanical Ventilation

Noninvasive ventilation, that is, positive-pressure ventilation by face mask, may be effective in some women in early stages of pulmonary insufficiency (Duarte, 2014). *Conventional ventilation* is done with tracheal intubation. Early intubation is preferred in the gravida if respiratory failure is more likely than not and especially if it appears imminent. Because of the physiological changes outlined in Chapter 4 (p. 67), $Paco_2$ is normally reduced in a gravida relative to a nonpregnant woman. Thus, intubation should be considered when $Paco_2$ levels reach 35 to 40 mm Hg.

Mechanical ventilation is used to assist or replace spontaneous respiration (Celli, 2018). It improves oxygenation by its application of high-oxygen-content gas and positive pressure. Many successful formulas for mechanical ventilation are employed, and initially a tidal volume ≤6 mL/kg is optimal (Fan, 2018; Schwaiberger, 2016). Adjustments are made to obtain a Pao_2 >60 mm Hg or a hemoglobin oxygen saturation ≥90 percent and to reach a $Paco_2$ of 35 to 45 mm Hg. Lower Pao_2 levels are avoided, because placental perfusion may be impaired.

The mode is the manner in which ventilator breaths are triggered, cycled, and limited. Three commonly used ventilation modes of include *assist-control*, *intermittent mandatory*, and *pressure-support ventilation*. Although not a support mode,

continuous positive airway pressure can be used in patients with an intact ventilatory system who require little ventilatory support.

Pregnancy

In a study of 51 women with ARDS, almost half had severe preeclampsia, and most required intubation postpartum. Eleven were delivered while being ventilated, and another six were discharged undelivered (Jenkins, 2003). Two mothers died, and this included a woman who died as a complication of tocolytic treatment. In a multicenter report, Lapinsky and associates (2015) described 29 pregnant women undergoing mechanical ventilation for various indications. Only a few had severe ARDS, and the mortality rate was 10 percent. Ten women delivered while being ventilated, but this had little beneficial effect on their respiratory status.

Positive End-Expiratory Pressure

With severe lung injury and high intrapulmonary shunt fractions, it may not be possible to provide adequate oxygenation with usual ventilatory pressures, even with 100-percent oxygen. Positive end-expiratory pressure is usually successful in decreasing the shunt by recruiting collapsed alveoli. At low levels of 5 to 15 mm Hg, positive pressure can typically be used safely. At higher levels, impaired right-sided venous return can result in decreased cardiac output, lowered uteroplacental perfusion, alveolar overdistention, falling compliance, and barotrauma (Celli, 2018; Schwaiberger, 2016).

Extracorporeal Membrane Oxygenation

As discussed in Chapter 33 (p. 600), extracorporeal membrane oxygenation (ECMO) has been successfully used for neonatal meconium aspiration syndrome. Some preliminary observations suggest that veno-venous ECMO may be useful in adults with ARDS (Combes, 2018; Ende, 2016; Matthay, 2018). In one case series, 12 pregnant women with influenza-induced lung failure were treated with ECMO, and of four maternal deaths, three were due to anticoagulation-related hemorrhage (Nair, 2011). ECMO use also has been reported for status asthmaticus (Clifford, 2018; Steinack, 2017). In multiple reviews, ECMO was used mostly for ARDS, and the maternal and perinatal mortality rate approximated 30 percent (Liu, 2018; Ramanathan, 2020; Saad, 2016). Maternal survival appears to be significantly lower compared with nonpregnant women requiring ECMO (Webster, 2019).

Fetal Oxygenation

The propensity of the hemoglobin molecule to release oxygen is described by the *oxyhemoglobin dissociation curve* (Fig. 50-2). For clinical purposes, the curve can be divided into an upper oxygen association curve representing the alveolar-capillary environment and a lower oxygen dissociation portion representing the tissue-capillary environment. Shifts of the curve have their greatest effect at the steep portion because they affect oxygen delivery. A rightward shift is associated with decreased hemoglobin affinity for oxygen and hence greater tissue-capillary oxygen interchange. Hypercapnia, metabolic acidosis, fever, and increased 2,3-diphosphoglycerate levels produce rightward

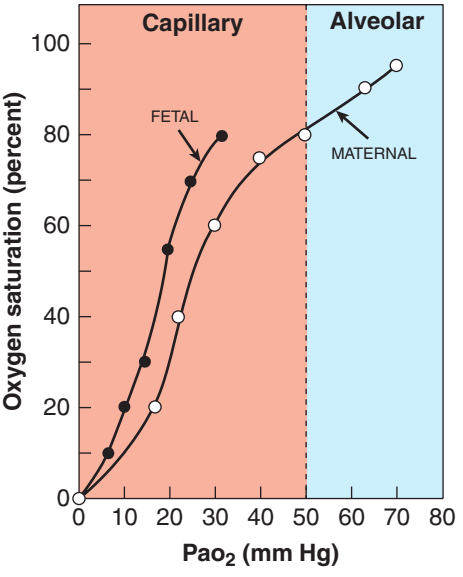

FIGURE 50-2 Oxyhemoglobin dissociation curve. With higher oxygen tension (Pao_2) in the pulmonary alveoli, adult hemoglobin is maximally saturated compared with that at the lower oxygen tension in the tissue capillaries. Note that at any given oxygen tension, fetal hemoglobin carries more oxygen than adult hemoglobin, as indicated by percent saturation.

shifts. During normal pregnancy, the erythrocyte concentration of 2,3-diphosphoglycerate rises by approximately 30 percent, which favors oxygen delivery.

Fetal hemoglobin has a higher oxygen affinity than adult hemoglobin. As seen in Figure 50-2, its oxyhemoglobin dissociation curve is positioned to the left of the adult curve. To achieve 50-percent hemoglobin saturation in the mother, the Pao_2 must be 27 mm Hg compared with only 19 mm Hg in the fetus. Under normal physiological conditions, the fetus is constantly on the dissociation, or tissue, portion of the curve. Even with severe maternal lung disease and very low Pao_2 levels, oxygen displacement to fetal tissues is favored. For example, in pregnant women who live at high altitudes, and despite a maternal Pao_2 of only 60 mm Hg, the fetal Pao_2 is equivalent to that seen at sea level (Subrevilla, 1971).

Intravenous Fluids

Although mortality rates are similar, conservative versus liberal fluid management is associated with fewer days of mechanical ventilation (Wiedemann, 2006). Some normal pregnancy-induced physiological changes predispose to a greater risk of permeability edema from vigorous fluid therapy. Serum albumin concentration determines colloid oncotic pressure (COP), and 1 g/dL exerts approximately 6 mm Hg of pressure. As discussed in Chapter 4 (p. 70), serum albumin concentrations normally drop in pregnancy. This results in a decline in COP from 28 mm Hg in the nonpregnant woman to 23 mm Hg at term and to 17 mm Hg in the puerperium (Dennis, 2012). With preeclampsia, endotheliopathy causes extravascular albumin loss and lowered serum albumin levels. These changes have a significant clinical effect on the *colloid oncotic pressure/wedge pressure gradient*. Normally, this gradient exceeds 8 mm Hg. However, when it is ≤4 mm Hg, the risk for pulmonary edema rises due

to Starling forces. Finally, no benefits are gained by albumin versus crystalloid infusions in these women (Uhlig, 2014).

Long-Term Outcomes

Most patients with ARDS regain nearly normal lung function (Baron, 2018). In nonpregnant subjects, however, risks for impaired global cognitive function at 3 and 12 months are significant (Pandharipande, 2013). Moreover, return to basic normal activity is delayed 1 to 2 years. In a 5-year follow-up study, Herridge and coworkers (2011) reported normal lung function but significant exercise limitation as well as physical and psychological sequelae. Long-term follow-up studies of pregnant women who recover from ARDS are lacking.

SEPSIS AND SEPTIC SHOCK

Sepsis is defined as infection with organ dysfunction, and *septic shock* manifests with unresponsive hypotension (Cecconi, 2018). The Third International Consensus Definition—"Sepsis-3"—denotes clinical criteria for sepsis to include suspected infection and acute organ dysfunction (Seymour, 2018). Use of the terms *systemic inflammatory response syndrome (SIRS)* and *severe sepsis* are no longer recommended. The syndrome is induced by a systemic inflammatory response to bacteria or viruses or their by-products such as endotoxins or exotoxins. Its severity is a continuum (Fig. 50-3). In an analysis of 55 million births, Kendle and associates (2019) found an incidence of 2.4 cases per 10,000 deliveries. The Society for Maternal-Fetal Medicine cites the incidence to be 4 to 10 cases per 10,000 births. According to the Centers for Disease Control and Prevention (CDC), infection and sepsis caused 12 percent of pregnancy-related deaths in the United States from 2013 to 2017 (Petersen, 2019).

Infections that most commonly cause sepsis syndrome in obstetrics are pyelonephritis (Chap. 56, p. 997), chorioamnionitis and puerperal sepsis (Chap. 37, p. 651), pneumonia (Chap. 54, p. 962), septic abortion (Chap. 11, p. 203), and necrotizing fasciitis (Chap. 37, p. 654). Septic shock is defined by the need for vasopressor therapy despite fluid resuscitation. The mortality rate for this in nonpregnant patients is 20 percent (Snyder, 2013). The maternal mortality risk from sepsis is significantly underestimated (Bauer, 2015; Chebbo, 2016). However, most evidence indicates that case-fatality rates are lower for pregnant women compared with age-matched nonpregnant controls (Kidson, 2018).

Etiopathogenesis

Most information concerning sepsis pathogenesis derives from study of lipopolysaccharide (LPS), which is the endotoxin portion of gram-negative bacteria. The lipid A moiety is bound by mononuclear blood cells, becomes internalized, and stimulates release of mediators and a series of complex downstream perturbations. Clinical aspects of sepsis manifest when cytokines that have endocrine, paracrine, and autocrine actions are released (Seymour, 2018; Suffredini, 1989).

Although sepsis in obstetrics may be caused by several pathogens, most cases stem from a small group. Sepsis and bacteremia complicating pyelonephritis are commonly caused by *Escherichia coli* and *Klebsiella* species (Cunningham, 1987; Snyder, 2013). Although pelvic infections are usually polymicrobial, bacteria that cause severe sepsis are frequently endotoxin-producing Enterobacteriaceae, and most commonly *E coli* (Eschenbach, 2015). Other pelvic pathogens are aerobic and anaerobic streptococci, *Bacteroides* species, and *Clostridium* species. Of these, group A streptococcal infections are a significant source of infection (Leonard, 2019). Some strains of group

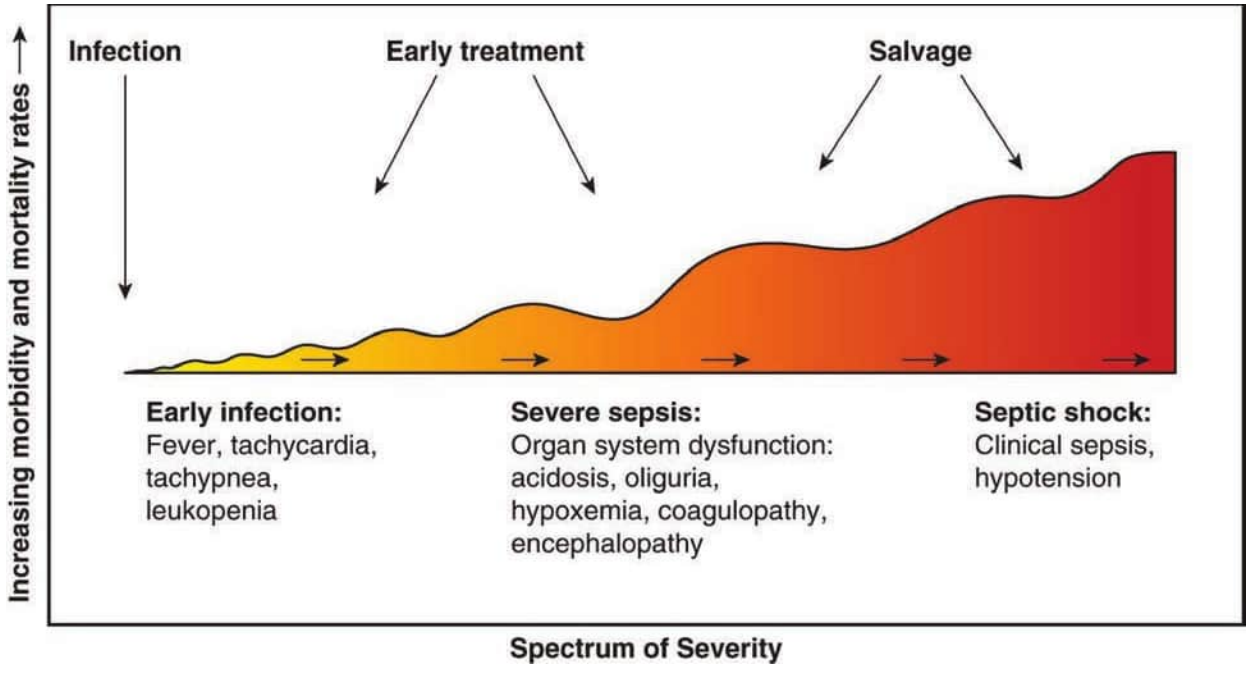

FIGURE 50-3 Sepsis begins with a systemic inflammatory response to infection that may progress to septic shock.

TABLE 50-5. Clinical Manifestations of Sepsis

Central nervous system: confusion, delirium, somnolence, coma, combativeness, fever, hypothermia
Cardiovascular: tachycardia, hypotension
Pulmonary: tachypnea, arteriovenous shunting with dysoxia and hypoxemia, exudative infiltrates from endothelial-alveolar damage, pulmonary hypertension
Gastrointestinal: gastroenteritis—nausea, vomiting, and diarrhea; ileus; hepatocellular necrosis—jaundice, transaminitis
Renal: prerenal oliguria, azotemia, acute kidney injury, proteinuria
Hematological: leukocytosis or leukopenia, thrombocytopenia, activation of coagulation with disseminated intravascular coagulation
Endocrinological: hyperglycemia, adrenal insufficiency
Cutaneous: acrocyanosis, erythroderma, bullae, digital gangrene

A β-hemolytic streptococci and *Staphylococcus aureus*—including community-acquired methicillin-resistant *S aureus* strains (CA-MRSA)—produce a superantigen that activates T cells to rapidly cause all features of sepsis. This manifests as *toxic shock syndrome*, which is discussed further in Chapter 37 (p. 659) (Moellering, 2011; Soper, 2011).

Potent bacterial exotoxins also can cause severe sepsis syndrome. Examples include exotoxins from *Clostridium perfringens* or *sordellii,* toxic shock syndrome toxin 1 (TSST-1) from *S aureus*, and toxic shock–like exotoxin from group A β-hemolytic streptococci (Herrera, 2016; Kaiser, 2018). These last exotoxins cause rapid and extensive tissue necrosis and gangrene, especially of the postpartum uterus, and may cause profound cardiovascular collapse and maternal death. In a review discussed subsequently, the maternal mortality rate from these infections was 58 percent (Yamada, 2010).

Sepsis begins with an inflammatory response that is directed against microbial endotoxins and exotoxins. CD4 T cells and leukocytes are stimulated to produce proinflammatory compounds that include tumor necrosis factor α (TNF-α), several interleukins, and other cytokines, proteases, oxidants, and bradykinin that result in a "cytokine storm." Many other cellular reactions then follow and include stimulation of pro- and anti-inflammatory compounds, procoagulant activity, gene activation, receptor regulation, and immune suppression (Seymour, 2018). It is also likely that interleukin 6 (IL-6) mediates myocardial suppression (Pathan, 2004).

The pathophysiological response to this cascade is selective vasodilation with maldistribution of blood flow. Leukocyte and platelet aggregation cause capillary plugging. Worsening endotheliopathy causes profound permeability, capillary leakage, and interstitial fluid accumulation. Depending on the degree of endothelial injury and inflammatory response, a pathophysiological and clinical continuum evolves as depicted in Figure 50-3. The clinical syndrome begins with subtle signs of sepsis from infection and terminates with septic shock. In its early stages, clinical shock results primarily from lowered systemic vascular resistance that is not compensated fully by increased cardiac output. Hypoperfusion worsens lactic acidosis, decreases tissue oxygen extraction, and leads to end-organ dysfunction that includes acute lung and kidney injury. Finally, *septic cardiomyopathy* with global involvement is common with severe sepsis (Beesley, 2018; Martin, 2018).

Clinical Manifestations

Sepsis has myriad clinical manifestations that, at least in part, are dependent on the specific invading microorganism and its particular endo- or exotoxins. Some of the general effects of LPS are shown in Table 50-5.

Thus, although capillary leakage initially causes hypovolemia, if intravenous crystalloid is given at this point, sepsis hemodynamically can be described as a high-cardiac-output, low-systemic-vascular-resistance condition (Fig. 50-4).

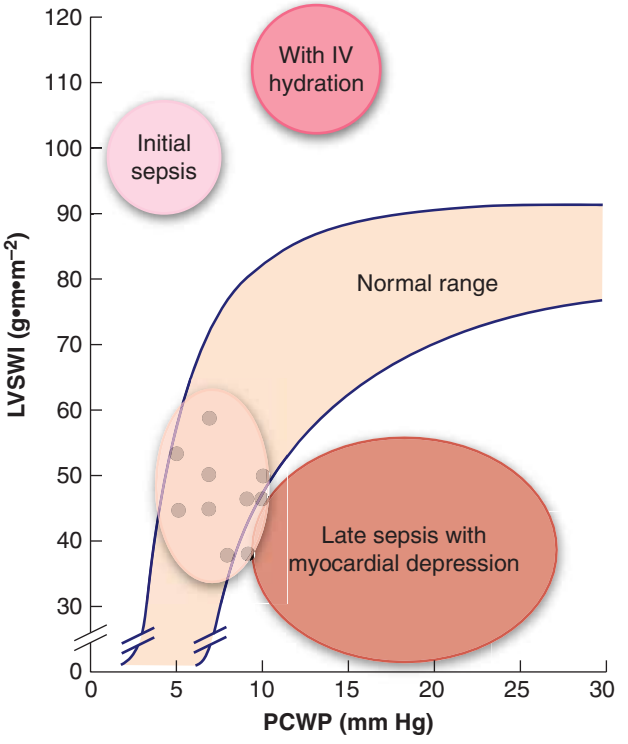

FIGURE 50-4 Hemodynamic effects of sepsis. Values for normal women at term are shown by dots. With early sepsis, there is high cardiac output and low vascular resistance. With fluid resuscitation, cardiac output increases even more, but so does capillary hydraulic pressure. With continued sepsis, there may be myocardial depression to further increase capillary hydraulic pressure. Decreased plasma oncotic pressure (serum albumin [g] × 6 mm Hg) contributes to interstitial lung fluid and endo/epithelial leak causes alveolar flooding. IV = intravenous; LVSWI = left ventricular stroke work index; PCWP = pulmonary capillary wedge pressure.

Concomitantly, pulmonary hypertension develops, and despite the high cardiac output, severe sepsis also causes myocardial depression (Seymour, 2018). This is often referred to as the *warm phase* of septic shock. These findings are the most common cardiovascular manifestations of early sepsis, but they can be accompanied by some of the other clinical or laboratory aberrations listed in the prior section.

The response to initial intravenous hydration may be prognostic. Most pregnant women who have early sepsis show a salutary response with crystalloid and antimicrobial therapy, and if indicated, debridement of infected tissue. Conversely, if following vigorous fluid infusion, septic shock results, then the prognosis is more guarded. At this juncture, if β-adrenergic inotropic agents fail to improve cardiovascular status, this indicates severe and unresponsive extracellular fluid extravasation with vascular insufficiency, overwhelming myocardial depression, or both. Oliguria and continued peripheral vasoconstriction characterize a secondary, *cold phase* of septic shock that is rarely survived. Another poor prognostic sign is continued renal, pulmonary, and cerebral dysfunction once hypotension is corrected (Chebbo, 2016; Seymour, 2018). The average risk of death rises by 15 to 20 percent with failure of each organ system.

Management

In 2004, an international consensus effort was launched as the *Surviving Sepsis Campaign* (Dellinger, 2013). The cornerstone of management was termed *early goal-directed therapy (EGDT)*, which stressed prompt recognition of serious bacterial infection and close monitoring of vital signs and urine flow. After three multicenter trials did not show that this protocol improved survival rates, this strategy is no longer recommended (PRISM Investigators, 2017; Seymour, 2018).

Similar conclusions were reached with sets of early warning systems in obstetrics (Edwards, 2015; Mhyre, 2014). *Modified Early Warning Score (MEWS)* failed to predict sepsis in obstetrical populations with positive predictive values as low as 1 to 2 percent (Lappen, 2010). Reasons for such poor performance in pregnant women include physiological changes of vital signs; relatively fewer comorbidities in a younger, healthier population; and predominantly genitourinary infections. Thus, current efforts such as the *Sepsis in Obstetrics Score* have been designed to identify women who benefit from ICU admission early in their hospital course (Albright, 2017). However, the validity of these findings beyond a single center and against controls is yet unstudied.

Still, the major tenets of EGDT are employed for sepsis treatment. Management of sepsis stresses prompt administration of broad-spectrum antimicrobials, collection of specimens for culture, serum lactate level measurement, an intravenous fluid bolus, and vasopressors as needed (Seymour, 2018). An algorithm for management of sepsis is shown in Figure 50-5. The three basic steps are performed as simultaneously as possible and include evaluation of the sepsis source and its sequelae, cardiopulmonary function assessment, and immediate management. The most important step in sepsis management is rapid infusion of 2 L and sometimes as many as 4 to 6 L of crystalloid fluids to restore renal perfusion in severely affected women (Vincent, 2013). Simultaneously, appropriately chosen broad-spectrum antimicrobials are begun, preferentially within 1 hour (Chen, 2019; Society for Maternal-Fetal Medicine, 2019). Because hemoconcentration is caused by the capillary leak, if anemia coexists, blood is given. Specific thresholds for gravidas are lacking. In a group of nonpregnant individuals admitted to an ICU, maintaining the hemoglobin concentration ≥9 g/dL did not have superior outcomes compared with levels ≥7 g/dL (Holst, 2014). That said, fetal oxygenation is improved by the higher concentration, as discussed earlier (p. 886).

The use of a colloid solution such as hetastarch is controversial (Seymour, 2018). One Scandinavian randomized trial comparing hydroxyethyl starch and Ringer acetate solutions reported a higher mortality rate with the starch solution (Perner, 2012). Another study found equivalent results with 6-percent hydroxyethyl starch compared with normal saline (Myburgh, 2012). Additionally, albumin was not found to be superior to crystalloids (Caironi, 2014).

Aggressive volume replacement ideally is promptly followed by urinary output of at least 30 and preferably 50 mL/h, as well as other indicators of improved perfusion. If not, vasoactive drug therapy is considered (Pacheco, 2014). As discussed, mortality rates are high when sepsis is further complicated by respiratory or renal failure. With severe sepsis, damage to pulmonary capillary endothelium and alveolar epithelium causes alveolar flooding and pulmonary edema. This may occur even with low or normal pulmonary capillary wedge pressures, as with the ARDS (p. 884). Therefore, in some women, mechanical ventilation is indicated.

Broad-spectrum antimicrobials are chosen empirically based on the probable source of infection. They are given promptly in maximal doses after appropriate cultures are taken of blood, urine, or exudates not contaminated by normal flora. In severe sepsis, appropriate and early empirical coverage results in better survival rates (Seymour, 2017, 2018). Acute pyelonephritis is usually caused by Enterobacteriaceae, as discussed in Chapter 56 (p. 997). For pelvic infections, empirical selection of a regimen such as ampicillin, gentamicin, plus clindamycin, which in sum covers aerobic and anaerobic pathogens, generally suffices (Chap. 37, p. 651). Associated incisional and other soft-tissue infections are increasingly likely to be caused by MRSA, thus vancomycin may be added (Klevens, 2007). With septic abortion or deep fascial infections, a Gram-stained smear may be helpful in identifying *Clostridium* species or group A streptococcal organisms.

Surgical Treatment

Continuing sepsis may prove fatal, and debridement of necrotic tissue or drainage of purulent material is crucial (Pacheco, 2014). Puerperal pelvic infections include metritis and infections of perineal lacerations or of hysterotomy or laparotomy incisions. If complicated by abscess, these may require drainage. With a septic abortion, uterine contents must be removed expeditiously by curettage as described in Chapter 11 (p. 203). Hysterectomy is seldom indicated unless gangrene has resulted.

For women with pyelonephritis, continuing sepsis should prompt a search for obstruction caused by calculi or by a perinephric or intrarenal phlegmon or abscess. Renal sonography or "one-shot" pyelography can help diagnose obstruction and calculi. With obstruction, ureteral catheterization, percutaneous nephrostomy, or flank exploration may be lifesaving (Chap. 56, p. 998).

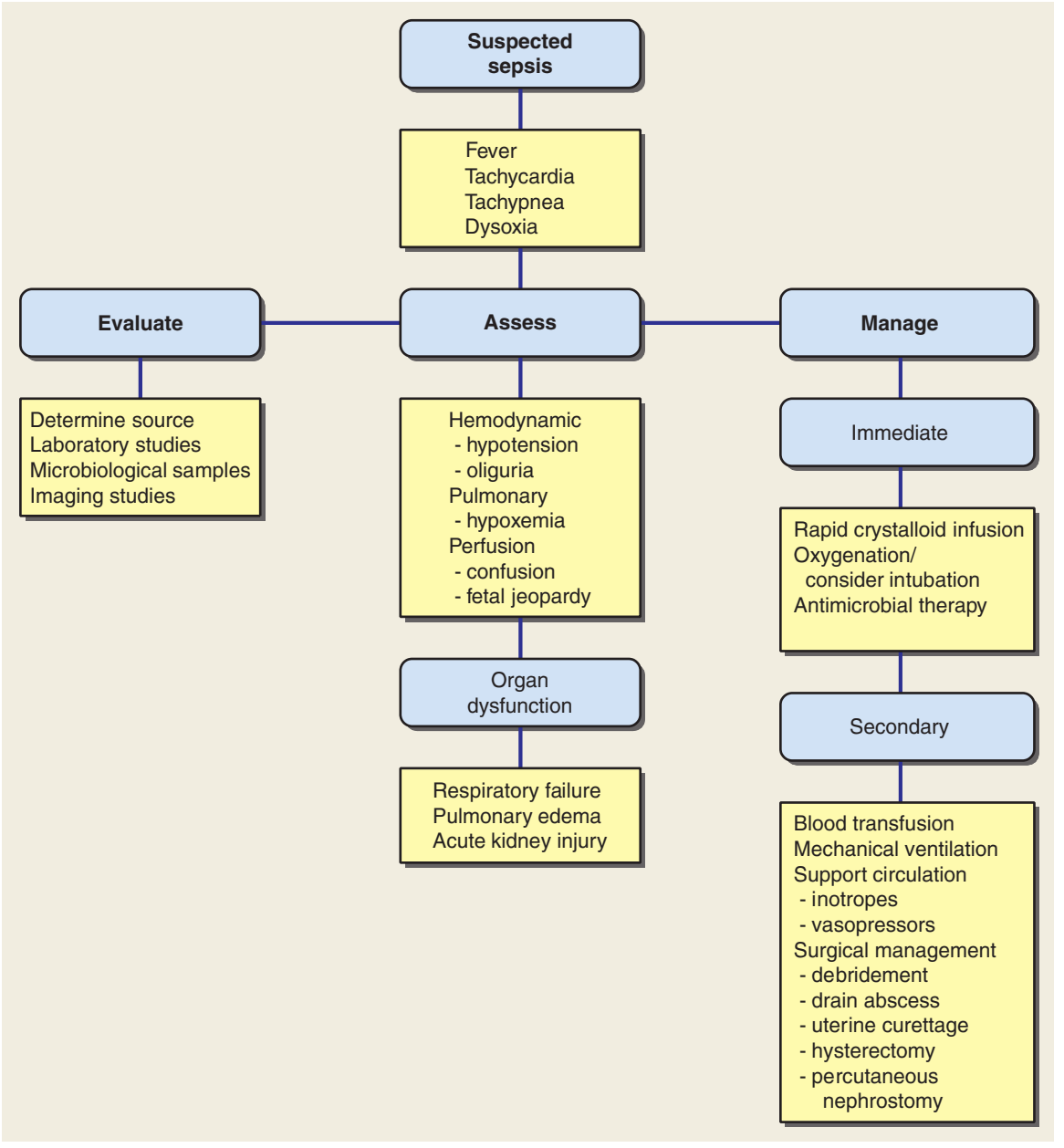

FIGURE 50-5 Algorithm for evaluation and management of sepsis. Rapid and aggressive implementation is paramount for success. The three steps—Evaluate, Assess, and Manage—are carried out as simultaneously as possible.

Computed tomography (CT) or magnetic-resonance imaging aids identification of a renal phlegmon or abscess.

Puerperal Infections. Most cases of puerperal pelvic sepsis are clinically manifested in the first several postpartum days, and intravenous antimicrobial therapy without tissue debridement is generally curative. At least four exceptions are notable.

First, massive uterine myonecrosis can be caused by group A β-hemolytic streptococcal or clostridial infections (Kaiser, 2018; Soper, 2011). Those with early-onset disease present with findings listed in Table 50-6. The mortality rate in these women with gangrene, shown in Figure 50-6 is high, and prompt hysterectomy may be lifesaving. Group A β-hemolytic streptococci and clostridial colonization or infection also cause toxic-shock syndrome without obvious gangrene (Mason, 2012). These are due to either streptococcal toxic shock syndrome–like toxin or clostridial exotoxin that evolved from *S aureus* (Chap. 37, p. 659). In many of these cases, bacteremia and widespread tissue invasion develops, but uterine and abdominal incisions are intact. If uterine necrosis can be excluded—usually by CT scanning—then in our experiences, as well as in others, hysterectomy may not be necessary (Soper, 2011). Still, these infections can be highly lethal (Chen, 2019; Yamada, 2010).

A second exception, necrotizing fasciitis of the episiotomy site or of the abdominal surgical incision, is a surgical emergency. Described by Gallup and coworkers (2002), these infections are aggressively managed as discussed in Chapter 37 (p. 655). In one instance, Sinha and colleagues (2015) described a woman with *Fournier gangrene* who required radical debridement and colostomy.

TABLE 50-6. Clinical Findings in 126 Women with Group A β-Hemolytic Streptococcal Infection

High fever
Respiratory symptoms
Gastrointestinal symptoms
Uterine hypertonus
Uterine tenderness
Capillary leak
Dyspnea, cough
Pulmonary edema
Bloating, distention
Shock

Data from Kaiser, 2018; Yamada, 2010.

Third, persistent or aggressive postpartum uterine infection with necrosis, uterine incision dehiscence, and severe peritonitis may lead to sepsis (Chap. 37, p. 651). In this regard, women following cesarean delivery who are suspected of having peritonitis should be carefully evaluated for uterine incisional necrosis or bowel perforation. These infections tend to be less aggressive than necrotizing group A streptococcal infections and develop later postpartum. CT imaging of the abdomen and pelvis can frequently disclose these. If either is suspected, timely surgical exploration is considered. With uterine incision necrosis, hysterectomy is usually necessary (Fig. 37-5, p. 657). Last, peritonitis and sepsis much less commonly may result from a ruptured parametrial, intraabdominal, or ovarian abscess (Chap. 37, p. 656).

Adjunctive Therapy

A woman with severe sepsis is supported with continuing crystalloid infusion, blood transfusions, and ventilation. In some cases, other measures are needed. Vasoactive drugs are not given unless aggressive fluid treatment fails to correct hypotension and perfusion abnormalities. First-line vasopressors are norepinephrine and vasopressin (Seymour, 2018). According to the Society for Maternal-Fetal Medicine (2019), norepinephrine has been studied most in pregnant women.

Glucocorticoid use in this setting remains controversial, and some but not all studies show a favorable effect (Marik, 2018; Venkatesh, 2018). In a recent study by Annane and colleagues (2018), hydrocortisone plus fludrocortisone compared with placebo resulted in a significantly lower mortality rate at 90 days. Thus, low-dose corticosteroid therapy can be considered with septic shock (Suffredini, 2018).

Endotoxin stimulates endothelial cells to upregulate tissue factor and thus procoagulant production (Cunningham, 2015). Consumptive coagulopathy associated with sepsis is discussed in Chapter 44 (p. 776). At the same time, endotoxin decreases the anticoagulant action of activated protein C. Several agents developed to block coagulation, however, do not improve outcomes. Last, induced hypothermia does not improve survival in patients with septic shock and respiratory failure (Itenov, 2018).

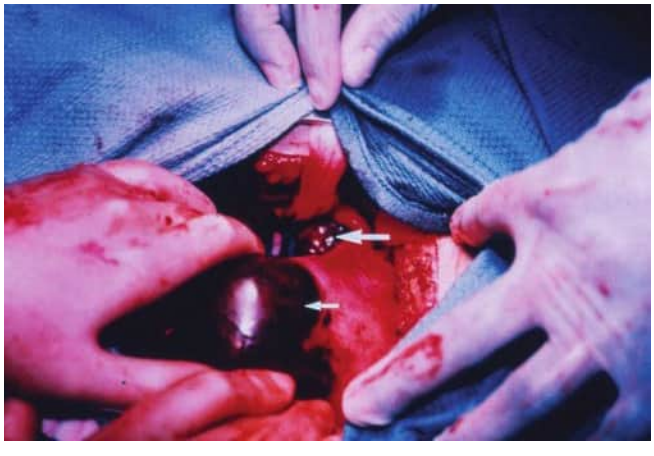

FIGURE 50-6 A fatal case of group A β-hemolytic *Streptococcus pyogenes* puerperal infection following an uncomplicated vaginal delivery at term. The infection caused uterine gangrene and overwhelming sepsis. Arrows point to overtly "ballooned-out" black gangrenous areas of the postpartum uterus at the time of laparotomy for hysterectomy.

TRAUMA

Depending on definitions used, 10 to 20 percent of gravidas suffer physical trauma (Al-Thani, 2018; Mendez-Figueroa, 2017). Moreover, injury-related deaths are the most commonly identified nonobstetrical cause of maternal mortality (Huls, 2018; La Rosa, 2020). According to Deshpande and coworkers (2017), pregnant victims of trauma are twice as likely to die compared with nonpregnant affected women. In an audit from Parkland Hospital, motor vehicle accidents and falls accounted for 85 percent of injuries sustained by gravidas (Hawkins, 2007). From the National Violent Death Reporting System, Palladino and colleagues (2011) found 2 pregnancy-associated suicides per 100,000 live births. The rate was 3 per 100,000 for pregnancy-associated homicides. Notably, intimate partner violence may be linked to these suicides (Chisholm, 2017). Last, injury prevention and education of high-risk patients may help decrease morbidity rates (Globevnik, 2018).

■ Intimate Partner Violence

According to the CDC, intimate partner violence (IPV) describes physical, sexual, or psychological harm by a current or former partner or spouse (Breiding, 2015). Such violence affects 1 in 5 women in their lifetime (Miller, 2019). One goal in violence prevention for *Healthy People 2020* is the reduction of physical abuse directed at women by male partners.

Even more appalling is that IPV continues during pregnancy (Hahn, 2018). Abuse is linked to poverty, poor education, and use of tobacco, alcohol, and illicit drugs. Unfortunately, abused women tend to remain with their abusers, and one major risk factor for intimate partner homicide is prior IPV (Globevnik, 2018). Last, women seeking pregnancy termination have a higher incidence of IPV (Bourassa, 2007).

In one study, pregnant women hospitalized in California as a result of assault had significantly increased perinatal morbidity rates (El Kady, 2005). Immediate sequelae were uterine rupture, preterm delivery, and maternal and perinatal death. Subsequent outcomes included higher rates of placental abruption, preterm

TABLE 50-7. Guidelines for Prophylaxis Against Sexually Transmitted Disease in Pregnant Victims of Sexual Assault

Prophylaxis Against	Regimen[a]	Alternative
Neisseria gonorrhoeae	Ceftriaxone 250 mg IM single dose ***plus*** Azithromycin 1 g single dose	Cefixime 400 mg single dose ***plus*** azithromycin 1 g single dose
Chlamydia trachomatis	Azithromycin 1 g single dose[b] ***or*** Amoxicillin 500 mg three times daily for 7 days	Erythromycin-base 500 mg four times daily for 7 days
Trichomonas vaginalis	Metronidazole 2 g single dose ***or*** Tinidazole 2 g single dose	Metronidazole 500 mg twice daily for 7 days
Hepatitis B (HBV)	If not previously vaccinated, give first dose HBV vaccine IM, repeat at 1–2 and 4–6 months	
Human immunodeficiency virus (HIV)	If exposure ≤72 h ago, consider antiretroviral prophylaxis if risk for HIV exposure is high	Tenofovir disoproxil fumarate/emtricitabine (Truvada) once daily plus raltegravir 400 mg (Isentress) twice daily for 28 days

[a]Oral administration unless otherwise stated.
[b]For nonpregnant women, doxycycline, 100 mg orally twice daily for 7 days, can be given instead.
IM = intramuscularly.
From Centers for Disease Control and Prevention, 2015, 2016.

and low-birthweight newborns, and other adverse outcomes. Silverman and associates (2006) reported similar results from the Pregnancy Risk Assessment Monitoring System. In a meta-analysis, women suffering IPV had threefold increased risk for perinatal death (Pastor-Moreno, 2020).

The American Academy of Pediatrics and the American College of Obstetricians and Gynecologists (2017) recommend universal screening for IPV at the initial prenatal visit, during each trimester, and again at the postpartum visit (Chap. 10, p. 180). A challenge in these recommendations is that women who refuse to answer the screening question for IPV may be most at risk (Yost, 2005). Moreover, the woman who is physically abused tends to present late, if at all, for prenatal care.

Sexual Assault

The lifetime prevalence of sexual assault in the United States is 20 percent (American College of Obstetricians and Gynecologists, 2019c; Vrees, 2017). Satin and associates (1992) reviewed more than 5700 female sexual assault victims in Dallas County and reported that 2 percent were pregnant. Associated physical trauma is common. From a forensic standpoint, the evidence collection protocol is not altered (Linden, 2011).

In addition to attention to physical injuries, exposure to sexually transmitted diseases must be considered. The CDC (2015, 2016) recommends antimicrobial prophylaxis against gonorrhea, chlamydial infection, and trichomoniasis (Table 50-7). At Parkland Hospital, we also offer at-risk exposed assault victims HIV prophylaxis. If the woman is not pregnant, another very important aspect is emergency contraception, as recommended by the American College of Obstetricians and Gynecologists (2018a; 2019c) and discussed in Chapter 38 (p. 676).

Last, the importance of psychological counseling for the rape victim and her family cannot be overemphasized. As discussed in Chapter 64 (p. 1142), a 30- to 35-percent lifetime risk each for posttraumatic stress disorder, major depression, and suicide contemplation follows sexual assault (Linden, 2011).

Automobile Accidents

At least 3 percent of pregnant women are involved in motor vehicle accidents each year in the United States. These crashes account for 90 percent of nonviolent blunt trauma in pregnancy (Sakamoto, 2019). Thus, they are the most common causes of serious, life-threatening, or fatal blunt trauma during pregnancy (Al-Thani, 2018; Greco, 2019; Petrone, 2017). Mattox and Goetzl (2005) report these accidents to be the leading cause of traumatic fetal deaths as well. This also was true from our experiences from Parkland Hospital (Hawkins, 2007). As with all motor vehicle crashes, alcohol use is often associated. Up to half of accidents occur without seat-belt use, and many of these deaths would likely be preventable by the three-point restraints shown in Figure 50-7 (Schuster, 2016). Seat belts prevent contact with the steering wheel, and they reduce abdominal impact pressure.

Original concerns regarding injuries caused by airbag deployment have been somewhat allayed. In a retrospective cohort study that included 2207 pregnant women in crashes with airbag deployment, perinatal outcomes were not clinically different from 1141 controls without airbags (Schiff, 2010). Importantly, 96 percent of both groups used seat belts. Logically, it appears that injuries with airbag deployment are related to the severity of the crash (Mendez-Figueroa, 2017).

Other Blunt Trauma

Some other common causes of blunt trauma are falls and aggravated assaults. In the California review reported by El

FIGURE 50-7 Illustration showing correct use of three-point automobile restraint. The upper belt is *above* the uterus, and the lower belt fits snugly across the upper thighs and well *below* the uterus.

Kady and associates (2005), approximately a third of pregnant women who were hospitalized for trauma suffered intentionally inflicted injuries. Less common are blast or crush injury.

With blunt trauma, intraabdominal injuries can be serious. Even so, bowel injuries are less frequent because of the protective effect of a large uterus. Still, diaphragmatic, splenic, liver, and kidney damage also may be sustained. Particularly worrisome is the specter of amnionic-fluid embolism, which has been reported with even mild trauma (Ellingsen, 2007; Pluymakers, 2007). Retroperitoneal hemorrhage is likely more common than in nonpregnant women (Takehana, 2011).

Orthopedic injuries also are encountered with some regularity (Desai, 2007). From the Parkland Hospital trauma unit, 6 percent of 1682 pregnant women evaluated had orthopedic injuries. Additionally, this subset was at increased risk for placental abruption, preterm delivery, and perinatal mortality. In a review of 101 pelvic fractures during pregnancy, the maternal mortality rate was 9 percent, and the fetal rate was 35 percent (Leggon, 2002). In another study of pelvic and acetabular fractures during 15 pregnancies, one maternal and four fetal deaths were reported (Almog, 2007). Last, head trauma and neurosurgical care raise unique issues (Qaiser, 2007).

Fetal Injury and Death

Perinatal death rates rise with the severity of maternal injuries. Fetal death is more likely with direct fetoplacental injury, maternal shock, pelvic fracture, maternal head injury, or hypoxia (Mendez-Figueroa, 2017; Pearlman, 2008). In an earlier study, motor vehicle accidents caused 82 percent of fetal deaths from trauma. Death resulted from placental injury in half and from uterine rupture in 4 percent (Weiss, 2001).

Although uncommon, fetal skull and brain injuries are more likely if the head is engaged and the maternal pelvis is fractured. Conversely, fetal head injuries, presumably from a contrecoup effect, may be sustained in unengaged vertex or nonvertex presentations. Fetal skull fractures are rare and best seen using CT imaging (Sadro, 2012). One example is shown in Figure 50-8.

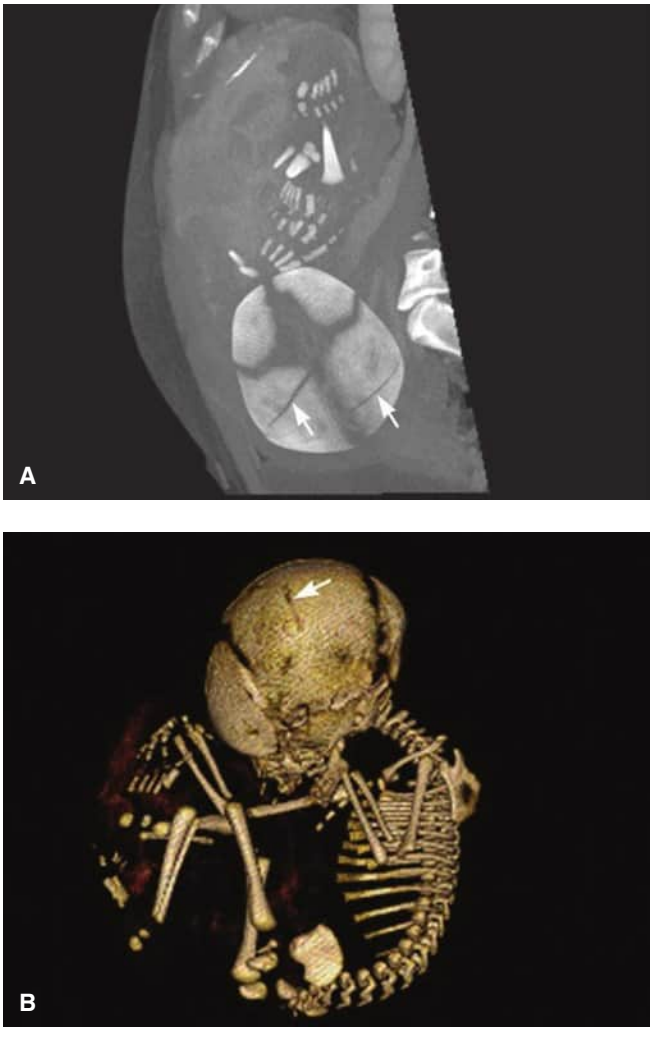

FIGURE 50-8 This woman in her third trimester was involved in a high-speed motor vehicle accident. **A.** Maximum intensity projection acquired for maternal indications readily identifies fetal skull fractures (*arrows*). **B.** Three-dimensional reformatted computed tomography (CT) image in a bone algorithm demonstrates the fetal skeleton from data acquired during the maternal examination. Again, the arrow marks one fracture site. (Photograph contributed by Dr. Travis Browning. Reproduced with permission from Bailey AA, Twickler DM: Perioperative imaging. In Yeomans ER, Hoffman BL, Gilstrap LC III, et al [eds]: Cunningham and Gilstrap's Operative Obstetrics, 3rd ed. New York, NY: McGraw Hill; 2017.)

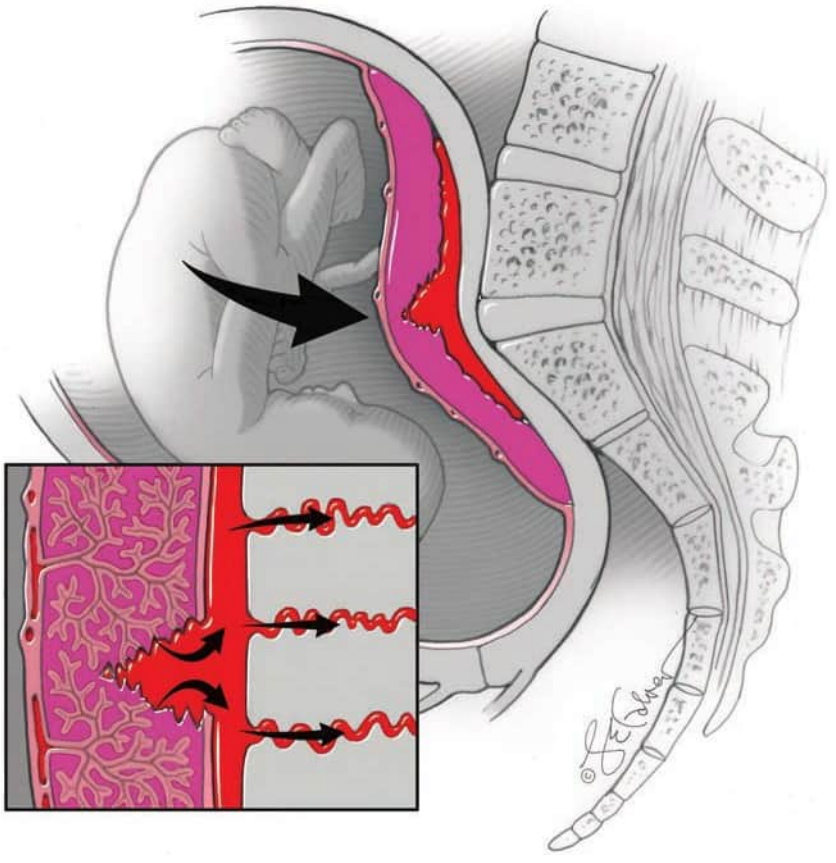

FIGURE 50-9 Mechanism of placental tear or "fracture" caused by a coup-contrecoup injury. Although not shown here, forward momentum of the uterus at the time of initial impact propels it forward. This is followed by a contrecoup, in which forces are directed backward. In this image, the inelastic placenta fractures against the sacral promontory. During each phase, tremendous intraabdominal pressure is generated that can lead to abruption, shown here as blood collecting in the retroplacental space. **Inset**. Blood can be forced into placental bed venules and enter maternal circulation. Such maternofetal hemorrhage may be identified with Kleihauer-Betke testing.

Intracranial hemorrhage may be another sequela (Gherman, 2014). Other injuries have included fetal decapitation or incomplete midabdominal fetal transection at midpregnancy (Rowe, 1996; Weir, 2008).

Placental Injuries

Catastrophic events that potentially accompany blunt trauma include placental abruption or placental tear or both. Placental abruption caused by trauma is likely due to deformation of the elastic myometrium around the relatively inelastic placenta (Crosby, 1968). This may result from a deceleration injury as the forward-moving uterus meets the immovable steering wheel or seat belt. Instead, placental injury may follow a contrecoup injury, which is illustrated in Figure 50-9.

Some degree of abruption complicates 1 to 6 percent of minor injuries and up to 50 percent of major ones (Schiff, 2002). Abruption is more likely if vehicle speed exceeds 30 mph (Reis, 2000).

Clinical findings with traumatic abruption may be similar to those for spontaneous placental abruption (Chap. 42, p. 753). Kettel and coworkers (1988) emphasized that traumatic abruption may be occult and not accompanied by uterine pain, tenderness, or bleeding. In our experiences with 13 such women at Parkland Hospital, 11 had uterine tenderness, but only five had vaginal bleeding. Because traumatic abruption is more likely to be concealed and generate higher intrauterine pressures, associated coagulopathy is more often seen than with atraumatic abruption (Cunningham, 2015). Partial separation also may generate uterine activity, which is described more fully later (p. 896). Evidence of fetal compromise such as fetal tachycardia, sinusoidal pattern, late decelerations, acidosis, and fetal death are other worrisome features. CT imaging has been shown to be accurate for diagnosis of traumatic abruption (Kopelman, 2013, 2016; Sadro, 2012). However, because routine placental evaluation by radiologists is not common, these authors did not advocate for CT screening for abruption.

With a placental tear, life-threatening fetal hemorrhage may follow, and blood enters either the amnionic sac or maternal circulation. As shown in Figure 50-10, the tear is linear or stellate. Also shown is a Kleihauer-Betke stain of maternal blood that is used to quantify fetomaternal hemorrhage. A small amount of fetal-maternal bleeding has been described in up to a third of trauma cases, and in 90 percent of these, the volume is <15 mL (Pearlman, 1990). Parenthetically, atraumatic placental abruption is much less often associated with significant fetomaternal hemorrhage because only minimal fetal blood enters into the intervillous space. With traumatic abruption, however, massive fetomaternal hemorrhage may follow. In one study, the risk of associated uterine contractions and preterm labor was 20-fold if there was evidence for a fetomaternal bleed (Muench, 2004). With severe fetal bleeding, long-term adverse neurological outcomes are frequent (Kadooka, 2014).

Uterine Rupture

Blunt trauma leads to uterine rupture in <1 percent of severe cases (American College of Obstetricians and Gynecologists, 2017a; Greco, 2019). Rupture is more likely in a previously scarred uterus and is usually associated with a direct impact of substantial force. Decelerative forces following a 25-mph collision can generate up to 500 mm Hg of intrauterine pressure in a properly restrained woman (Crosby, 1968). Clinical findings may be identical to those for placental abruption with an intact uterus, and maternal and fetal deterioration are inevitable. Weir and colleagues (2008) described supracervical uterine avulsion and fetal transection at 22 weeks.

Penetrating Trauma

In a study of 321 pregnant women with abdominal trauma, Petrone (2011) reported a 9-percent incidence of penetrating

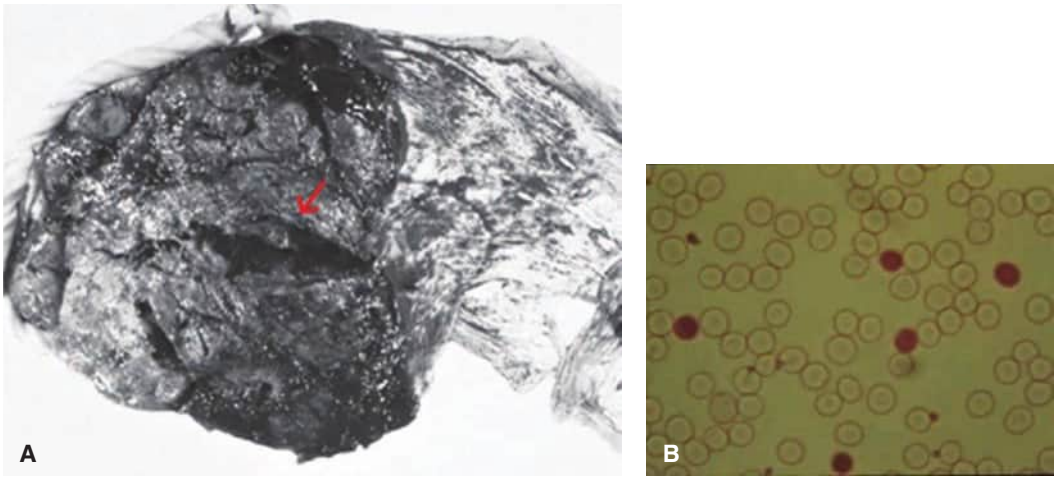

FIGURE 50-10 A. Partial placental abruption in which the adherent blood clot has been removed. Note the laceration of the placenta (*arrow*), which caused fetal death from massive fetomaternal hemorrhage. **B.** Kleihauer–Betke stain of a peripheral smear of maternal blood from the same woman. The dark cells containing hemoglobin that constituted 4.5 percent of red blood cells are fetal in origin, whereas the empty cells are maternal.

injuries. Of these, 77 percent were gunshot wounds, and 23 percent were stab wounds. The incidence of maternal visceral injury with penetrating trauma is only 15 to 40 percent compared with 80 to 90 percent in nonpregnant individuals (Stone, 1999). However, the large, intervening uterus is disproportionately involved (Awwad, 1994). When the uterus sustains penetrating wounds, the fetus is more likely than the mother to be seriously injured. The fetus sustains injury in two thirds of cases, whereas maternal visceral damage is seen in only 20 percent. Still, their seriousness is underscored in that maternal-fetal mortality rates are significantly higher than those seen with blunt abdominal injuries. Specifically, maternal mortality rates were 7 versus 2 percent, and fetal mortality rates were 73 versus 10 percent, respectively.

Management of Trauma

As discussed, maternal and fetal outcomes are directly related to injury severity. That said, commonly used methods of severity scoring do not account for the significant morbidity and mortality rates related to placental abruption and thus to pregnancy outcomes. In a study of 582 pregnant women hospitalized for injuries, the injury severity score did not accurately predict adverse pregnancy outcomes (Schiff, 2005). Importantly, relatively minor injuries were associated with preterm labor and placental abruption. In a study of 317 women at ≥24 weeks' gestation who had "minor trauma," 14 percent had clinically significant uterine contractions requiring extended fetal evaluation past 4 hours (Cahill, 2008).

With few exceptions, treatment priorities in injured pregnant women are multidisciplinary (MacArthur, 2019; Mendez-Figueroa, 2017). Primary goals are to evaluate and stabilize maternal injuries. Attention to fetal assessment during the acute evaluation may divert attention from life-threatening maternal injuries (American Academy of Pediatrics, 2017). Basic rules of resuscitation include ventilation, arrest of hemorrhage, and treatment of hypovolemia with crystalloid and blood products. After midpregnancy, the large uterus is positioned off the great vessels to relieve vessel compression, which decreases cardiac output (Nelson, 2015).

Following emergency resuscitation, fractures, internal injuries, bleeding sites, and placental, uterine, and fetal trauma are sought (Greco, 2019; MacArthur, 2019). Radiography is not proscribed, but special attention is given each indication. Not surprisingly, one report observed that pregnant trauma victims had less radiation exposure than nonpregnant controls (Ylagan, 2008). Some advocate screening abdominal sonography followed by CT scanning for positive sonographic findings (Saphier, 2014). Procedures used include the *FAST scan—focused assessment with sonography for trauma.* This is a 5-minute, four- to six-view imaging study that evaluates perihepatic, perisplenic, pelvic, and pericardial views (Mendez-Figueroa, 2017). In nonpregnant women, if fluid is seen in the upper abdominal views, the hemoperitoneum volume is >500 mL (Fig. 50-11)

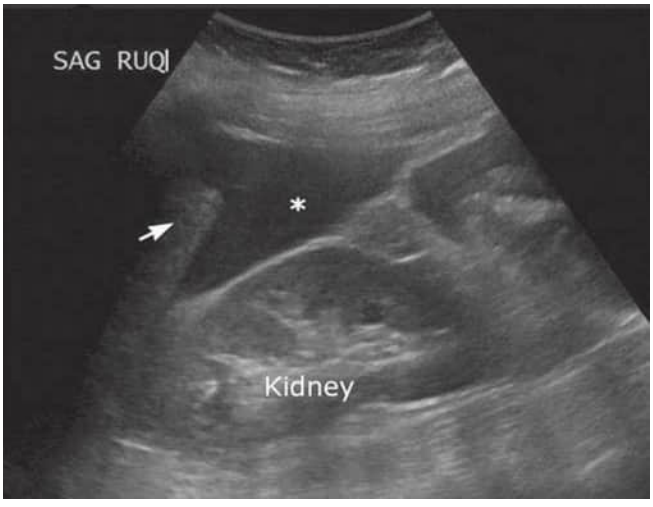

FIGURE 50-11 Fast scan. Upper quadrant scans show free fluid (blood) between the liver and kidney (Morison pouch) and around the spleen. The patient had 2500 mL of blood in the peritoneal cavity. (Reproduced with permission from Mendez-Figueroa H, Rouse DJ: Trauma in pregnancy. In Yeomans ER, Hoffman BL, Gilstrap LC III, et al [eds]: Cunningham and Gilstrap's Operative Obstetrics, 3rd ed. New York, NY: McGraw Hill; 2017.)

(Branney, 1995; Rodgerson, 2001). Importantly, this amount has not been corroborated for pregnancy. In some cases, open peritoneal lavage may be informative (Tsuei, 2006).

Penetrating injuries in most cases must be evaluated using radiography. Because clinical response to peritoneal irritation is blunted during pregnancy, an aggressive approach to exploratory laparotomy is pursued. Whereas exploration is mandatory for abdominal gunshot wounds, some clinicians advocate close observation for selected stab wounds. Diagnostic laparoscopy also has been used (Chap. 49, p. 868).

Cesarean Delivery

The necessity for cesarean delivery depends on several factors. Laparotomy itself is not an indication for hysterotomy. Some considerations include gestational age, fetal condition, extent of uterine injury, and whether the large uterus hinders adequate management of other intraabdominal injuries (Tsuei, 2006).

Electronic Monitoring

Because fetal well-being may reflect the status of the mother, fetal monitoring is another "vital sign" that helps evaluate the extent of maternal injuries. Even if the mother is stable, electronic monitoring may suggest placental abruption. In a study by Pearlman and coworkers (1990), no woman had an abruption if uterine contractions were less often than every 10 minutes within the 4 hours after trauma was sustained. Almost 20 percent of women who had contractions more frequently than every 10 minutes in the first 4 hours had an associated placental abruption. In these cases, abnormal tracings were common and included fetal tachycardia and late decelerations. Conversely, no adverse outcomes were reported in women who had normal monitor tracings (Connolly, 1997). Importantly, if tocolytics are used for these contractions, they may obfuscate findings, and we do not recommend them.

Because placental abruption usually develops early following trauma, fetal monitoring is begun as soon as the mother is stable. The ideal duration of posttrauma monitoring is not precisely known. From data just cited, observation for 4 hours is reasonable if the fetal heart rate tracing is normal and no other sentinel findings such as contractions, uterine tenderness, or bleeding are noted. Certainly, monitoring should be continued as long as there are uterine contractions, nonreassuring fetal heart patterns, vaginal bleeding, uterine tenderness or irritability, serious maternal injury, or ruptured membranes (Mendez-Figueroa, 2017). In rare cases, placental abruption has developed days after trauma (Higgins, 1984).

Fetal-Maternal Hemorrhage

It is unclear whether routine use of the Kleihauer-Betke or an equivalent test in pregnant trauma victims might modify adverse outcomes associated with fetal anemia, cardiac arrhythmias, and death (Pak, 1998). In a retrospective review of 125 pregnant women with blunt injuries, the Kleihauer-Betke test was judged to be of little value during acute trauma management (Towery, 1993). Others have reached similar conclusions, although a positive test result with fetal cells composing 0.1 percent predicted uterine contractions or preterm labor (Muench, 2003, 2004).

For the woman who is D-negative, administration of anti-D immunoglobulin should be considered (American College of Obstetricians and Gynecologists, 2017b). This may be omitted if a test result for fetal bleeding is negative. Even with anti-D immunoglobulin, alloimmunization may still develop if the fetal-maternal hemorrhage exceeds 15 mL of fetal cells. Immunoglobulin dose calculations are described in Chapter 18 (p. 357).

For the pregnant trauma patient, confirmation of current tetanus immunization status is pertinent. When indicated, a dose of tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis (Tdap) vaccine is preferred for its neonatal pertussis immunity benefits (Chap. 10, p. 188).

THERMAL INJURY

Treatment of the burned gravida is similar to that for nonpregnant individuals (Correia-Sa, 2021). It is generally agreed that pregnancy does not alter maternal outcome from thermal injury compared with that of nonpregnant women of similar age. As perhaps expected, maternal and fetal survival parallels the percentage of burned surface area. Karimi and colleagues (2009) reported higher mortality rates for both with burns from suicide attempts and inhalational injuries. The composite mortality rate for more than 200 women from six studies rose in a linear fashion as the percentage of burned body surface area increased (Fig. 50-12). For 20-, 40-, and 60-percent burns, the maternal mortality rates were approximately 4, 30, and 93 percent, respectively. The corresponding fetal mortality rates were 20, 48, and 96 percent, respectively. With severe burns, the woman usually enters labor spontaneously within a few days to a week and often delivers a stillborn. Contributory factors are hypovolemia, pulmonary injury, septicemia, and the burn-associated, intense catabolic state (Radosevich, 2013).

Following serious abdominal burns, skin contractures that develop may be painful during a subsequent pregnancy and may even require surgical decompression and split-skin autografts (Mitsukawa, 2015; Radosevich, 2013). Loss or distortion of nipples may cause problems in breastfeeding. Mitsukawa and associates (2015) reported that contracture release was indicated with scars spanning >75 percent of the total abdominal area. Alternatively, normal abdominal tissue expansion due to

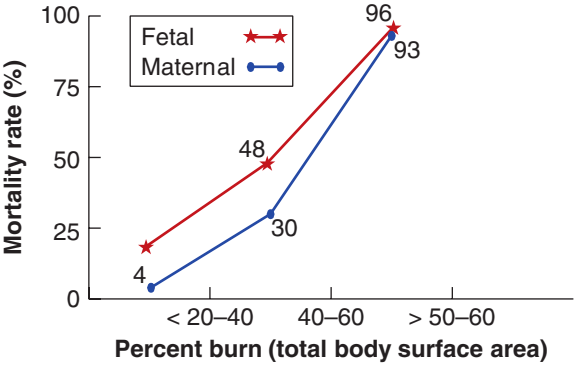

FIGURE 50-12 Maternal and fetal mortality rates by burn severity in 211 women. (Data from Akhtar, 1994; Amy, 1985; Mabrouk, 1977; Maghsoudi, 2006; Rayburn, 1984; Rode, 1990.)

pregnancy appears to be an excellent source for obtaining skin grafts postpartum to correct scar deformities at other body sites (Del Frari, 2004).

■ Electrical and Lightning Injuries

Earlier case reports suggested a high fetal mortality rate with electric shock (Fatovich, 1993). In a prospective cohort study, however, Einarson and associates (1997) showed similar perinatal outcomes in 31 injured women compared with those of noninjured controls. They concluded that traditional 110-volt North American electrical current likely is less dangerous than the 220-volt currents available in Europe. Thermal burns with electrocution may be extensive, and a woman with brain death from cardiac arrest has been described (Sparic, 2014).

The pathophysiological effects of lightning injuries can be devastating. García Gutiérrez and colleagues (2005) reviewed 13 case reports of lightning injuries during pregnancy and cited a 50-percent stillbirth rate.

CARDIOPULMONARY RESUSCITATION

Maternal cardiac arrest complicates from 1 in 12,000 to 36,000 delivery admissions (Balki, 2017; Beckett, 2017; Zelop, 2018). The most common causes are hemorrhage, anesthesia, heart failure, amnionic-fluid embolism, and sepsis. Shown in Table 50-8 is the alphabetical A–H checklist of cardiac arrest causes. General topics regarding planning and equipment have been reviewed by the American College of Obstetricians and Gynecologists (2018b) and the Society for Obstetric Anesthesia and Perinatology (Lipman, 2014).

Special considerations for cardiopulmonary resuscitation (CPR) conducted in the second half of pregnancy are outlined in the American Heart Association 2010 guidelines (Jeejeebhoy, 2015). The committee acknowledges the following as standards: (1) relieve possible vena caval compression by left lateral uterine displacement; (2) administer 100-percent oxygen; (3) establish intravenous access above the diaphragm; (4) assess for hypotension that warrants therapy, which is defined as systolic blood pressure <100 mm Hg or <80 percent of baseline; and (5) review possible causes of critical illness and treat these as early as possible.

TABLE 50-8. Possible Etiologies for Cardiac Arrest During Pregnancy

Anesthesia: high neuraxial block, intravenous local anesthetic, airway complications
Accidents: trauma
Bleeding: atony, abnormal placentation, DIC
Cardiovascular: valvar or congenital heart disease, arrhythmias, ischemia, aortic dissection
Drugs: tocolysis, overdose, anaphylaxis, uterotonics, magnesium sulfate
Embolism: venous, amnionic fluid
Fever: sepsis, viral syndromes, ARDS
General: metabolic abnormalities, hypocalcemia or hyperkalemia with massive hemorrhage
Hypertension: shock, preeclampsia syndrome, HELLP syndrome

ARDS = acute respiratory distress syndrome; DIC = disseminated intravascular coagulation; HELLP = hemolysis, elevated liver transaminases, low platelets.
Adapted from Jeejeebhoy, 2015; Soar, 2021; Zelop, 2018.

TABLE 50-9. High-Quality Cardiopulmonary Resuscitation in Pregnancy

Components
Place provider hands in lower half of sternum
Displace uterus laterally during resuscitation
Provide rapid chest compressions (100 per minute)
Achieve a compression depth of at least 2 inches
Assure adequate chest recoil between compressions
Minimize interruptions of chest compressions
Avoid prolonged pulse checks (no more than 5–10 seconds)
Resume chest compressions immediately after defibrillating
Switch provider of compressions every 2 minutes to avoid fatigue

The position of the heart for external compressions is not different from that in nonpregnant women (Holmes, 2015). In nonpregnant women, external chest compressions result in a cardiac output that is approximately 30 percent of normal. However, in late pregnancy, this may be less because of uterine aortocaval compression (Nelson, 2015). Thus, uterine displacement should accompany other resuscitative efforts. This can be accomplished by tilting the operating table laterally, by placing a wedge under the right hip, or by pushing the uterus to the left manually (Rose, 2015). Components of high-quality cardiopulmonary resuscitation in pregnancy are shown in Table 50-9 (Society for Maternal–Fetal Medicine, 2018).

■ Perimortem Cesarean Delivery

The maternal survival rate from cardiac arrest is 60 to 70 percent, and many deaths are associated with out-of-hospital arrest (Beckett, 2017; He, 2021). Because of pregnancy-induced hindrances on CPR efforts, emergent *perimortem cesarean delivery* for improved maternal resuscitation and fetal salvage is recommended by most. Specifically, the American Heart Association and the Society for Obstetric Anesthesia and Perinatology recommend operative delivery within 4 to 5 minutes of beginning CPR if the fetus is viable and circulation is not restored (Zelop, 2018). In women delivered by perimortem cesarean, neurologically intact neonatal survival and the cardiac arrest-to-delivery interval are inversely related (Beckett, 2017; Katz, 2012). Specifically, of newborns delivered within 5 minutes of arrest, 98 percent are neurologically intact; within 6 to 15 minutes, 83 percent are intact; within 16 to 25 minutes, 33 percent are intact; and within 26 to 35 minutes, only 25 percent are intact (Clark, 1997).

This serious and sometimes contentious issue is far from evidence based. For example, the American College of Obstetricians and Gynecologists (2019a) recommends *consideration* for

perimortem cesarean delivery beginning at 4 minutes. Katz and associates (2005) reviewed 38 perimortem cesarean deliveries with a "large selection bias." They concluded that these reports supported—but "fell far from proving"—that perimortem cesarean delivery within 4 minutes of maternal cardiac arrest improves maternal and fetal outcomes. Even so, as emphasized by Clark (1997) and Rose (2015) and their coworkers, and in our experiences, these goals rarely can be met in actual practice. For example, many cases of cardiac arrest occur in uncontrolled circumstances, and thus, the time to CPR initiation alone would consume the first 5 minutes. Thus "crash" cesarean delivery would supersede resuscitative efforts, would possibly be done without appropriate anesthesia or surgical equipment, and might lead to otherwise preventable maternal death. Moreover, the distinction between a perimortem versus postmortem cesarean operation is imperative (Katz, 2012; Rose, 2015). Last, in the balance, any choice *may* favor survival of the mother over the fetus, or vice versa, and thus there are immediate unresolvable ethical concerns. Katz (2012) and Zelop and colleagues (2018) have provided scholarly reviews of perimortem cesarean delivery.

Successful CPR can have morbid complications. Severe neurological injury is the most feared (Romagano, 2017). Cox and coworkers (2018) described liver lacerations in 3 of 7 survivors. Takotsubo cardiomyopathy also has been reported (Kraft, 2017).

Maternal Brain Death

Occasionally, a pregnant woman with a supposedly healthy intact fetus will be kept on somatic support to await fetal viability or maturity. This is discussed in Chapter 63 (p. 1138).

ENVENOMATION

According to their review, Brown and coworkers (2013) reported that clinically significant envenomations in pregnant women are from snakes, spiders, scorpions, jellyfish, and hymenoptera. This last group includes bees, wasps, hornets, and ants. Adverse outcomes are related to maternal effects. Available evidence supports a venom-specific approach that incorporates symptomatic care, antivenom administration when appropriate, anaphylaxis treatment, and fetal assessment (Ghosh, 2018). One management scheme for North American snakebites was provided by Lei and associates (2015).

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CHAPTER 51

Obesity

Extensive weight gain is a major health problem today in many affluent societies. The Centers for Disease Control and Prevention (CDC) (2020) reported the prevalence in the United States during 2017 to 2018 to be 42 percent among all adults. The adverse health aspects of obesity are staggering and include increased risks for type 2 diabetes, heart disease, hypertension, and osteoarthritis. Importantly, obese women and their fetuses are predisposed to numerous pregnancy-related complications and to long-term morbidity and mortality.

GENERAL CONSIDERATIONS

Definitions and Prevalence

Of systems to classify obesity, the *body mass index (BMI)*, also known as the *Quetelet index*, is most often used. The BMI is calculated as weight in kilograms divided by the square of the height in meters (kg/m^2). Calculated BMI values are available in various chart and graphic forms (Fig. 51-1). The National Institutes of Health (2000) classifies adults according to BMI as follows: *normal* is 18.5 to 24.9 kg/m^2, *overweight* is 25 to 29.9 kg/m^2, and *obese* is ≥30 kg/m^2. Obesity is further divided into: *class 1* is 30 to 34.9 kg/m^2, *class 2* is 35 to 39.9 kg/m^2, and *class 3* is ≥40 kg/m^2. Class 3 obesity is often referred to as *morbid* obesity, and *supermorbid* obesity describes a BMI ≥50 kg/m^2.

Using these definitions, from 2015 to 2016 in the United States, among girls and women, the prevalence of obesity rose with age and varied among ethnicities (Fig. 51-2) (Centers for Disease Control and Prevention, 2020). Overall, severity also advances with increasing poverty. Last, a genetic predisposition has been identified (Locke, 2015; Shungin, 2015).

Adipose Pathophysiology

Fat tissue is much more complex than merely its energy storage function. Many fat tissue cells communicate with all other tissues via endocrine and paracrine factors, which are cytokines specifically termed *adipokines*, *lipokines*, and *exosomal microRNAs* (Scheja, 2019). Some of these with metabolic functions include adiponectin, leptin, tumor necrosis factor α (TNF-α), interleukin 6 (IL-6), resistin, visfatin, apelin, vascular endothelial growth factor (VEGF), lipoprotein lipase, and insulin-like growth factor. Adiponectin is a principal adipokine. It enhances insulin sensitivity, blocks hepatic glucose release, and has cardioprotective effects on circulating plasma lipids. An adiponectin deficit is linked with diabetes, hypertension, endothelial cell activation, and cardiovascular disease.

Cytokines that result in insulin resistance are leptin, resistin, TNF-α, and IL-6, and higher levels of these are found during pregnancy. Indeed, adipokines, especially the inflammatory cytokines, may be the primary stimulant of insulin resistance (Yang, 2016). Conversely, adiponectin has antiinflammatory and insulin-sensitizing roles and is negatively regulated by fat mass. Perivascular adipose tissue also serves as a signaling mediator in regulating vascular function (Ahmadieh, 2020). Placental production of these adipokines is also important (Sartori, 2016) (Chap. 5, p. 99).

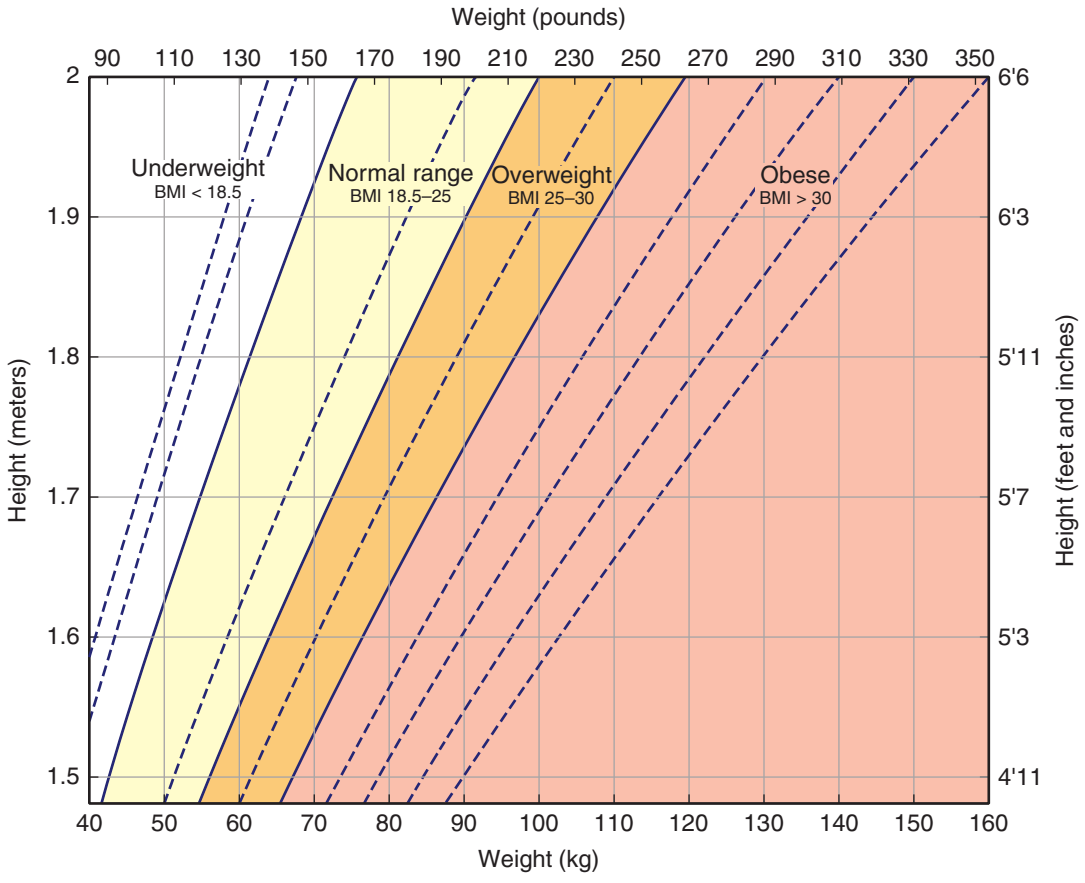

FIGURE 51-1 Chart for estimating body mass index (BMI). To find the BMI category for a particular subject, locate the point at which the height and weight intersect.

Metabolic Syndrome

Given its multifaceted endocrine and paracrine functions, the detrimental effects of excessive adipose tissue are not surprising (Gilmore, 2015). Obesity interacts with inherited factors to cause insulin resistance. This resistance is characterized by impaired glucose metabolism and a predisposition to type 2 diabetes. Insulin resistance also causes several subclinical abnormalities that predispose to cardiovascular disease and accelerate its onset. The most important among these are type 2 diabetes, dyslipidemia, and hypertension, which are constituents of the *metabolic syndrome*.

Criteria to define this syndrome are found in Table 51-1. Waist circumference is the preferred measurement for screening, but any three of five factors listed are sufficient to diagnose the metabolic syndrome. Notably, most patients with type 2 diabetes have metabolic syndrome according to these criteria. Also, obese women with hypertension typically demonstrate elevated plasma insulin levels.

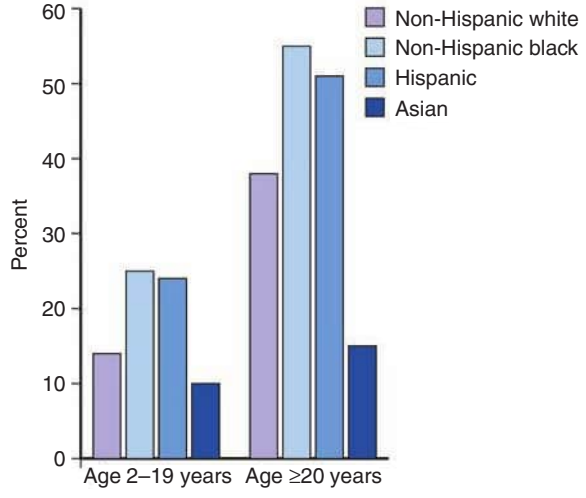

FIGURE 51-2 Prevalence of obesity in the United States by race: United States 2015–2016.

TABLE 51-1. Criteria for Diagnosis of the Metabolic Syndrome

Patients with three or more of the following:	
Elevated waist circumference[a]	
Elevated triglycerides[b]:	≥150 mg/dL
Reduced high-density lipoprotein cholesterol[b]:	
	<40 mg/dL in males
	<50 mg/dL in females
Elevated blood pressure[b]:	systolic ≥130 mm Hg and/or
	diastolic ≥ 85 mm Hg
Elevated fasting glucose[b]:	≥100 mg/dL

[a]According to country- and population-specific thresholds.
[b]Those with normal values while taking medications are considered to meet these criteria.
From the National Heart, Lung, and Blood Institute, 2019.

The National Health and Nutrition Examination Survey (NHANES) of the CDC documented an overall prevalence of 34 percent for the metabolic syndrome in the United States by 2012 (Moore, 2017). As expected, the prevalence rose with age. It was 20 percent for those aged 18 to 29 years and was 36 percent for those aged 30 to 49 years.

Nonalcoholic Fatty Liver Disease

Generally speaking, visceral adiposity correlates with hepatic fat content (Cornier, 2011). With obesity, excessive fat accumulates in the liver and is termed *hepatic steatosis*. This is also called *nonalcoholic fatty liver disease (NAFLD)*. In persons with the metabolic syndrome, steatosis can progress to *nonalcoholic steatohepatitis (NASH)* and then potentially to cirrhosis and hepatocellular carcinoma. It is the major cause of cirrhosis and liver cancer, and annual medical costs of NAFLD in the United States exceed $100 billion (Diehl, 2017). Moreover, NAFLD is strongly associated with cardiovascular disease (Targher, 2016). These interactions are explored further in Chapter 58 (p. 1040).

Obesity-associated Morbidity

Obese individuals suffer well-known consequences such as glucose intolerance, hypertension, dyslipidemia, and metabolic syndrome. Furthermore, metabolic syndrome and obesity are linked with cardiovascular disease, including myocardial infarction, atrial fibrillation, heart failure, and stroke (Koliaki, 2019). Excessive adiposity raises blood pressure and accounts for up to 75 percent of primary hypertension (Hall, 2019). Insulin resistance and metabolic syndrome cause structural cerebral changes in the hippocampus and lower executive functioning and memory in adults (Kullman, 2016). And cytokine-induced osteoarthritis has long been linked to obesity (Tu, 2019).

Because of the foregoing, it is not surprising that obesity is associated with higher rates of all-cause early mortality. Cardiovascular mortality data from 19 prospective studies are shown in Figure 51-3 (Gonzalez, 2010). In these and other studies, mortality risk from cardiovascular disease and cancer grew proportionally with increasing BMI. However, an obesity paradox—whereby certain groups actually derive a survival advantage from being obese—is hypothesized (Hainer, 2013). Despite this, the health benefits of weight normalization are well documented (Cheung, 2017).

Obesity Treatment

Weight loss is tremendously difficult. If achieved, long-term maintenance poses equally daunting challenges. Obstetrician-gynecologists are encouraged to aid weight loss in obese adult women. Successful approaches include behavioral, pharmacological, and surgical techniques or a combination of these (Dixon, 2016; Heymsfield, 2017). Dietary changes and exercise reduce weight and rates of the associated metabolic syndrome (Garvey, 2016; Martin, 2018). When used in conjunction with bariatric surgery, glucose control in those with type 2 diabetes is improved. However, both surgical and medical interventions are associated with appreciable long-term failure rates. Indeed, the failure rate is 50 percent in patients with diabetes undergoing bariatric surgery (Mingrone, 2015).

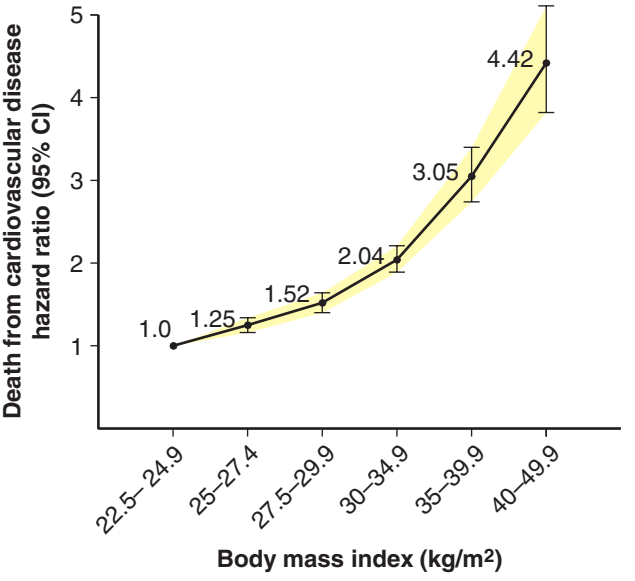

FIGURE 51-3 Estimated hazard ratios (95% CI) for death due to cardiovascular disease according to body mass index among 1.46 million white adult men and women.

PREGNANCY AND OBESITY

Obese women unequivocally have reproductive disadvantages (Lainez, 2019). This translates into difficulty in achieving pregnancy, early and recurrent pregnancy loss, preterm delivery, and several obstetrical, medical, and surgical complications with pregnancy, labor, delivery, and the puerperium (American College of Obstetricians and Gynecologists, 2021). Also, oral contraceptive pill failure and associated thromboembolism may be more likely. Second-trimester surgical abortion in obese women also carries an increased complication risk (Mark, 2018). Last, infants—and later, adult children—of obese mothers have correspondingly higher morbidity rates (Godfrey, 2017; He, 2020).

Obesity complicating pregnancy has grown substantially in this country. Our experiences at Parkland Hospital over three epochs are shown in Figure 51-4. Most recently, obese women constitute >60 percent of pregnant gravidas in our health system.

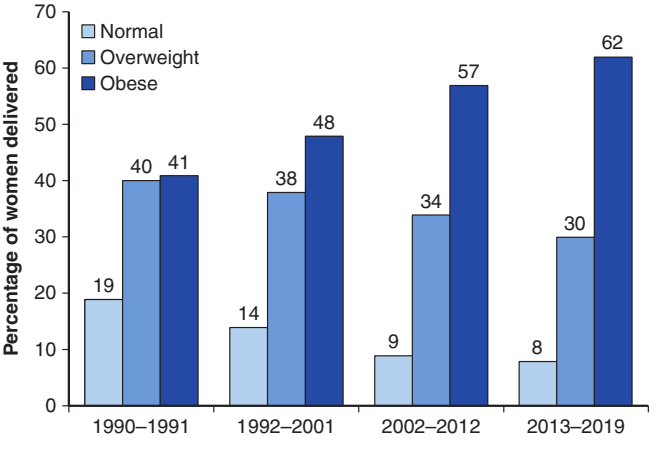

FIGURE 51-4 Increasing prevalence of obesity during four epochs in pregnant women classified at the time of their first prenatal visit at Parkland Hospital.

TABLE 51-2. Adverse Pregnancy Effects in Overweight and Obese Women

Complication	Prevalence (%) Normal BMI 18.5–24.9 n = 621,048	Prevalence (%) with Odds Ratios[a] Overweight BMI 25–29.9 n = 228,945	Obese BMI >30 n = 78,043
Gestational diabetes	2.3	4.3 (OR 1.91, 1.86–1.96)	8.6 (OR 4.04, 3.94–4.15)
Preeclampsia	2.7	4.3 (OR 1.60, 1.56–1.64)	8.1 (OR 3.17, 3.08–3.25)
Preterm birth	3.8	4.1 (OR 1.09, 1.05–1.13)	4.8 (OR 1.28, 1.23–1.34)
Labor induction	20.9	23.8 (OR 1.19, 1.17–1.21)	29.7 (OR 1.60, 1.57–1.64)
Prelabor or elective cesarean delivery	6.6	8.3 (OR 1.28, 1.26–1.31)	11.5 (OR 1.85, 1.81–1.89)
Cesarean delivery	25.2	31.5 (OR 1.37, 1.34–1.39)	39.3 (OR 1.92, 1.88–1.96)
Shoulder dystocia	2.0	2.4 (OR 1.22, 1.17–1.28)	2.3 (OR 1.14, 1.08–1.21)
Postpartum hemorrhage	6.7	8.4 (OR 1.29, 1.26–1.31)	8.7 (OR 1.34, 1.31–1.37)
Pelvic infection	0.6	0.7 (OR 1.16, 1.06–1.26)	0.8 (OR 1.28, 1.15–1.43)
Wound infection or complication	0.4	0.5 (OR.1.42, 1.28–1.58)	1.0 (OR 2.70, 2.42–3.01)
Large for gestational age	8.7	13.1 (OR 1.57, 1.54–1.61)	16.3 (OR 2.04, 1.99–2.10)
Macrosomia	2.0	3.6 (OR 1.81, 1.74–1.88)	5.1 (OR 2.60, 2.50–2.71)
Stillbirth	0.3	1.8 (OR 5.89, 5.57–6.22)	0.5 (OR 1.71, 1.56–1.87)

[a]Odds ratios with 95% CI are significant when compared to normal BMI group.
BMI = body mass index.
Data from Kim, 2016; Lisonkova, 2017; Ovesen, 2011; Santos, 2019; Schummers, 2015.

Maternal Morbidity

For *overweight* women, higher rates of adverse outcomes complicate pregnancy. Shown in Table 51-2 are results from five studies including more than 1 million singleton pregnancies. Although not as magnified as in the obese cohort, rates of almost all complications are significantly greater in *overweight* women than in those with normal BMI.

For *obese* women, definitions used in studies of adverse outcomes vary widely, and BMIs from >30 kg/m^2 to >50 kg/m^2 have served as thresholds (Crane, 2013; Pratt, 2020; Stamilio, 2014). In one study, Mariona (2017) reviewed maternal deaths in Michigan and found that the maternal mortality rate was nearly fourfold higher in obese women. Women with supermorbid obesity experience very high rates of maternal and neonatal complications including preeclampsia, macrosomia, and cesarean delivery, along with higher rates of neonatal meconium aspiration, ventilator support, and neonatal death (Marshall, 2014; Smid, 2016). Data from one large study are shown in Figure 51-5 (Weiss, 2004).

Especially striking are the markedly elevated rates of hypertension and gestational diabetes. As discussed previously, obesity and the metabolic syndrome are characterized by insulin resistance, which creates low-grade inflammation, endothelial activation, and increased sodium reabsorption (Hall, 2019). These latter effects play a central role in preeclampsia (Chap. 40, p. 691). The overwhelming association between rising maternal BMI and the incidence of preeclampsia is depicted in Figure 51-6 (HAPO Study Cooperative Research Group,

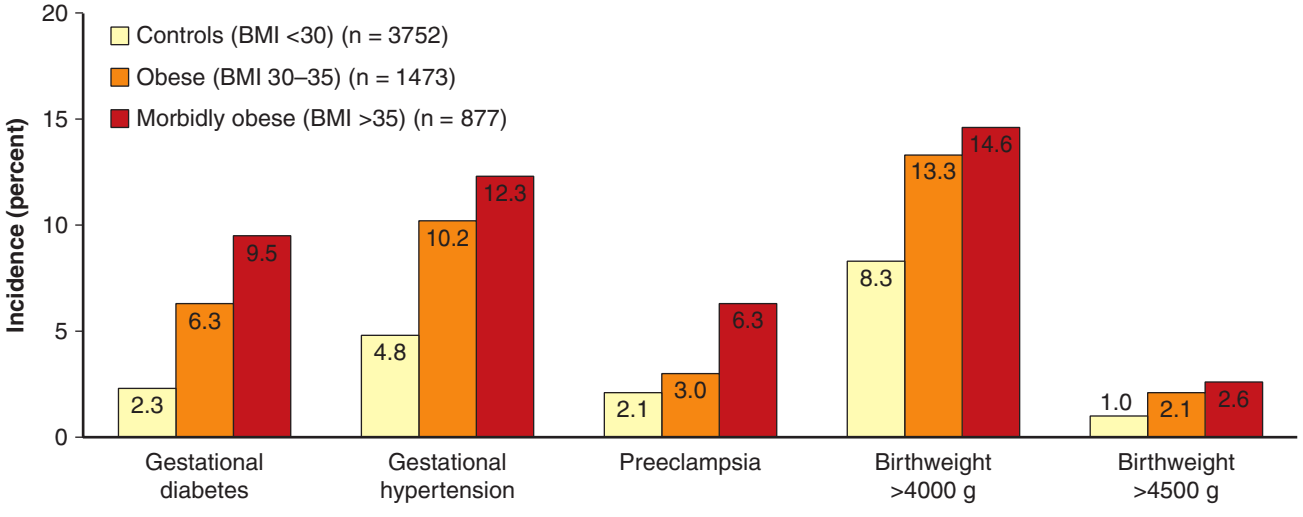

FIGURE 51-5 Incidence of selected pregnancy outcomes in women enrolled in the FASTER (First-and Second-Trimester Evaluation of Risk) trial according to BMI.

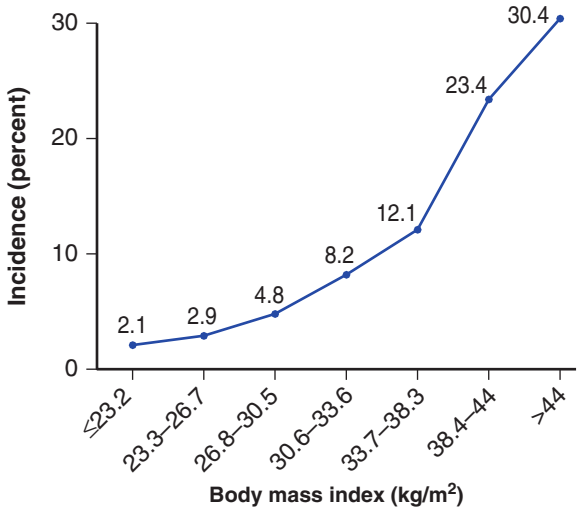

FIGURE 51-6 Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study: frequency of preeclampsia according to BMI.

2008). The risks for hypertension are highest in women with a BMI >50 kg/m^2 (Pratt, 2020). Similar observations were reported from a large Canadian study and by the Safe Labor Consortium (Kim, 2016; Schummers, 2015).

Obesity and hypertension are common cofactors in peripartum heart failure (Cunningham, 2012). Stewart and colleagues (2016) used magnetic resonance imaging to prospectively study the effect of obesity on cardiac remodeling in pregnancy. Concentric remodeling, which was considered abnormal, was greater in overweight or obese women (Fig. 51-7). This, however, regressed to normal by 3 months postpartum. Triebwasser and coworkers (2019) found that women with abnormal cardiac remodeling had a higher incidence of pregnancy-associated hypertensive disorders.

Obesity and gestational diabetes are inextricably linked as shown in Table 51-2. Their coexistence and associated adverse pregnancy outcomes are discussed in Chapter 60 (p. 1068). Nonalcoholic fatty liver disease is associated with several adverse pregnancy outcomes (Chap. 58, p. 1040). In a cohort of women

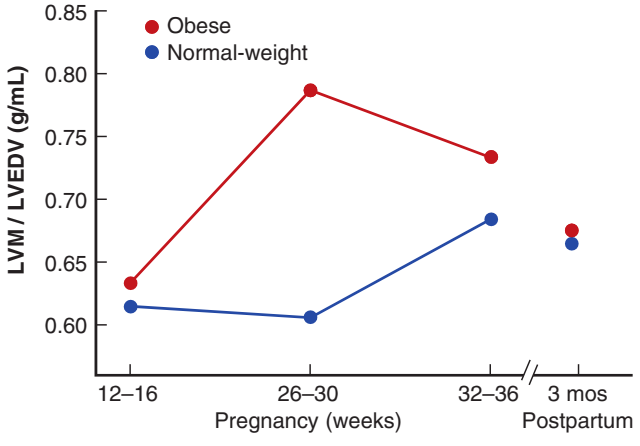

FIGURE 51-7 Geometric changes of ventricular remodeling across pregnancy in obese and normal-weight women determined by cardiac MR imaging. LVM = left ventricular mass, LVEDV = left ventricular end-diastolic volume.

with NAFLD, risks for preeclampsia, preterm birth, low-birthweight neonates, cesarean delivery, and gestational diabetes were elevated (Hagström, 2016). In one prospective study of 476 pregnancies, first-trimester sonographic evidence of maternal NAFLD was strongly associated with gestational diabetes (De Souza, 2016a,b). Meyer and associates (2013) found that overweight and obese gravidas had a higher proportion of low-density lipoprotein III (LDL-III) compared with that of normal-weight women. LDL-III predominance is a hallmark of the ectopic liver fat accumulation that is typical of NAFLD. At Parkland Hospital, we are now frequently encountering obese gravidas who have NAFLD and evidence of steatohepatitis manifest by elevated serum hepatic transaminase levels. In rare cases, liver biopsy is necessary to exclude other causes for these findings.

Quality-of-life measures also are negatively affected by obesity during pregnancy (Ruhstaller, 2017). One systematic review found significantly higher risks of depression in overweight and obese women during and after pregnancy (Molyneaux, 2014). Obese women were also significantly more likely to experience anxiety during pregnancy.

Perinatal Mortality

Stillbirths are more prevalent as the degree of obesity accrues (Schummers, 2015). In a review of almost 100 studies, obesity was the highest-ranking modifiable risk factor for stillbirth (Flenady, 2011). In women with supermorbid obesity compared with normal-weight gravidas, Yao and associates (2014) found 5.7 and 13.6-fold higher stillbirth rates at 39 and 41 weeks' gestation, respectively. Remarkably, 25 percent of term stillbirths in this study involved obese women. Chronic hypertension with superimposed preeclampsia associated with obesity is one cause of excessive stillbirths. These fetal deaths may be associated with placental lesions of decidual arteriopathy and infarctions (Avagliano, 2020).

Evaluating perinatal death rates, Lindam and coworkers (2016) reported that high maternal BMI in early pregnancy was a risk factor. The risk of neonatal death also is greater for obese women (Johansson, 2014; Meehan, 2014). Last, one study found that accruing weight between pregnancies is a risk factor for perinatal mortality, whereas weight loss between pregnancies for overweight women lowers this risk (Cnattingius, 2016).

Perinatal Morbidity

Both fetal and neonatal complication rates are increased in obese women. Two important and interrelated cofactors that contribute to excessive rates of perinatal morbidity are chronic hypertension and diabetes, both of which are associated with maternal obesity. These comorbidities each may play a role in the higher rates of fetal-growth restriction and indicated preterm birth that are seen in obese women (Liu, 2019; Tanner, 2020). Perinates of obese women with preterm prematurely ruptured membranes have a higher incidence of respiratory complications than those born to normal-weight women (Lynch, 2020). Pregestational diabetes also raises the birth defect rate, and gestational diabetes is complicated by excessive numbers of large-for-gestational-age and macrosomic fetuses (Chap. 47, p. 833).

Even when diabetes and hypertension are not considered, the prevalence of neonatal morbidity is greater in offspring

of obese women (Kim, 2016; Polnaszek, 2018; Schummers, 2015). The propensity for preterm birth may be related to increased adipokines and cytokines causing chronic inflammation (Tersigni, 2020). The group from MetroHealth Medical Center in Cleveland has extensively studied prepregnancy obesity, gestational weight gain, and diabetes and their relationship to adverse pregnancy outcomes and to greater newborn weight and fat mass (Catalano, 2015; Ma, 2016; Yang, 2016). Although each of these variables is associated with larger and more corpulent newborns, prepregnancy BMI and its effect on inflammation and placental gene expression has the strongest influence on the prevalence of macrosomic neonates.

Rates of birth defects also are higher with obesity (Auger, 2019). For neural-tube defects, elevated risks of 1.2-, 1.7-, and 3.1-fold have been described for overweight, obese, and severely obese women, respectively (Rasmussen, 2008). The National Birth Defect Prevention Study reported a correlation between BMI and congenital heart defects (Gilboa, 2010). However, this may be related to diabetes as a cofactor (Biggio, 2010). Importantly, obesity degrades the accuracy of obstetrical ultrasound examination and antepartum identification of birth defects (Adekola, 2015; Dashe, 2009; Yaqub, 2021).

Long-term Offspring Morbidity

Obese women beget obese children, who themselves become obese adults. Catalano and coworkers (2009) studied offspring at a mean age of 9 years and found a direct association with maternal prepregnancy obesity and childhood obesity. They also reported associations with central obesity, elevated systolic blood pressure, increased insulin resistance, and lipid abnormalities—all elements of the metabolic syndrome. Reynolds and associates (2013) reported higher rates of cardiovascular disease and all-cause mortality in 37,709 adult offspring of overweight and obese mothers. Similar cardiometabolic health effects in offspring were echoed by Gaillard and colleagues (2016). Other data suggest that excessive maternal weight gain in pregnancy may predict obesity in adult offspring (Lawrence, 2014). Last, rates of glucose intolerance and metabolic syndrome are higher among offspring of obese women (Gaillard, 2016).

The potential biological mechanisms of these associations are unclear. But such studies raise the possibility of *fetal programming*, that is, the fetal environment may lead to adverse adult health outcomes. Elucidation is limited by insufficient data regarding the influence of maternal and genetic predisposition compared with the diet and activity environment of the infant and child (Gluck, 2009). The science of *epigenetics* has provided some support for the possibility that perturbations of the maternal–fetal environment can adversely alter postdelivery events (Kitsiou-Tzeli, 2017).

ANTEPARTUM MANAGEMENT

Maternal Weight Gain

The Institute of Medicine (2009) has updated its previous maternal weight gain determinants (Table 10-4, p. 183). For overweight women, weight gain of 15 to 25 pounds is suggested. For obese women, the Institute recommends a gain of 11 to 20 pounds. Intuitively, maternal weight must increase sufficiently to provide for fetal and placental tissue accrual and for amnionic fluid and maternal blood volume expansion. Thus, maternal weight loss during pregnancy is discouraged. The American College of Obstetricians and Gynecologists (2021) endorses these guidelines.

It is emphasized that these recommendations were issued without firm scientific evidence to support them, and their value remains unproven (Comstock, 2019; Most, 2019). For example, recent studies differ with respect to the effect of insufficient weight gain for obese women. Bodnar and colleagues (2016) reported no greater risk for low-birthweight or small-for-gestational-age newborns among 47,494 obese women who had inadequate weight gain during pregnancy. Bogaerts and associates (2015) also found that even weight loss among obese women did not yield poor fetal growth. In contrast, however, Hannaford and coworkers (2017) reported that obese women who gained less than the Institute recommendations were almost three times more likely to deliver a small-for-gestational-age neonate. Another study similarly found an almost twofold greater risk of growth-restricted newborns among obese women who lost weight during pregnancy (Cox Bauer, 2016).

Excessive gestational weight gain may portend greater risks for the obese mother. Berggren and coworkers (2016) noted that overweight and obese women accrued maternal fat with excessive gestational weight gain. From another analysis, overall higher rates of hypertensive disorders, cesarean delivery, and fetal overgrowth and lower rates of spontaneous preterm birth and fetal undergrowth were found among women gaining more than recommended (Johnson, 2013). However, when analyzed according to BMI category, significantly higher rates of preeclampsia, cesarean delivery, and fetal overgrowth were identified among the 1937 overweight women, but not the 1445 obese women, who gained excess weight. Last, overweight and obese women have excessive postpartum weight retention (Siegel, 2020).

Dietary Intervention

Several dietary interventions can help limit and achieve the weight gain targets listed in the previous section. Options include lifestyle changes such as changes in physical activity. In one randomized trial of exercise in 300 overweight women, risks for gestational diabetes were lowered (Wang, 2017). In other trials, however, dietary intervention had no effect on weight gain (Okasene-Gafa, 2019; Seneviratne, 2016). Also, a Cochrane database analysis of 11,444 women suggests that lifestyle interventions confer only a modest reduction in maternal weight gain, and their benefits for fetal overgrowth, cesarean delivery rate, and adverse neonatal outcome are not significant (Muktabhant, 2015). Last, metformin treatment for obese pregnant women does not improve pregnancy outcomes (Dodd, 2018).

Regarding neonatal outcomes, the poor success of lifestyle interventions during pregnancy has been attributed to their late introduction. In this regard, it is presumed that early gene expression within the placenta has already been programmed (Catalano, 2015).

Prenatal Care

Close prenatal monitoring detects most early signs of diabetes or hypertension. Early gestational diabetes screening did not result in less morbidity compared with standard screening (Harper, 2020). Obstructive sleep apnea is common in obese women (Dominquez, 2018). Standard screening tests for fetal anomalies are sufficient, while remembering the sonographic limitations for fetal anomaly detection in this group. Even so, ultrasound predicts fetal weight accurately in these women (O'Brien, 2020). Accurate fetal-growth surveillance in obese women usually requires serial sonographic assessment. Dude and coworkers (2019) reported that ultrasound as a detection tool had high specificity but poor sensitivity for growth restriction and a low positive predictive value for macrosomia. Antepartum external fetal heart rate monitoring is likewise more difficult.

INTRAPARTUM MANAGEMENT

Obesity poses increased risk for multiple labor or intrapartum complications. These include postterm pregnancy or labor abnormalities (Carpenter, 2016; Shenouda, 2020). In one study of 143,519 women, the odds of spontaneous labor at term in obese women was approximately half that of normal-weight women (Denison, 2008). In an analysis of more than 5000 parturients, women with a BMI >30 kg/m^2 had a longer duration and slower early progression of first-stage labor (Norman, 2012). Epidural analgesia apparently does not affect the length of labor in obese women (Polónia Valente, 2020).

Labor Induction

As shown in Table 51-2, compared with normal-weight women, obese women are nearly twice as likely to undergo labor induction (Denison, 2008). However, obese women are more likely to experience a failed induction, and this risk rises with increasing obesity (Kerbage, 2020). The duration of labor resulting in vaginal delivery lengthens with increasing maternal BMI (Carlhäll, 2020). In a retrospective analysis of 470 nulliparous women with a BMI >30 kg/m^2, those who underwent labor induction at 39 weeks' gestation had a greater cesarean delivery rate—26 versus 40 percent compared with a cohort expectantly managed (Wolfe, 2014). In a study of 485 women with class III obesity, the overall cesarean delivery rate after failed induction was 49 percent (Paidas Teefey, 2020). The rate was 46 percent for those with a BMI 30–40, 63 percent for a BMI 40–50, and 69 percent for a BMI >60.

Although perhaps not unexpected, these findings have been challenged. Lee and associates (2016) reviewed statistics from 74,725 deliveries in obese women and reported that elective induction at 37 to 39 weeks' gestation was actually associated with a lower cesarean delivery rate. Additionally, in a secondary analysis of one randomized trial, obese nulliparas who were randomly assigned to Foley catheter cervical ripening plus misoprostol for labor induction had a reduced labor duration and lower rate of cesarean delivery compared with those given solely misoprostol (Seasely, 2021). These conflicting results highlight the difficulties faced by obstetricians as they contemplate the seemingly competing interests of the fetus and the obese mother.

Anesthesia Risks

Obese women present anesthesia challenges that include difficult epidural and spinal analgesia placement and complications from failed or difficult intubations. Evaluation of gravidas with supermorbid obesity by the anesthesiologist is recommended during prenatal care or upon arrival to the labor unit (American College of Obstetricians and Gynecologists, 2019b).

Regional analgesia for morbidly obese women is associated with longer neuraxial procedure times and more failed placement attempts (Li, 2019). Importantly, however, spinal analgesia in obese women for cesarean delivery does not appear to have greater benefits than combined spinal-epidural. One study comparing single-shot spinal analgesia and combined spinal-epidural analgesia found that both methods could be placed with equal expediency and efficacy in morbidly obese gravidas (Ross, 2014).

Obese women who undergo neuraxial analgesia that is complicated by relative hypotension more frequently have neonates with umbilical artery cord blood acidemia, which probably stems from delayed delivery. One study of 572 obese women showed that cord blood pH significantly dropped and base deficit rose with increasing BMI (Edwards, 2013). The rate of gases with a pH <7.1 doubled from 3.5 percent for a BMI <25 kg/m^2 to 7.1 percent for a BMI ≥40 kg/m^2. Anesthetic risks and complications are discussed in Chapter 25.

Cesarean Delivery

As shown in Table 51-2, rates of cesarean delivery are significantly greater in obese women compared with normal-weight gravidas. In an analysis of 226,958 women, cesarean delivery rates rose significantly for overweight (34 percent), class I (38 percent), class II (43 percent), and class III (50 percent) obesity (Schummers, 2015). Our experiences at Parkland Hospital are similar (Fig. 51-8). Moreover, obese women had less composite morbidity when labor was attempted compared with cesarean delivery (Gibbs Pickens, 2018; Grasch, 2017). More worrisome is that obese women also have higher rates of *emergency* cesarean delivery, and obesity lengthens times for decision-to-incision and for delivery (Girsen, 2014; Pulman, 2015).

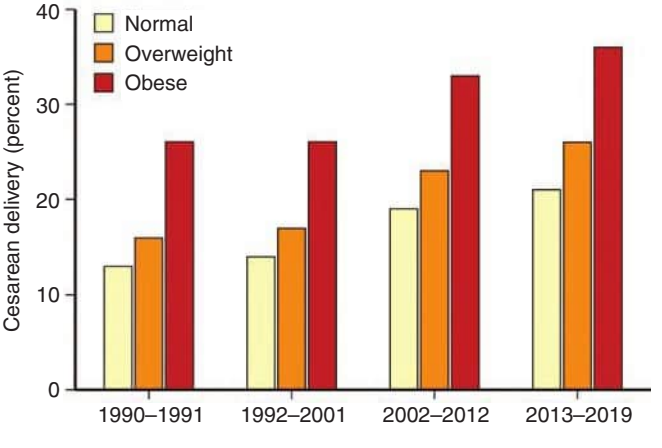

FIGURE 51-8 Cesarean delivery rates in more than 300,000 women according to BMI categories over a 30-year period at Parkland Hospital.

Discussed in Chapter 31 (p. 577), the incidence of failed trial of labor after cesarean is higher in obese women (Grasch, 2017; Wilson, 2020). Women who gain weight between pregnancies also have significantly lower rates of vaginal birth after cesarean.

Surgical Concerns

For cesarean delivery, forethought is given to optimal placement and type of abdominal incision to provide access to the fetus and to effect the best wound closure. We prefer a vertical incision in obese women to provide the most direct access (Fig. 51-9). Others prefer a low transverse abdominal incision, with or without rostral taping of the pendulous abdomen (Karimyar, 2020; Lakhi, 2018). Individual differences in maternal body habitus preclude naming any one approach as superior (Turan, 2016). Some observational studies have compared wound outcomes associated with vertical and transverse skin incisions, but results are conflicting as to a superior option (Karimyar, 2020; Marrs, 2014; Sutton, 2016).

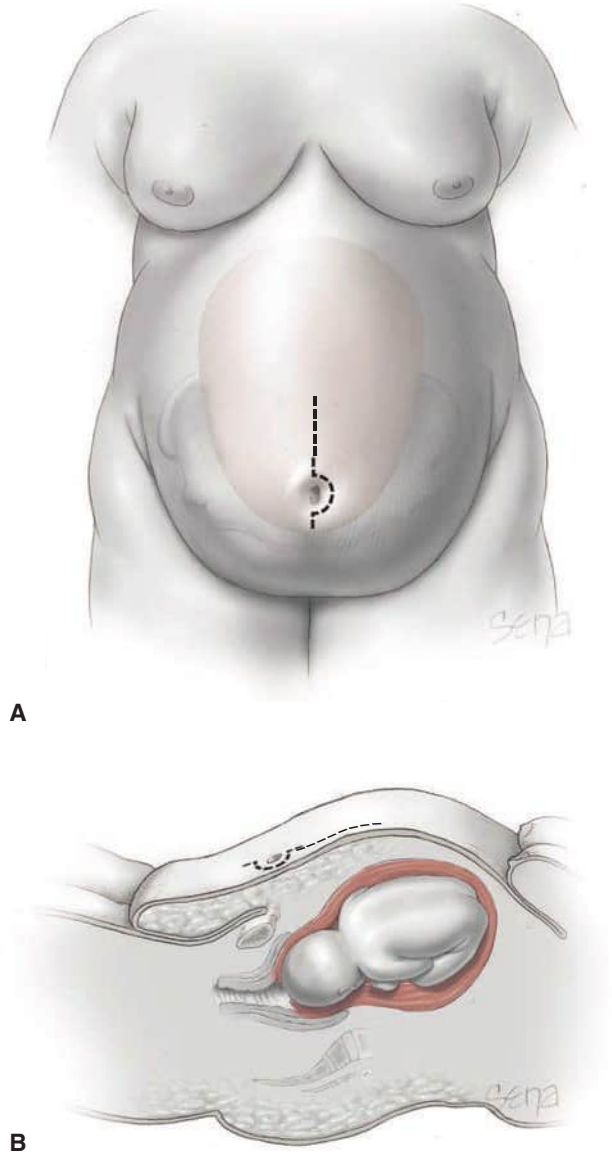

FIGURE 51-9 Abdominal incision for the obese woman. **A.** Frontal view. The dotted line indicates an appropriate skin incision for abdominal entry relative to the panniculus. As shown by the uterus in the background, selection of this periumbilical site permits access to the lower uterine segment. **B.** Sagittal view.

The frequency of abdominal wound infections is directly related to BMI. Conner and associates (2014) found the risk of wound infection is threefold higher—23 versus 7 percent—in women with supermorbid obesity compared with nonobese patients. Among women with a BMI >45 kg/m^2, reported wound complication rates range from 14 to 19 percent (Smid, 2015; Stamilio, 2014). Comorbid diabetes apparently raises this risk (Leth, 2011). Other studies describe wound complication rates ranging from 2 to >40 percent in obese women (Conner, 2014; Marrs, 2014; Smid, 2015; Thornburg, 2012).

Several interventions may be preventive. Closure of subcutaneous tissue when at least 2 cm deep reduces wound complication rates (Tipton, 2011). Steel staples and subcuticular skin closure produce identical results (Zaki, 2018). Studies have also examined the use of higher doses of perioperative prophylactic antibiotics. Pharmacokinetic studies indicate that tissue concentrations of prophylactic antibiotics are lower with increasing BMI (Pevzner, 2011; Young, 2015). One prospective study showed that a 3-g dose of cefazolin resulted in higher tissue concentrations compared with a 2-g dose (Swank, 2015). A retrospective analysis of 335 women with a median weight of 310 pounds found that the higher dose of cefazolin did not result in fewer surgical site infections (SSIs) (Ahmadzia, 2015). The American College of Obstetricians and Gynecologists (2020) recognizes either 2- or 3-g doses of cefazolin as suitable for those with weights ≥80 kg. The Centers for Disease Control and Prevention recommends a 2-g dose for weights ≥80 kg and 3-g dose for those ≥120 kg (Berríos-Torres, 2017). One pharmacokinetic analysis in obese women showed sufficient tissue levels with a 2-g dose for cesarean deliveries lasting 1.5 hours. Authors recommended consideration for redosing in obese women if surgeries were longer (Grupper, 2016). Last, some early evidence may support extending oral antibiotic prophylaxis for 48 hours postcesarean in obese women to lower SSIs (Valent, 2017). Obese women administered preoperative cephalosporin prophylaxis had a surgical infection rate of 13.4 percent compared with a rate of 6.4 percent for those given a 2-day *postoperative* course of oral cephalexin and metronidazole in addition to routine preoperative prophylaxis.

Negative-pressure wound therapy (NPWT) also has been used prophylactically (Mark, 2014). To address this, Hussamy and colleagues (2019) designed a randomized trial of NPWT versus routine dressing in 441 obese women undergoing cesarean delivery. Such therapy did not significantly lower the postoperative wound complication rate compared with routine care—17 versus 19 percent, respectively. A subsequent report confirmed these findings (Tuuli, 2020).

For the obese woman who is delivered vaginally, puerperal tubal sterilization is safe regardless of BMI (Byrne, 2020). These procedures are described in Chapter 39. The risks for postpartum venous thromboembolism are increased in obese women. This is despite the fact that velocity of lower-extremity blood flow is increased in obese pregnant women (Dutta, 2020). As discussed in Chapter 55 (p. 990), thromboprophylaxis is controversial. To lower thromboembolic complications, graduated

compression stockings, hydration, and early mobilization after cesarean delivery in obese women are recommended by the American College of Obstetricians and Gynecologists (2019b). If there are additional risk factors other than class III obesity, the Society for Maternal-Fetal Medicine (2020) recommends enoxaparin. We do not routinely use thromboprophylaxis for obesity alone at Parkland Hospital. This practice has recently been confirmed by Lu and associates (2021).

BARIATRIC SURGERY

Several surgical procedures are designed to treat morbid obesity either by diminishing gastric volume (*restrictive*) or by bypassing gastrointestinal absorption (*restrictive malabsorptive*). In nonpregnant patients, these procedures serve to improve or resolve diabetes, hyperlipidemia, hypertension, and obstructive sleep apnea and to reduce risks of myocardial infarction and death (Beamish, 2016).

Restrictive Procedures

Of options, the approved laparoscopic adjustable silicone gastric banding (LASGB) procedure—*LAPBAND*—places a band 2 cm below the gastroesophageal junction to create a small stomach pouch above the ring. The ring diameter is controlled by a saline reservoir in the band.

These procedures can have positive effects on pregnancy outcomes. One study compared pregnancy outcomes in bariatric surgery patients whose surgery was done after the first pregnancy. Following bariatric surgery, the incidences of hypertension, gestational diabetes, and preterm birth were significantly lower in the bariatric surgery patients (Ibiebele, 2020). The results from these and other studies are shown in Table 51-3.

Deflation of the band during pregnancy affects maternal and fetal weight gain. Pilone and coworkers (2014) studied 22 pregnancies after band placement and reported that all women underwent full deflation of the band in the first trimester and gained an average of 14.7 kg during pregnancy. In another study, 42 women underwent deflation of the band, whereas 54 women maintained band inflation. A deflated band was associated with higher mean maternal weight gain—15.4 kg versus 7.6 kg, increased birthweight—3712 versus 3380 g, and a twofold greater risk of macrosomia compared with an inflated band (Cornthwaite, 2015). Rarely, the band may slip due to nausea and vomiting, especially with advancing gestation or after delivery (Pilone, 2014; Schmitt, 2016; Suffee, 2012). One fetus suffered a fatal cerebral hemorrhage caused by maternal vitamin K deficiency secondary to prolonged vomiting due to band slippage that created a gastric outlet obstruction (Van Mieghem, 2008).

TABLE 51-3. Pregnancy Outcomes Following Bariatric Surgery

Outcome[a]	Gastric Banding[b]	Gastric Bypass[c]
Hypertension	11%	4%
Gestational diabetes	7%	4%
Cesarean delivery	35%	33%
Mean birthweight	3206 g	3084 g
Low birthweight	7%	11%
Stillbirth	3/1000	3/1000

[a]Data not reported identically—frequencies are approximations.
[b]Data from Adams, 2015; Bar-Zohar, 2006; Carelli, 2011; Dixon, 2005; Ducarme, 2013; Facchiano, 2012; Lapolla, 2010; Pilone, 2014; Sheiner, 2009.
[c]Data from Adams, 2015; Ducarme, 2013; Facchiano, 2012; González, 2015; Kwong, 2018; Sheiner, 2009.

Restrictive Malabsorptive Procedures

The laparoscopically performed *Roux-en-Y* gastric bypass is the most commonly used procedure for gastric restriction and selective malabsorption. Pregnancy outcomes are changed remarkably following Roux-en-Y bypass (Adams, 2015). As shown in Table 51-3, rates of hypertension, gestational diabetes, and fetal macrosomia are reduced.

Serious complications with bypass operations are uncommon, however, upper abdominal pain is frequent in pregnancy and may be associated with internal herniation, which is protrusion of the bowel through a window defect in the mesentery. Petersen and associates (2017) described outcomes in a birth cohort including 139 pregnancies. Upper abdominal pain complicated 46 percent, and a third of these had internal herniation. The preterm birth rate was 14 of 64 among those with upper abdominal pain versus 1 of 75 in those without pain. Intussusception and small bowel obstruction can develop from internal herniation, and maternal deaths from herniation and obstruction are reported (Moore, 2004; Renault, 2012). Bowel obstruction is notoriously difficult to diagnose during pregnancy (Vannevel, 2016; Wax, 2013).

Pregnancy

Because of its associated health successes, bariatric surgery is popular, and many women subsequently become pregnant (Narayanan, 2016). From studies, fertility improves and obstetrical complication rates decline in women after bariatric surgery compared with morbidly obese controls (Getahun, 2021; Kominiarek, 2017; Yi, 2015). In one of these studies, despite surgical treatment, almost half of 670 women were still obese at the time of their first pregnancy after bypass (Johansson, 2015). Nevertheless, the frequency of large-for-gestational-age newborns dropped from 22 to 8.6 percent and of small-for-gestational-age neonates rose from 7.6 to 15.6 percent. In a systematic review, Kwong and colleagues (2018) confirmed these fetal weight trends after bariatric surgery. According to Maric and colleagues (2020), fetuses are smaller because of lower maternal glucose levels rather than alterations of the fetoplacental circulation. Also, risks for diabetes and preeclampsia were reduced. Last, evidence suggests that the risk for congenital anomalies is decreased (Auger, 2019; Neovius, 2019).

Currently, the American College of Obstetricians and Gynecologists (2019b) recommends that women who have undergone bariatric surgery be assessed for vitamin and nutritional

sufficiency. When indicated, vitamins B_{12} and D, folic acid, and calcium supplementation are given. Vitamin A deficiency also is possible (Chagas, 2013). Women with a gastric band should be monitored by their bariatric team during pregnancy because band adjustments may be necessary. Last, special vigilance for signs of internal herniation with intestinal obstruction is encouraged (Stuart, 2017; Wax, 2013).

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CHAPTER 52

Cardiovascular Disorders

In an analysis of maternal mortality in the United States between 2011 and 2013, deaths related to hemorrhage, hypertensive disorders, and embolism showed declining rates. In contrast, deaths attributable to cardiovascular diseases are rising and are responsible for one fourth of all pregnancy-related mortalities (Creanga, 2017; Petersen, 2019). Recent development of state-level maternal mortality review committees have emphasized this issue and highlighted the relatively protracted timeline of illness. Up to a year after delivery, cardiac events were among the leading causes of death for women in Texas in 2013 (Texas Maternal Morbidity Task Force, 2020). These disorders account also for significant maternal morbidity and are a common reason for intensive care unit admissions (Small, 2012).

Cardiovascular disease complicates 1 to 4 percent of pregnancies in the United States (American College of Obstetricians and Gynecologists, 2019). The increasing prevalence is likely multifactorial and includes the higher rates of obesity, hypertension, and diabetes (Klingberg, 2017). According to the National Center for Health Statistics, almost half of adults aged 20 and older have at least one risk factor for cardiovascular disease (Fryar, 2012). Another related reason is delayed childbearing. Last, as discussed subsequently (p. 927), an increasing number of women with congenital heart disease are now becoming pregnant.

The importance of heart disease and its adverse effect on pregnancy morbidity and mortality led the American College of Obstetricians and Gynecologists to create a Task Force on Pregnancy and Heart Disease. Its purpose is to emphasize the prevalence and effect of heart disease in pregnancy, provide guidance for risk factor identification, outline common cardiovascular disorders, provide recommendations for management, and develop a comprehensive interpregnancy plan. Multidisciplinary care is essential (Quinones, 2021).

PHYSIOLOGICAL CONSIDERATIONS IN PREGNANCY

Cardiovascular Physiology

The marked pregnancy-induced anatomical and functional changes in cardiac physiology can have a profound, negative effect on underlying heart disease. These changes are discussed in detail in Chapter 4 (p. 62), and some are listed in Table 52-1

TABLE 52-1. Hemodynamic Changes in 10 Normal Pregnant Women at Term Compared with Repeat Values Obtained 12 Weeks Postpartum

Parameter	Change (%)
Cardiac output	+43
Heart rate	+17
Left ventricular stroke work index	+17
Vascular resistance	
Systemic	−21
Pulmonary	−34
Mean arterial pressure	+4
Colloid osmotic pressure	−14

(Clark, 1989). Importantly, cardiac output increases approximately 40 percent during pregnancy. Almost half of this total takes place by 8 weeks' gestation and is maximal by midpregnancy (Capeless, 1989). This early rise stems from augmented stroke volume, which results from lowered vascular resistance. Later in pregnancy, resting pulse and stroke volume are even higher because of greater end-diastolic ventricular volume that results from augmented pregnancy blood volume. These adaptations are even more profound in multifetal pregnancies (Ghi, 2019). Intrinsic left ventricular contractility does not change, and thus normal left ventricular function is maintained during pregnancy. Namely, pregnancy is not characterized by hyperdynamic function or a high cardiac-output state.

Women with underlying cardiac disease may not always accommodate these changes, and ventricular dysfunction leads to cardiogenic heart failure. A few women with severe cardiac dysfunction can experience evidence of heart failure before midpregnancy. In others, heart failure may develop after 28 weeks' gestation, when pregnancy-induced hypervolemia and cardiac output reach their maximum. In most, however, heart failure develops peripartum, when labor, delivery, and several common obstetrical conditions add undue cardiac burdens. Some of the latter include preeclampsia, hemorrhage and anemia, and sepsis.

■ Ventricular Function in Pregnancy

Ventricular volumes and mass accrue to accommodate pregnancy-induced hypervolemia. This is reflected by greater end-systolic and end-diastolic dimensions. At the same time, however, septal thickness and ejection fraction are unchanged. This is because these alterations are accompanied by substantive ventricular remodeling—*plasticity*—which is characterized by eccentric expansion of left-ventricular mass that averages 30 to 35 percent near term. All of these adaptations return to prepregnancy values within a few months postpartum.

Certainly for clinical purposes, ventricular function during pregnancy is normal as estimated by the *Braunwald ventricular function* graph (Fig. 4-9, p. 63). Thus, for given filling pressures, cardiac output is appropriate and allows eudynamic cardiac function during pregnancy. Esoteric changes in pregnancy-related cardiac physiology continue to be clarified. In nonpregnant subjects with a normal heart who sustain a high-output state, the left ventricle undergoes *longitudinal remodeling*, and echocardiographic functional indices of its deformation show normal values. In pregnancy, the ventricle instead undergoes *spherical remodeling*, and the calculated indices that measure longitudinal deformation are depressed. Thus, normal nonpregnant indices are likely less accurate when used to assess function in pregnant women because they do not account for the spherical remodeling (Savu, 2012; Stewart, 2016).

Adjusting for these geometrical changes, Melchiorre and coworkers (2016) studied normal cardiac echocardiographic findings in 559 nulliparas at four points during pregnancy and again at 1 year postpartum. At term, significant chamber diastolic dysfunction was present in 18 percent and impaired myocardial relaxation was evident in 28 percent of the women. Also, a significant proportion of women demonstrated a drop in stroke volume index and a tendency toward eccentric remodeling. These findings suggest cardiovascular maladaptation to the expanded volume demands in a substantial proportion of apparently normal pregnancies. Significant dyspnea at rest was reported by 7.4 percent of the women at term, most of whom had chamber diastolic dysfunction. Cardiac function and all signs of dyspnea fully recovered at 1 year postpartum.

Cardiac magnetic resonance (MR) imaging increasingly is used to evaluate cardiac structure and function. Stewart and associates (2016) performed cardiac MR imaging studies in 23 women longitudinally across pregnancy and at 12 weeks postpartum. Compared with studies performed at 12 to 16 weeks' gestation, left ventricular mass grew significantly for both normal-weight and overweight women. The calculated geometrical ratio of left ventricular mass to left ventricular end-diastolic volume demonstrated concentric remodeling throughout gestation, which resolved by 12 weeks' postpartum. The right ventricle also undergoes remodeling (Martin, 2017). These observations likely mean that pregnancy causes a mixture of eccentric and concentric ventricular remodeling.

DIAGNOSIS OF HEART DISEASE

The physiological adaptations of normal pregnancy can induce symptoms and alter clinical findings that may confound the diagnosis of heart disease. For example, in normal pregnancy, functional systolic heart murmurs are common, respiratory effort is accentuated, edema frequently accrues in lower extremities after midpregnancy, and fatigue and exercise intolerance often develop. Some systolic flow murmurs can be loud, and normal changes in the various heart sounds depicted in Figure 52-1 may erroneously suggest cardiac disease. In contrast, clinical findings that are more likely to suggest heart disease are listed in Table 52-2.

■ Diagnostic Studies

Noninvasive cardiovascular studies such as electrocardiography, chest radiography, and echocardiography will provide the data necessary for cardiac functional evaluation in most women.

In the *electrocardiogram (ECG)*, an average 15-degree left-axis deviation is found as the diaphragm is elevated in advancing pregnancy. Other findings are described in Figure 52-2

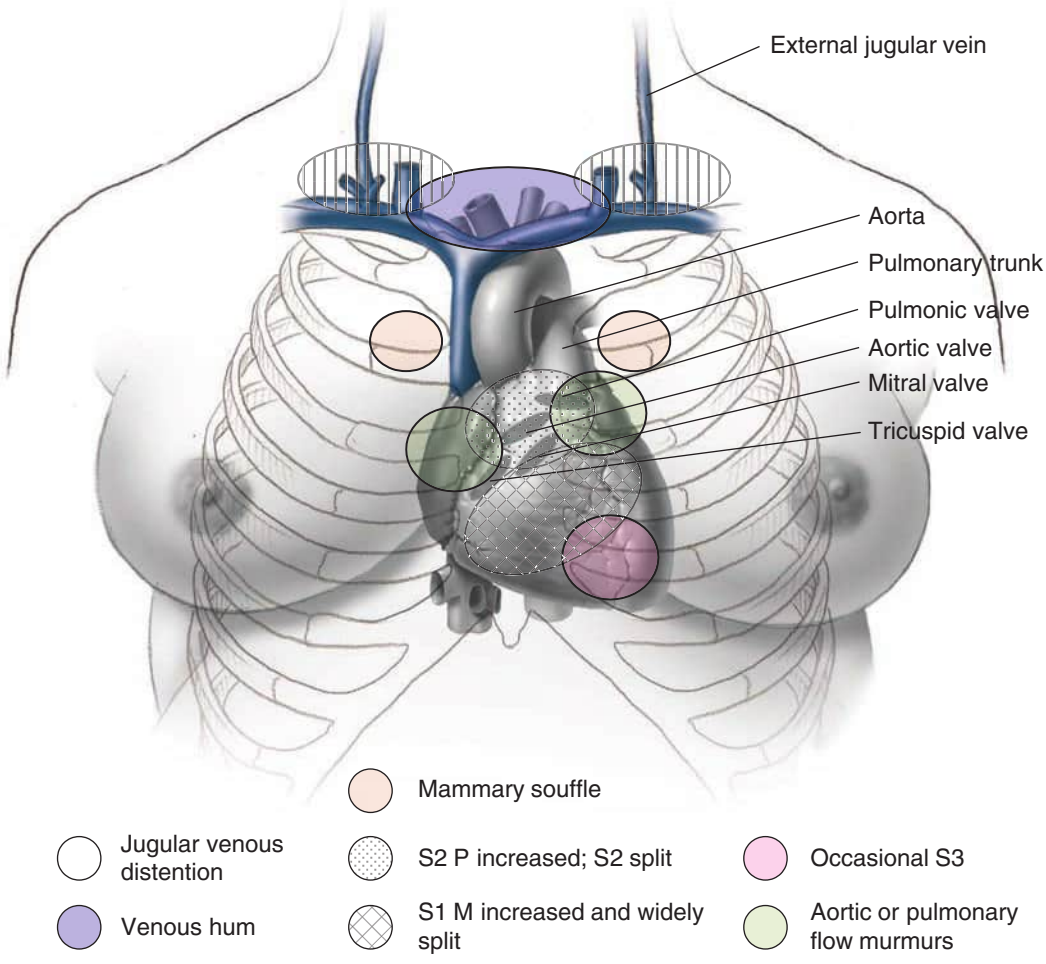

FIGURE 52-1 Normal cardiac examination findings in the pregnant woman. S_1 = first sound; M_1 = mitral first sound; S_2 = second sound; P_2 = pulmonary second sound. (Data from Gei, 2001; Hytten, 1991.)

TABLE 52-2. Clinical Indicators of Heart Disease During Pregnancy

Symptoms
Progressive dyspnea or orthopnea
Nocturnal cough
Hemoptysis
Syncope
Chest pain
Clinical Findings
Cyanosis
Clubbing of fingers
Persistent neck vein distention
Systolic murmur grade 3/6 or greater
Diastolic murmur
Cardiomegaly
Persistent tachycardia and/or arrhythmia
Persistent split second sound
Fourth heart sound
Criteria for pulmonary hypertension

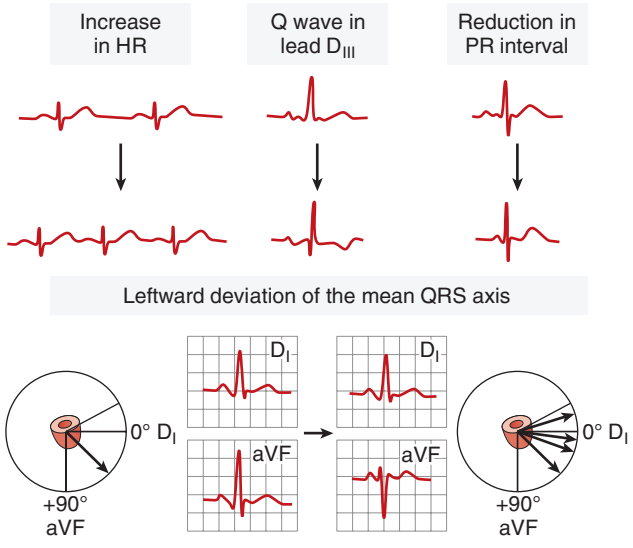

FIGURE 52-2 Normal electrocardiograph (ECG) adaptations during pregnancy, including a reduced mean PR interval, increased heart rate, left axis deviation, inverted or flattened T waves, and a Q wave in lead D_{III}. HR = heart rate. (Reproduced with permission from Angeli F, Angeli E, Verdecchia P: Electrocardiographic changes in hypertensive disorders of pregnancy, Hypertens Res 2014 Nov;37(11):973–975.)

(Angeli, 2014). Pregnancy does not alter voltage findings. Atrial and ventricular premature contractions are relatively frequent.

With *radiography*, anteroposterior (AP) and lateral chest radiographs are useful, and when a lead apron shield is used, fetal radiation exposure is minimal. Gross cardiomegaly can usually be excluded, but slight heart enlargement is poorly detected because the heart silhouette normally is larger in pregnancy. This is accentuated further with a portable posterior-anterior chest radiograph.

Echocardiography is now widely used and permits accurate diagnosis of most heart diseases during pregnancy. Some normal pregnancy-induced changes include a small increase in the dimensions of all cardiac chambers, a slight but significant growth in left ventricular mass, and greater tricuspid and mitral valve regurgitation (Grewal, 2014). Of note, systolic function normally does not change and ejection fraction is preserved. Late geometric changes such as interventricular septum dimension (IV_d) are likely to be abnormal before changes in ejection fraction. Savu (2012) and Vitarelli (2011) and their colleagues have provided normal echocardiographic parameters for pregnancy, which are listed in the Appendix (p. 1233). In some situations, such as complex congenital heart disease, *transesophageal echocardiography* may be useful.

Cardiovascular MR imaging, compared with echocardiography, is associated with higher reproducibility and is less hindered by ventricular geometry and body habitus. It is useful for assessment of the right ventricle and visualization of congenital heart lesions and myocarditis (Herrey, 2019; Martin, 2017). Ducas and coworkers (2014) have published normal reference values for pregnancy.

Exercise stress testing is an objective assessment of maternal functional capacity. It is also useful to diagnose exercise-induced arrhythmias. Stress testing can be performed in women with known heart disease prior to pregnancy or, if necessary, in the asymptomatic pregnant women (Regitz-Zagrosek, 2018). Dennis and associates (2019) have described findings in normal pregnant women using the *6-minute walk test*.

Myocardial perfusion studies using albumin or red cells tagged with technetium-99m are rarely needed during pregnancy to evaluate ventricular function. That said, the estimated fetal radiation exposure from nuclear medicine studies of myocardial perfusion is negligible (Chap. 49, p. 875). *Cardiac catheterization* with limited fluoroscopy time also is safe to perform. During coronary angiography, the mean radiation exposure to the unshielded abdomen is 1.5 mGy, and less than 20 percent of this reaches the fetus (Regitz-Zagrosek, 2018). Shortening the fluoroscopic time may help to minimize radiation exposure (Raman, 2015; Tuzcu, 2015). In women with clear indications, any minimal theoretical fetal risk is outweighed by maternal benefits, and such studies should be performed as indicated.

■ Functional Classification of Heart Disease

Pregnancy is a stress test of cardiovascular reserve. However, no clinically applicable test accurately measures functional cardiac capacity. The clinical classification of the New York Heart Association (NYHA) is based on past and present disability and is uninfluenced by physical signs:

- Class I. *Uncompromised—no limitation of physical activity:* These women do not have symptoms of cardiac insufficiency or experience anginal pain.
- Class II. *Slight limitation of physical activity:* These women are comfortable at rest, but with ordinary physical activity, discomfort in the form of excessive fatigue, palpitation, dyspnea, or anginal pain results.
- Class III. *Marked limitation of physical activity:* These women are comfortable at rest, but less than ordinary activity causes excessive fatigue, palpitation, dyspnea, or anginal pain.
- Class IV. *Severely compromised—inability to perform any physical activity without discomfort:* Symptoms of cardiac insufficiency or angina may develop even at rest. If any physical activity is undertaken, discomfort is increased.

At least four predictive systems detect and classify heart disease in pregnant women. These include CARPREG I and II, ZAHARA, and the World Health Organization (WHO) system (Wolfe, 2019). Of these, the most comprehensive risk stratification system is the modified WHO Risk Classification of Cardiovascular Disease and Pregnancy (Table 52-3). This classification system was validated in an international cohort of 2742 pregnant women with heart disease (van Hagen, 2016). It is especially useful for assessing maternal risk and for preconceptional counseling. Lu (2015) and Pijuan-Domènech (2015) and their colleagues concluded that the modified WHO classification provides the greatest predictive accuracy for cardiac complications during pregnancy.

GENERAL PREGNANCY CONSIDERATIONS

■ Preconceptional Counseling

Women with severe heart disease will benefit immensely from counseling before pregnancy, and they usually are referred for maternal-fetal medicine or cardiology consultation (Clark, 2012; Wolfe, 2019). Optimizing cardiac function to mitigate complications during pregnancy is the goal. Maternal mortality rates generally correlate directly with functional classification, however, this relationship may change as pregnancy progresses. Siu and coworkers (2001b) observed significant worsening of NYHA class in 4.4 percent of 579 pregnancies in which the baseline class was I or II.

As described later, some women have life-threatening cardiac abnormalities that can be reversed by corrective surgery, and subsequent pregnancy becomes less dangerous. In other cases, such as women with mechanical valves taking warfarin, fetal teratogenic concerns predominate. Last, because many congenital heart lesions are inherited as polygenic characteristics, some women with congenital heart lesions give birth to similarly affected neonates. This risk varies widely based on the specific abnormality (Table 52-4) (Lupton, 2002).

Risk Factors

According to the American College of Obstetricians and Gynecologists (2019), four maternal risk factors are linked to

TABLE 52-3. World Health Organization (WHO) Risk Classification of Cardiovascular Disease and Pregnancy with Management Recommendations

Risk Category	Associated Conditions
WHO 1—Morbidity or mortality risk no higher than general population	Uncomplicated, small, or mild: Pulmonary stenosis Patent ductus arteriosus Mitral valve prolapse with no more than trivial mitral regurgitation Successfully repaired simple lesions: Ostium secundum atrial septal defect Ventricular septal defect Patent ductus arteriosus Total anomalous pulmonary venous drainage Isolated ventricular extrasystoles and atrial ectopic beats
• Cardiology consultation once or twice during pregnancy. Local hospital care suitable	
WHO 2—Small increase in risk of maternal mortality and moderate increase in morbidity risk	If otherwise uncomplicated: Unoperated atrial or ventricular septal defect Repaired Fallot tetralogy Most arrhythmias Turner syndrome without aortic dilation
• Cardiology consultation each trimester. Local hospital care suitable	
WHO 2 or 3—Intermediate increase in maternal mortality risk and moderate to severe rise in morbidity risk	Mild left ventricular impairment Hypertrophic cardiomyopathy Native or tissue disease not considered WHO 1 or 4 Marfan syndrome without aortic dilation Repaired coarctation Prior heart transplantation
• Cardiology consultation bimonthly. Care at referral hospital	
WHO 3—Significantly increased risk of maternal mortality and severe increase in morbidity risk	Mechanical valve Systemic right ventricle Post-Fontan operation Unrepaired cyanotic heart disease Other complex congenital heart disease Moderate left ventricular impairment Prior peripartum cardiomyopathy with no residual effect Moderate mitral stenosis Severe asymptomatic aortic stenosis Moderate aortic dilation (40–50 mm) Ventricular tachycardia
• Cardiology consultation monthly or bimonthly. Care at tertiary-care hospital	
WHO 4—Very high risk of maternal mortality or severe morbidity; pregnancy contraindicated and termination discussed	Pulmonary arterial hypertension Severe systemic ventricular dysfunction (NYHA III–IV or LVEF <30%) Prior peripartum cardiomyopathy with residual effects Severe left heart obstruction Severe aortic dilation Severe coarctation Fontan procedure with residual complications
• Pregnancy contraindicated • If pregnancy occurs, cardiology consultation monthly. Care at tertiary-care hospital	

Summarized from European Society of Gynecology, 2018; Nanna, 2014; Thorne, 2006.

TABLE 52-4. Risks for Fetal Heart Lesions Related to Affected Family Members

Cardiac Lesion	Congenital Heart Disease in Fetus (%)		
	Previous Sibling Affected	Father Affected	Mother Affected
Aortic stenosis	2	3	15–18
Pulmonary stenosis	2	2	6–7
Ventricular septal defect	3	2	10–16
Atrial septal defect	2.5	1.5	5–11
Patent ductus arteriosus	3	2.5	4
Coarctation of the aorta	NS	NS	14
Fallot tetralogy	2.5	1.5	2–3
Marfan syndrome	NS	50	50

NS = not stated.

cardiovascular disease morbidity and mortality: (1) *race/ethnicity*, with morbidity highest in African-American women; (2) *age*, with increased morbidity in women older than 40 years; (3) *hypertension* of all varieties; (4) *obesity*, with higher morbidity associated with increasing degrees of obesity (Ackerman, 2019). To these, social and health disparities could be added because lower income, food and housing insecurity, and lack of childcare are directly linked to underutilization of prenatal care (Gadson, 2017). In turn, lack of prenatal care is a risk factor for maternal morbidity and mortality (Howland, 2019).

Antepartum Care

In most instances, management involves a team approach with an obstetrician, cardiologist, anesthesiologist, and other specialists as needed. With complex lesions or other high-risk cases, evaluation by a multidisciplinary team is recommended early in pregnancy. Both prognosis and management are influenced by the type and severity of the specific lesion and by the maternal functional classification. In some, pregnancy termination may be advisable.

With rare exceptions, women in NYHA class I and most in class II negotiate pregnancy without morbidity. Special attention is directed toward both prevention and early recognition of heart failure. Of specific risks, infection with sepsis can precipitate decompensation. Also, bacterial endocarditis is a deadly complication of valvular heart disease (p. 934). Each woman is instructed to avoid contact with persons who have respiratory infections, including the common cold, and to immediately report any evidence for infection. Pneumococcal vaccine, if not previously administered, and yearly influenza vaccine are recommended (Chap. 10, p. 188).

Cigarette smoking is prohibited. Illicit drug use may be particularly harmful, an example being the cardiovascular effects of cocaine or amphetamines. In addition, intravenous drug use raises the infective endocarditis risk.

Fortunately, gravidas in NYHA class III and IV are uncommon today. In the Canadian study, only 3 percent of the approximately 600 pregnancies were complicated by NYHA class III heart disease, and no women had class IV when first seen (Siu, 2001b). If a woman chooses pregnancy, she must understand the risks and is encouraged to be compliant with planned care. In some women, prolonged hospitalization or bed rest is often necessary.

Labor and Delivery

In general, vaginal delivery is preferred, and labor induction is usually safe (Thurman, 2017). From the large Registry on Pregnancy and Cardiac Disease, Ruys and associates (2015) compared pregnancy outcomes between 869 women who had a planned vaginal delivery and 393 gravidas who had a planned cesarean delivery. Planned cesarean delivery conferred no advantage for maternal or neonatal outcome. Similar results were reported from Brigham and Women's Hospital (Easter, 2020).

Cesarean delivery is usually limited to obstetrical indications, and considerations are given for the specific cardiac lesion, overall maternal condition, and availability of experienced anesthesia personnel and hospital capabilities. Some of these women tolerate major surgical procedures poorly and are best delivered in a unit experienced with management of complicated cardiac disease. Occasionally, pulmonary artery catheterization may be needed for hemodynamic monitoring (Chap. 50, p. 883). In our experiences, however, invasive monitoring is rarely indicated.

Based on her review, Simpson (2012) recommends cesarean delivery for women with the following: (1) dilated aortic root >4 cm or aortic aneurysm; (2) acute severe congestive heart failure; (3) recent myocardial infarction; (4) severe symptomatic aortic stenosis; (5) need for emergency valve replacement immediately after delivery; and (6) warfarin administration within 2 weeks of delivery due to fetal risk for intracerebral hemorrhage because the fetal liver takes up to 2 weeks to metabolize warfarin. Although we agree with most of these, we have some caveats. For congestive heart failure, we prefer aggressive medical stabilization of pulmonary edema followed by vaginal delivery if possible.

During labor, the mother with significant heart disease should be kept in a semirecumbent position with a lateral tilt. Vital signs are taken frequently between contractions. Elevations in pulse rate much above 100 beats per minute (bpm) or respiratory rate above 24 breaths per minute, particularly when associated with dyspnea, may suggest impending ventricular failure. For evidence of cardiac decompensation, intensive medical management must be instituted immediately. Delivery itself does not necessarily improve the maternal condition and, in fact, may worsen it. Moreover, emergency cesarean delivery may be particularly hazardous. Clearly, both maternal and fetal status must be considered in the decision to hasten delivery under these circumstances.

Analgesia and Anesthesia

Relief from pain and from apprehension is important. Although intravenous analgesics provide satisfactory pain relief for some women, continuous epidural analgesia is recommended for most. The major problem with conduction analgesia is maternal

hypotension (Chap. 25, p. 473). This is especially dangerous in women with intracardiac shunts in whom flow may be reversed. Hypotension can also be life-threatening if there is pulmonary arterial hypertension or aortic stenosis. In these, ventricular output is dependent on adequate preload. In women with these conditions, narcotic regional analgesia; low-dose, slow-infusion epidural; or general anesthesia may be preferable.

For vaginal delivery in women with only mild cardiovascular compromise, epidural analgesia given with intravenous sedation often suffices. This minimizes intrapartum cardiac output fluctuations and allows forceps or vacuum-assisted delivery. Incrementally dosed subarachnoid blockade is approached especially cautiously in women with significant heart disease due to associated hypotension. For cesarean delivery, epidural analgesia is preferred by most clinicians with caution for its use with pulmonary arterial hypertension (p. 932).

Intrapartum Heart Failure

From the Nationwide Inpatient Sample, one fourth of cases of heart failure during pregnancy were encountered intrapartum (Mogos, 2018). Women with underlying cardiovascular disorders are at higher risk (Schlichting, 2019). The physiological stress and fluid shifts associated with labor and delivery explain this risk. Catecholamine release due to pain and second stage Valsalva increase left ventricular work, which can precipitate heart failure (Anthony, 2016).

Obstetrical complications can either advance or precipitate heart failure. Preeclampsia is common and may provoke afterload failure (Vaught, 2018). Findings from the Registry on Pregnancy and Cardiac Disease indicate that women with preexisting heart disease who develop preeclampsia have a 30-percent risk of developing heart failure during pregnancy (Ruys, 2014). Obesity is another common cofactor (Vonck, 2019). Also, high-output states caused by hemorrhage and acute anemia elevate cardiac workload and magnify the physiological effects of compromised ventricular function. Similarly, infection and sepsis increase cardiac output and oxygen utilization and depress myocardial function.

Chronic hypertension with superimposed preeclampsia is the most frequent cause of heart failure in pregnancy in numerous populations. Many of these women have preexisting concentric left ventricular hypertrophy (Ambia, 2017, 2018). In some, mild antecedent undiagnosed hypertension causes covert cardiomyopathy, and when superimposed preeclampsia develops, together they may cause otherwise inexplicable peripartum heart failure. Obesity is frequently comorbid with chronic hypertension, and it also is associated with ventricular hypertrophy (Kenchaiah, 2002).

Cardiovascular decompensation during labor may manifest as pulmonary edema with hypoxia or as hypotension, or both. The proper therapeutic approach depends on the specific hemodynamic status and the underlying cardiac lesion. Continuous pulse oximetry and invasive blood pressure monitoring with an arterial line is helpful in some cases (Easter, 2020) In general, pulmonary edema due to fluid overload is often best treated with aggressive diuresis. If precipitated by tachycardia, heart rate control with β-blocking agents is preferred. However, unless the underlying pathophysiology is understood and the cause of the decompensation is clear, empirical therapy may be hazardous. Details of heart failure management and specific cardiovascular disorders are discussed below.

Puerperium

Women who have shown little or no evidence of cardiac compromise during pregnancy, labor, or delivery may still decompensate postpartum (Mogos, 2018). Fluid mobilized into the intravascular compartment and reduced peripheral vascular resistance place higher demands on myocardial performance. Therefore, meticulous care is continued into the puerperium (Sliwa, 2018; Zeeman, 2006). Postpartum hemorrhage, anemia, infection, and thromboembolism are much more serious complications with heart disease. Indeed, these factors often act in concert to precipitate postpartum heart failure. In addition, sepsis and severe preeclampsia cause or worsen pulmonary edema because of endothelial activation and capillary-alveolar leakage. For example, women with pregnancy-associated hypertensive diseases have a greater risk for readmission for heart failure within 90 days of delivery (Nizamuddin, 2019).

For puerperal tubal sterilization after vaginal delivery, the procedure can be delayed up to several days to ensure that the mother has normalized hemodynamically and that she is afebrile, not anemic, and ambulatory. For those desiring future fertility, contraception is crucial (Abarbanell, 2019; Sobhani, 2019). Detailed contraceptive advice is available in the *U.S. Medical Eligibility Criteria for Contraceptive Use* guidelines (Curtis, 2016). These are discussed in Chapter 38 (p. 664).

HEART FAILURE

Primary structural or functional cardiac disorders can lead to this clinical syndrome caused by impaired ventricular function. Mitral stenosis, pulmonary hypertension, and peripartum cardiomyopathy are some examples. Chronic pressure overload leads to ventricular dilation and impaired function over time. Associated perinatal mortality rates are high (Bright, 2021).

Diagnosis

Heart failure is best thought of as chronic underlying ventricular myopathy with episodic worsening causing clinical symptoms (Packer, 2019). Thus, failure can have a gradual onset or may present as acute "flash" pulmonary edema. In pregnant women, onset is most likely at the end of the second or beginning of the third trimester and peripartum (Ruys, 2014). Of symptoms, dyspnea is universal and others are orthopnea, palpitations, substernal chest pain, nocturnal cough, and a sudden decline in the ability to complete usual duties. Clinical findings include persistent basilar rales, hemoptysis, progressive edema, tachypnea, and tachycardia. According to Malhamé and associates (2019), serum levels of brain natriuretic peptide (BNP) are variably elevated (Appendix, p. 1231). Cardiomegaly and pulmonary edema are hallmark radiographic findings. Acutely, there is usually systolic failure. Echocardiography may show an ejection fraction <0.45 or a fractional shortening <30 percent, or both, and an end-diastolic dimension >2.7 cm/m^2 (Hibbard, 1999).

Coincidental diastolic failure also may be found, depending on the underlying cause (Redfield, 2016). Last, the cause of ventricular dysfunction—such as valvular abnormalities or concentric hypertrophy—may become apparent.

Management

Pulmonary edema from heart failure usually responds promptly with diuretic administration to reduce preload. Recall that furosemide (Lasix) is a potent venodilator in addition to its diuretic action. Hypertension is common in pregnancy, and afterload reduction is accomplished with hydralazine, nifedipine, or another vasodilator. Angiotensin-converting enzyme inhibitors are withheld until after delivery because of marked fetal effects (Chap. 8, p. 150). β-blocking agents lower mortality rates in the setting of heart failure, and carvedilol (Coreg) is commonly used in pregnancy. Last, digoxin provides inotropic support and is associated with decreased hospitalizations. With chronic heart failure, the incidence of associated thromboembolism is high, and therefore prophylactic heparin is often recommended.

Left ventricular assist devices are now employed more frequently for acute and chronic heart failure treatment. A few reports describe their use during pregnancy (Hamdan, 2017; Makdisi, 2017). *Extracorporeal membrane oxygenation (ECMO)* was reported to be lifesaving in a woman with fulminating peripartum cardiomyopathy, and it may be used in women with pulmonary hypertension (Meng, 2017; Pacheco, 2018).

SURGICALLY CORRECTED HEART DISEASE

Most clinically significant congenital heart lesions are repaired during childhood. Those frequently not diagnosed until adulthood include atrial septal defects, pulmonic stenosis, bicuspid aortic valve, and aortic coarctation (Brickner, 2014). In some cases, the defect is mild and does not require repair. In others, a significant anomaly is amenable to corrective surgery, performed ideally before pregnancy. Rarely, surgical corrections are necessary during pregnancy.

Valve Replacement Before Pregnancy

Numerous reports describe subsequent pregnancy outcomes in women who have a prosthetic mitral or aortic valve placed before pregnancy. From one review, the overall estimated maternal mortality rate was 1.2 percent (Lawley, 2015). Using the Registry of Pregnancy and Cardiac Disease, the maternal mortality rate was 1.4 percent in women with a mechanical heart valve and 1.5 percent in women with a tissue heart valve (van Hagen, 2015). Compared with the general maternal mortality rate measured per 100,000 births, this risk is more than 50-fold higher (Chap. 1, p. 4).

The type of valve, either mechanical or bioprosthetic, is paramount. From the just-described cohort, mechanical heart valve thrombosis complicated 4.7 percent. Only 58 percent of women with a mechanical heart valve had a pregnancy free of serious adverse events compared with 79 percent of patients with a tissue heart valve (Table 52-5) (van Hagen, 2015). A study of 417 women showed that pregnancy loss occurred in 61 and 15 percent with mechanical and bioprosthetic valves, respectively (Batra, 2018). Anticoagulation is a requisite with mechanical valves because of thrombosis risks, and its complications are described in the next section. Thus, pregnancy is undertaken only after serious consideration for women with a mechanical valve.

TABLE 52-5. Selected Outcomes in Pregnancies Complicated by Heart-Valve Replacement

Outcome	Mechanical Valve (n = 212)	Tissue Valve (n = 134)
Maternal mortality	3 (1.4)	2 (1.5)
Heart failure	162 (7.5)	1 (8.2)
Thrombotic complication	13 (6.1)	1 (0.7)
Hemorrhagic complication	49 (23)	7 (5.1)
Pregnancy loss <24 weeks	33 (15.6)	2 (1.5)
Stillbirth	6 (2.8)	0 (0)
Preterm birth <37 weeks	29 (18)	24 (19)

Data presented as n (%).

Bouhout and associates (2014) reported the outcomes of 27 pregnancies in 14 women who underwent an *aortic valve* replacement prior to pregnancy. Seven of the 27 pregnancies occurred in five women with a mechanical valve. Complications in this group included two embolic myocardial infarctions and one each of miscarriage, postpartum hemorrhage, placental abruption, and preterm birth. In the bioprosthetic group, there were nine miscarriages.

Adverse maternal and fetal outcomes plague also women with a *mechanical mitral valve*. In one report of 28 pregnancies, Vause and colleagues (2017) described severe maternal morbidity and mortality in 57 percent. A review of pregnancy outcomes in 800 women reported similar results (Steinberg, 2017).

Porcine tissue mitral valves are safer during pregnancy, primarily because thrombosis is rare, and anticoagulation is not required (see Table 52-5). However, valvular dysfunction with cardiac deterioration poses a serious risk. Another drawback is that bioprostheses are less durable than mechanical ones, and valve replacement longevity averages 10 to 15 years. Batra and coworkers (2018) concluded that pregnancy accelerated the risk for subsequent replacement.

Anticoagulation

This is critical for women with mechanical valves. Unfortunately, warfarin is the most effective anticoagulant for preventing maternal thromboembolism but causes harmful fetal effects. As seen in Table 52-6, anticoagulation with heparin is less hazardous for the fetus, however, the risk of maternal thromboembolic complications is increased (Steinberg, 2017). As a compromise, some use heparin in early pregnancy, and then transition to warfarin in the second trimester.

Warfarin is teratogenic and causes miscarriages, stillbirths, and fetal malformations (Chap. 8, p. 156). In one study of

TABLE 52-6. Maternal and Fetal Composite Outcomes in 800 Women with a Mechanical Heart Value Receiving Anticoagulation

Treatment	Composite Adverse Outcome (%)	
	Maternal[a]	Fetal[b]
VKA	5	39
LMWH	16	14
LMWH[c] followed by VKA	16	16
UFH[c] followed by VKA	16	34

[a]Maternal death, valve failure, thromboembolism.
[b]Miscarriage, fetal death, congenital malformation.
[c]During first trimester.
LMWH = low-molecular-weight heparin; UFH = unfractionated heparin; vitamin K antagonist.

71 women given warfarin throughout pregnancy, the rates of miscarriage were 32 percent; stillbirth, 7 percent; and embryopathy, 6 percent (Cotrufo, 2002). The risk was highest when the mean daily dose of warfarin exceeded 5 mg. Similarly, the American College of Cardiology and the American Heart Association estimate that the risk of embryopathy is dose dependent, and the risk is <3 percent if the warfarin dose is ≤5 mg/d (Nishimura, 2014). Women treated with <5 mg/d of warfarin had fetal risks similar to the low-molecular-weight heparin (LMWH) regimen (Steinberg, 2017). If the dosage is >5 mg/d, the risk of embryopathy exceeds 8 percent.

Anticoagulation for mechanical valves using *low-dose* unfractionated heparin (UFH) is definitely inadequate and carries a high associated maternal mortality rate (Chan, 2000; Iturbe-Alessio, 1986). Even *full* anticoagulation with either UFH or one of the LMWHs is associated with valvular thrombosis (Leyh, 2002, 2003; Rowan, 2001). However, compliance with dosing and therapeutic monitoring may have contributed (McLintock, 2014). Therefore, if full anticoagulation with dose-adjusted UFH or LMWH is used, meticulous monitoring is recommended. The activated partial thromboplastin time (aPTT) should be at least 2 times control or anti-Xa levels should be 0.8 to 1.2 U/mL at 4 to 6 hours postdose (Nishimura, 2014).

Recommendations for Anticoagulation

Several different treatment options exist, although all are principally based on consensus opinion, and none is completely ideal. Warfarin and LMWH are associated with fewer valve thromboses and therefore favored over subcutaneous UFH (D'Souza, 2017). In addition, therapeutic subcutaneous UFH dosing is difficult to achieve due to lower peak plasma concentrations in pregnant women, especially with advancing gestation (Barbour, 1995; Brancazio, 1995). One guideline from the American College of Cardiology and the American Heart Association offers different treatment options based on trimester and baseline warfarin dose (Nishimura, 2014). Figure 52-3 displays a treatment algorithm based on these guidelines. All recommendations also include aspirin 75 to 100 mg orally daily.

Vaginal or cesarean delivery is ideally scheduled to allow controlled discontinuation of anticoagulation and partial reversal of its effects. This also permits administration of regional anesthesia, which requires a degree of coagulation to avoid epidural hematoma formation (Chap. 25, p. 478). If delivery intervenes while the anticoagulant is still effective, and extensive bleeding is encountered, protamine sulfate is given intravenously to reverse heparin effects. Patients should be counseled that in these situations regional anesthesia may not safely be possible.

Following vaginal delivery, anticoagulant therapy with warfarin or heparin may be restarted 6 hours later, usually with no problems. Following cesarean delivery, full anticoagulation is withheld, but the optimal duration is unclear. The American College of Obstetricians and Gynecologists (2018a) recommends resuming UFH or LMWH 6 to 12 hours after cesarean delivery. At Parkland Hospital, however, we wait at least 24 hours following a major surgical procedure given inherent bleeding risks. Following first-trimester dilation and curettage heparin is begun immediately.

Warfarin, LMWH, and UFH are compatible with breastfeeding. They do not accumulate in breast milk and thus do not induce anticoagulant effects in the newborn (Briggs, 2022).

Cardiac Surgery During Pregnancy

Although usually postponed until after delivery, valve replacement or other cardiac surgery during pregnancy may be lifesaving. Several reviews confirm that such surgery is associated with major maternal and fetal morbidity (Liu, 2021). Elassy and associates (2014) described 23 women who underwent urgent open cardiac surgery for severe valve malfunction. Two women and 10 fetuses—all at a gestational age below 28 weeks—died before hospital discharge. Only six fetuses were delivered at term. In a review of 154 women undergoing bypass surgery during pregnancy, the maternal mortality rate was 11 percent, and the fetal loss rate was 33 percent (Jha, 2018). To optimize outcomes, Chandrasekhar and coworkers (2009) recommend that surgery be elective when possible, pump flow rate should remain >2.5 L/min/m^2, perfusion pressure should exceed 70 mm Hg, and hematocrit should be kept >28 percent.

Pregnancy after Heart Transplantation

Many successful pregnancies have followed cardiac transplantation (D'Souza, 2018; Macera, 2018). Current recommendations from the International Society of Heart and Lung Transplantation do not discourage pregnancy in stable heart transplant recipients who are more than 1 year posttransplant (Costanzo, 2010). Obviously, a highly specialized level of care and multidisciplinary team is necessary.

The transplanted heart appears to respond normally to pregnancy-induced alterations (Cowan, 2012). Despite this, complications are common during pregnancy. Of 103 pregnancies in 57 heart recipients from the National Transplantation Pregnancy Registry, almost half developed hypertension, and 11 percent suffered at least one rejection episode during pregnancy (Coscia, 2010). They were usually delivered by cesarean at a mean of 37 weeks' gestation. Life expectancy following heart transplantation is known to be limited. At follow-up,

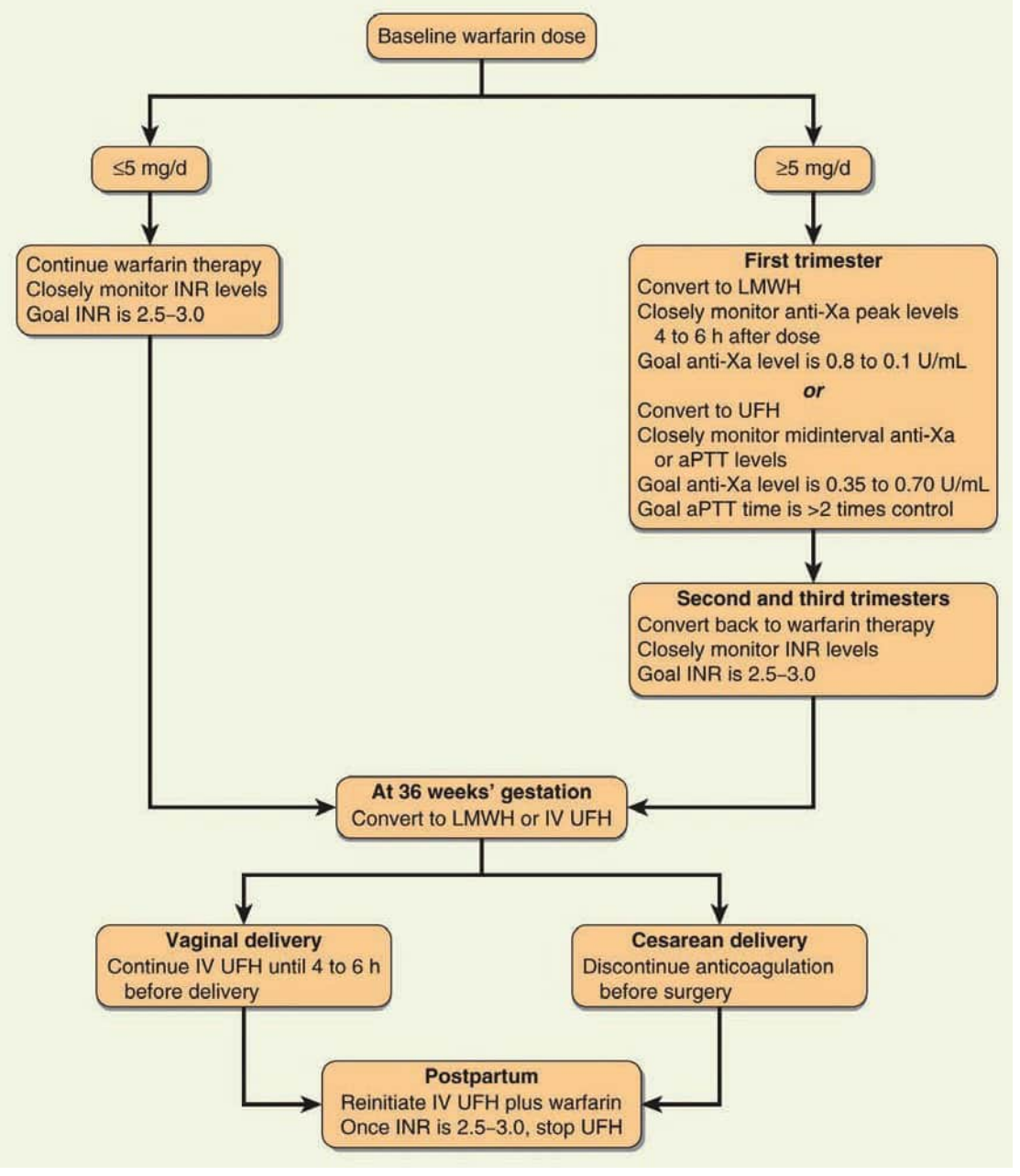

FIGURE 52-3 Algorithm for anticoagulation in gravidas with a mechanical heart valve. INR = international normalized ratio; IV = intravenous; LMWH = low-molecular-weight heparin; aPTT = activated partial thromboplastin time; UFH = unfractionated heparin. (From Elkayam, 2020; Nishimura, 2014; Roeder, 2011.)

at least 16 women had died more than 2 years postpartum. In another small study, pregnancy itself did not worsen long-term survival rates (Dagher, 2018).

VALVULAR HEART DISEASE

Rheumatic fever is uncommon in the United States because of less crowded living conditions, penicillin availability, and evolution of nonrheumatogenic streptococcal strains. Still, it remains the chief cause of serious mitral valvular disease in women of childbearing age in the nonindustrialized world (Liaw, 2021; van Hagen, 2018).

Mitral Stenosis

Rheumatic endocarditis causes most mitral stenosis lesions. The normal mitral valve surface area is 4.0 cm^2, and when stenosis narrows this to <2.5 cm^2, symptoms usually develop. The contracted valve impedes blood flow from the left atrium to the ventricle.

With more severe stenosis, the left atrium dilates, left atrial pressure is chronically elevated, and significant pulmonary hypertension develops (Table 52-7) (Galiè, 2016). These women have a relatively fixed cardiac output, and thus the increased preload of normal pregnancy and other factors that raise cardiac output may cause ventricular failure and

TABLE 52-7. Major Cardiac Valve Disorders

Type	Cause	Pathophysiology	Pregnancy
Mitral stenosis	Rheumatic valvulitis	LA dilation and passive pulmonary hypertension Atrial fibrillation	Heart failure from fluid overload, tachycardia
Mitral insufficiency	Rheumatic valvulitis Mitral valve prolapse LV dilation	LV dilation and eccentric hypertrophy	Ventricular function improves with afterload decrease
Aortic stenosis	Congenital bicuspid valve	LV concentric hypertrophy, decreased cardiac output	Moderate stenosis is tolerated; severe is life-threatening with decreased preload, e.g., obstetrical hemorrhage or regional analgesia
Aortic insufficiency	Rheumatic valvulitis Connective tissue disease Congenital	LV hypertrophy and dilation	Ventricular function improves with afterload decrease
Pulmonary stenosis	Rheumatic valvulitis Congenital	Severe stenosis associated with RA and RV enlargement	Mild stenosis usually well tolerated; severe stenosis associated with right heart failure and atrial arrhythmias

LA = left atrium; LV = left ventricle; RA = right atrium; RV = right ventricle.

pulmonary edema. Cardiac failure develops for the first time during pregnancy in one fourth of women with mitral stenosis (Caulin-Glaser, 1999). The resulting pulmonary venous hypertension and pulmonary edema create symptoms of dyspnea, fatigue, palpitations, cough, and hemoptysis. The classic murmur may not be heard in some women, and this clinical picture at term may be confused with idiopathic peripartum cardiomyopathy (Cunningham, 1986, 2019).

Also with significant stenosis, tachycardia shortens ventricular diastolic filling time and elevates the mitral gradient. This too may lead to pulmonary edema, and therefore, sinus tachycardia is often treated prophylactically with β-blocking agents. Atrial tachyarrhythmias, including fibrillation, are common in mitral stenosis and are treated aggressively. Atrial fibrillation predisposes to mural thrombus formation and cerebrovascular embolization that can cause stroke (Chap. 63, p. 1132). Atrial thrombosis can also develop despite a sinus rhythm (Hameed, 2005).

Pregnancy Outcomes

In general, complications are directly associated with the degree of valvular stenosis. Women with a mitral-valve area <2 cm^2 are at greatest risk (Siu, 2001b). In one study of 273 gravidas with mitral stenosis, 43 percent developed heart failure, and almost a fourth of these women required admission (van Hagen, 2018). For women with severe stenosis, half developed heart failure, and one woman died. Fetal-growth restriction was more common in women with a mitral valve area <1.0 cm^2.

Prognosis also is related to maternal functional capacity. Among 486 pregnancies complicated by rheumatic heart disease—predominantly mitral stenosis—8 of 10 maternal deaths were in women in NYHA classes III or IV (Sawhney, 2003).

Management

Limited physical activity is generally recommended in women with mitral stenosis. If symptoms of pulmonary congestion develop, activity is further reduced, dietary sodium is restricted, and diuretics are given. Also, β-blocker drug therapy slows the ventricular response to activity. If new-onset atrial fibrillation develops, intravenous verapamil, 5 to 10 mg, is given, or electrocardioversion is performed. For chronic fibrillation, digoxin, a β-blocker, or a calcium-channel blocker can slow ventricular response. Therapeutic anticoagulation is indicated with persistent fibrillation, left atrial thrombus, and/or a history of embolism (Nanna, 2014).

Surgical intervention is considered for women with symptomatic severe mitral stenosis. Other candidates are those with mitral-valve area 1.5 to 2.0 cm^2 complicated by recurrent systemic embolization or severe pulmonary hypertension. Balloon valvuloplasty is preferred if the valve is pliable (Bui, 2014). In one review of 71 pregnant women with severe mitral stenosis and heart failure who underwent percutaneous valvuloplasty, 98 percent were either NYHA class I or II by the time of delivery (Esteves, 2006). At a mean of 44 months, the total event-free maternal survival rate was 54 percent. However, eight women required another surgical intervention. All of the 66 newborns who were delivered at term had normal growth and development.

Labor and delivery are particularly stressful for women with symptomatic mitral stenosis. Pain, exertion, and anxiety cause tachycardia with possible rate-related heart failure. Epidural analgesia for labor is ideal. Fluid overload should be avoided, and these women are best managed on the "dry" side. As shown in Figure 52-4 uterine contractions raise cardiac output by increasing circulating blood volume. Abrupt expansion in preload may elevate pulmonary capillary wedge pressure and cause pulmonary edema. Wedge pressures rise immediately postpartum. One hypothesis for this suggests that the loss of the low-resistance placental circulation couples with venous "autotransfusion" from a now-empty, contracted uterus and from the lower extremities and pelvis (Clark, 1985). Thus, pulmonary edema may manifest immediately postpartum.

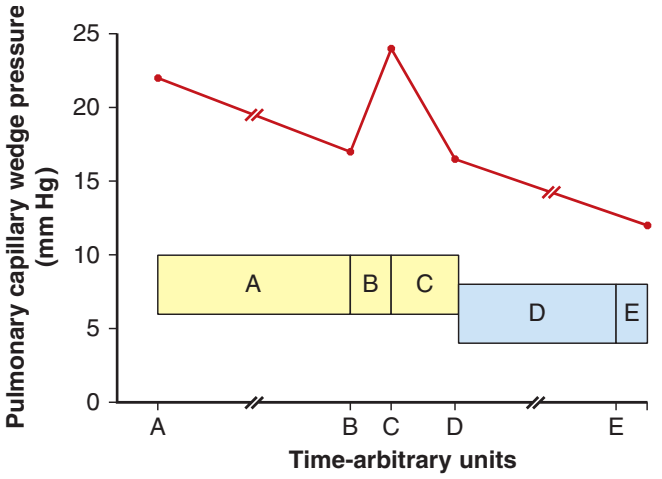

FIGURE 52-4 Mean pulmonary capillary wedge pressure measurements (*red graph line*) in eight women with mitral valve stenosis. Shaded yellow and blue boxes are mean (± 1 SD) pressures in nonlaboring normal women at term. **A.** First-stage labor. **B.** Second-stage labor 15 to 30 minutes before delivery. **C.** Postpartum 5 to 15 minutes. **D.** Postpartum 4 to 6 hours. **E.** Postpartum 18 to 24 hours. (Data from Clark, 1985, 1989.)

Most prefer vaginal delivery in women with mitral stenosis. Elective induction is reasonable so that labor and delivery are attended by a scheduled, experienced team. With severe stenosis and chronic heart failure, insertion of a pulmonary artery catheter may help guide management.

■ Mitral Insufficiency

A trivial degree of mitral insufficiency is found in most normal patients. But if mitral valve leaflets align improperly during systole, abnormal degrees of mitral regurgitation can develop. This is eventually followed by left ventricular dilation and eccentric hypertrophy (see Table 52-7). *Acute mitral insufficiency* is caused by chordae tendineae rupture, papillary muscle infarction, or leaflet perforation from infective endocarditis. *Chronic mitral regurgitation*, in contrast, may derive from rheumatic fever, connective tissue diseases, mitral valve prolapse, or left ventricular dilation of any etiology—for example, dilated cardiomyopathy. Less common causes include a calcified mitral annulus, possibly some appetite suppressants, and in older women, ischemic heart disease. Mitral valve vegetations—*Libman-Sacks endocarditis*—are relatively common in women with antiphospholipid antibodies (Shroff, 2012). These sometimes coexist with systemic lupus erythematosus (Chap. 62, p. 1114).

In nonpregnant patients, symptoms from mitral valve insufficiency are rare, and valve replacement is seldom indicated unless infective endocarditis develops. During pregnancy, mitral regurgitation is similarly well tolerated, probably because the lowered systemic vascular resistance yields less regurgitation. In the report by van Hagen and associates (2018), of 117 women with moderate or severe regurgitation, 23 percent developed heart failure during pregnancy. Occasionally tachyarrhythmias or severely depressed systolic function require treatment.

■ Mitral Valve Prolapse

This diagnosis implies the presence of a pathological connective tissue disorder—often termed *myxomatous degeneration*—which may involve the valve leaflets, the annulus, or the chordae tendineae. Mitral insufficiency may develop. Most women with mitral valve prolapse are asymptomatic and are diagnosed during routine examination or echocardiography. The few women with symptoms have anxiety, palpitations, atypical chest pain, dyspnea with exertion, and syncope (Guy, 2012).

Pregnant women with mitral valve prolapse rarely have cardiac complications. Hypervolemia may even improve alignment of the mitral valve, and women without pathological myxomatous degeneration generally have excellent pregnancy outcomes (Leśniak-Sobelga, 2004). For women who are symptomatic, β-blocking drugs diminish sympathetic tone, relieve chest pain and palpitations, and reduce the risk of life-threatening arrhythmias.

■ Aortic Stenosis

Since the decline in incidence of rheumatic disease, congenital bicuspid valve is now the most frequent cause of aortic stenosis in young women in the United States (Carabello, 2017). A normal aortic valve has an area of 3 to 4 cm^2, with a pressure gradient <5 mm Hg. If the valve area is <1 cm^2, flow is severely obstructed, and progressive pressure overload on the left ventricle develops. Concentric left ventricular hypertrophy follows, and if it is severe, end-diastolic pressures become elevated, ejection fraction decreases, and cardiac output is reduced (see Table 52-7). Severity is estimated by peak velocity of flow across the aortic valve. Mild stenosis has a peak velocity of 2–2.9 m/s, moderate 3-3.9 m/s, and severe ≥4 m/s. Corresponding mean pressure gradients are <20, 20–39, and ≥40 mm Hg, respectively (Carabello, 2017). Characteristic manifestations develop late and include chest pain, syncope, heart failure, and sudden death from arrhythmias. In asymptomatic patients, the mortality rate is 1 percent per year, but with symptoms it increases to 25 percent per year. Thus, valve replacement is indicated for symptomatic patients.

Pregnancy

In one single-center study, aortic stenosis accounted for 15 percent of cases of congenital heart disease in 178 pregnant women (Kim, 2019). That said, clinically significant aortic stenosis is infrequent during pregnancy. Mild to moderate degrees of stenosis are well tolerated. Severe disease is life-threatening and carries a 6-percent mortality risk (Lin, 2017). The principal underlying hemodynamic problem is the fixed cardiac output associated with severe stenosis. During pregnancy, several common events acutely lower preload further and thus aggravate the fixed cardiac output. These include vena caval occlusion from the gravid uterus, regional analgesia, sepsis, and hemorrhage. From the earlier-cited Canadian study, complication rates were higher if the aortic valve area measured <1.5 cm^2 (Siu, 2001b).

Management

For asymptomatic women with aortic stenosis, no treatment except close observation is required. Management of a symptomatic

woman is undertaken in conjunction with a cardiologist and includes strict limitation of activity and cautious use of diuretics. If symptoms persist, surgical intervention or preterm delivery may be considered. Catheter-based valvuloplasty is associated with risks to both the mother and fetus and shows poor long-term efficacy (Pessel, 2014). Namely, the aortic valve can again narrow or new aortic regurgitation may develop. The alternative surgical approach—valve replacement—is associated with significant risk of fetal demise due to the hypotension associated with cardiac bypass. Transcatheter aortic valve replacement (TAVR) has been performed in low-risk nonpregnant women, but there is little experience with this procedure during pregnancy (Hodson, 2016; Mack, 2019). Accordingly, the American College of Cardiology, the American Heart Association, and the European Society of Cardiology recommend delaying conception until after surgical correction for severe aortic stenosis (Nishimura, 2014; Regitz-Zagrosek, 2018). For those with uncorrected severe symptomatic aortic stenosis, cesarean delivery is preferred. For asymptomatic women with severe stenosis, care is individualized. In nonsevere stenosis, vaginal delivery is preferred (Regitz-Zagrosek, 2018).

For women with critical aortic stenosis, intensive monitoring during labor is essential. Pulmonary artery catheterization may be helpful because of the narrow margin separating fluid overload from hypovolemia. Women with aortic stenosis are dependent on adequate end-diastolic ventricular filling pressures to maintain cardiac output and systemic perfusion. Abrupt drops in end-diastolic volume may result in hypotension, syncope, myocardial infarction, and sudden death. Thus, avoiding diminished ventricular preload and maintaining cardiac output are key. During labor and delivery, affected women are best managed on the "wet" side. This provides a margin of safety in intravascular volume in anticipation of possible hemorrhage. In women with a competent mitral valve, pulmonary edema is rare.

During labor, narcotic or low-dose, slow-infusion epidural analgesia seems ideal and avoids potentially hazardous hypotension. Easterling and coworkers (1988) studied the effects of epidural analgesia in five women with severe stenosis and demonstrated immediate and profound effects from decreased filling pressures. Xia and colleagues (2006) emphasize slow administration of dilute local anesthetic agents into the epidural space. In hemodynamically stable women, forceps or vacuum delivery is used only for standard obstetrical indications. In those experiencing dizziness, shortness of breath, or tachycardia with pushing, an operative vaginal delivery is preferred.

Aortic Insufficiency

Aortic valve regurgitation or insufficiency allows diastolic flow of blood from the aorta back into the left ventricle. Frequent causes of insufficiency are rheumatic fever, connective tissue abnormalities, and congenital lesions (Carabello, 2017). With Marfan syndrome, the aortic root may dilate and create regurgitation (p. 936). Acute insufficiency may also develop with bacterial endocarditis or aortic dissection. Last, aortic and mitral valve insufficiency have both been linked to the appetite suppressants fenfluramine and dexfenfluramine and to the ergot-derived dopamine agonists cabergoline and pergolide (Schade, 2007; Zanettini, 2007). With chronic insufficiency, left ventricular hypertrophy and dilation develop. Slow-onset fatigue, dyspnea, and pulmonary edema follows ventricular dilation with subsequent rapid deterioration (see Table 52-7).

Aortic insufficiency is generally well tolerated during pregnancy. Like mitral valve insufficiency, reduced vascular resistance is thought to improve hemodynamic function. If symptoms of heart failure develop, diuretics are given, and bed rest is encouraged.

Pulmonic Stenosis

This lesion is usually congenital and may be associated with Fallot tetralogy or Noonan syndrome (Chikwe, 2017). The greater hemodynamic burden of pregnancy can precipitate right-sided heart failure or atrial arrhythmias in women with severe stenosis. Surgical correction ideally is done before pregnancy, but if symptoms progress, a balloon valvuloplasty may be necessary antepartum (Galal, 2015; Siu, 2001a).

In studying pregnancy outcomes, Drenthen and associates (2006) found infrequent cardiac complications in 81 pregnancies in 51 Dutch women with pulmonic stenosis. The NYHA classification worsened in two women, and nine experienced palpitations or arrhythmias. No changes in pulmonary valvular function or other adverse cardiac events were reported. However, noncardiac complication rates were significant—17 percent had preterm delivery, 15 percent had hypertension, and 4 percent developed thromboembolism.

CONGENITAL HEART DISEASE

The incidence of congenital heart disease in the United States approximates 1.9 percent of live births, and half of these are moderate to severe forms (Lin, 2017). With modern surgeries, approximately 90 percent of those born with congenital heart disease survive to childbearing age, and it is now the most common type of heart disease encountered during pregnancy (Hopkins, 2018). Specifically, analysis from the United States Nationwide Inpatient Sample database showed a linear rise in the prevalence of congenital heart disease between 2000 and 2010—from 6.4 to 9.0 per 10,000 women admitted for delivery (Thompson, 2015).

The odds of obstetrical and perinatal complications are increased two- to threefold in women with congenital heart disease compared with unaffected women (Ramage, 2019). Also, the maternal mortality rate was higher for women with congenital heart disease at 178 per 100,000 deliveries compared with 7 per 100,000 deliveries in unaffected gravidas (Thompson, 2015).

Atrial Septal Defects

A patent foramen ovale (PFO) is a persisting incompetence of the fossa ovale, and this flap has the potential to open under increased hydrostatic pressure. Of all adults, approximately one fourth have this defect (Silvestry, 2015). The small risk of PFO-related stroke, discussed subsequently, is likely higher in

pregnant than in nonpregnant women and mainly attributed to normal pregnancy hypercoagulability (Chen, 2016). Preventive PFO repair is not recommended (Kernan, 2014).

An atrial septal defect (ASD) is a true hole in the septum. The secundum-type defect accounts for 70 percent, and associated mitral valve myxomatous abnormalities with prolapse are common. Most ASDs are typically asymptomatic until the third or fourth decade of life (Lin, 2017). If an ASD is discovered in adulthood, most recommend repair.

Pregnancy with an unrepaired ASD is well tolerated unless pulmonary hypertension has developed, but this is uncommon (Bredy, 2018). Medical treatment during pregnancy is indicated for congestive heart failure or an arrhythmia. The risk of endocarditis with an ASD is negligible.

With the potential to shunt blood from right to left, a *paradoxical embolism* is possible. A venous thrombus enters the systemic arterial circulation through the ASD, causing an embolic stroke (Bredy, 2018). For this reason, filters should be placed on intravenous access sites. In a gravida with an ASD but without current venous thromboembolism (VTE), the decision to add anticoagulant prophylaxis to counter this potential embolism risk is problematic. However, for a pregnant woman with an ASD who is immobile or has another risk factor for thromboembolism, compression stockings and prophylactic heparin are reasonable.

Ventricular Septal Defects

These lesions close spontaneously during childhood in 90 percent of cases. Of the four main ventricular septal defect (VSD) types, most defects are paramembranous. This location is well below the outlet valves yet above the ventricular musculature. The degree of associated left-to-right shunt and physiological derangements are related to lesion size. In general, if the defect measures <1.25 cm^2, pulmonary hypertension and heart failure do not develop. If the effective defect size exceeds that of the aortic valve orifice, symptoms rapidly develop. For these reasons, most children undergo surgical repair before pulmonary hypertension develops. Adults with unrepaired large defects develop left ventricular failure and pulmonary hypertension and have a high incidence of bacterial endocarditis (Brickner, 2014).

Pregnancy is well tolerated with small- to moderate-sized VSD shunts. However, if pulmonary arterial pressures reach systemic levels, flow is reversed or bidirectional—*Eisenmenger syndrome* (p. 929). If this cyanotic condition develops, the maternal and fetal mortality rates are significantly higher, and thus pregnancy is generally not advisable (Lin, 2017). Bacterial endocarditis is more common with unrepaired defects, and antimicrobial prophylaxis is often required (p. 934). As shown in Table 52-4, 16 percent of offspring born to these women also have a VSD.

Atrioventricular Septal Defects

An atrioventricular (AV) septal defect is characterized by a common, ovoid AV junction. These account for approximately 3 percent of all congenital cardiac malformations and are distinct from isolated ASDs or VSDs. This defect is associated with aneuploidy, Eisenmenger syndrome, and other malformations (Foeller, 2018). Compared with simple septal defects, complications are more frequent during pregnancy. In a review of 48 pregnancies in 29 affected women, complications included persistent deterioration of NYHA class in 23 percent, significant arrhythmias in 19 percent, and heart failure in 2 percent (Drenthen, 2005). Congenital heart disease was identified in 15 percent of the offspring.

Persistent (Patent) Ductus Arteriosus

The ductus connects the proximal left pulmonary artery to the descending aorta just distal to the left subclavian artery. Functional closure of the ductus from vasoconstriction occurs shortly after term birth. The physiological consequences with its persistence are related to its size. Most significant lesions are repaired in childhood. However, in women with an unrepaired ductus, pulmonary hypertension, heart failure, or cyanosis will develop if systemic blood pressure falls and blood flow reverses from the pulmonary artery into the aorta (Foeller, 2018). A sudden blood pressure decline at delivery—such as with regional analgesia or hemorrhage—may lead to fatal collapse. Therefore, hypotension is avoided but treated vigorously if it develops. Prophylaxis for bacterial endocarditis is indicated at delivery for unrepaired defects (p. 934). As shown in Table 52-4, the incidence of inheritance approximates 4 percent.

Cyanotic Heart Disease

Cyanosis develops when congenital heart lesions produce right-to-left shunting of blood past the pulmonary capillary bed. The classic and most commonly encountered lesion in adults and during pregnancy is the *Fallot tetralogy* (Foeller, 2018). This is characterized by a large VSD, pulmonary stenosis, right ventricular hypertrophy, and an overriding aorta that receives blood from both the right and left ventricles. The magnitude of the shunt varies inversely with systemic vascular resistance. Hence, during pregnancy, when peripheral resistance decreases, shunt flow increases and cyanosis worsens.

Generally, women with cyanotic heart disease do poorly during pregnancy. Those with concomitant Eisenmenger syndrome are at greatest risk (p. 929). With uncorrected Fallot tetralogy, maternal mortality rates approach 10 percent. For fetal outcome, there is a relationship between chronic hypoxemia, polycythemia, and complications such as miscarriage and perinatal morbidity. When hypoxemia is intense enough to stimulate a rise in hemoglobin concentration >20 g/dL, pregnancy wastage is virtually 100 percent (Lin, 2017).

Although not all cyanotic lesions are repairable, with satisfactory surgical correction before pregnancy, maternal and fetal outcomes are much improved. In a review of 197 pregnancies in 99 women with surgically corrected Fallot tetralogy, pregnancy was usually well tolerated, and no mothers died (Cauldwell, 2017). Still, almost 9 percent of pregnancies were complicated by adverse cardiac events including new-onset or worsening arrhythmias and heart failure (Balci, 2011; Kamiya, 2012).

Some women with *Ebstein anomaly*, characterized by a malpositioned and malformed tricuspid valve, may reach

reproductive age. The right ventricle is small and the right atrium is severely dilated. Right-sided heart failure is common. These women are very preload dependent, and pregnancy-induced hypervolemia can worsen the tricuspid regurgitation (Kanoh, 2018). Arrhythmias also are common, especially Wolff-Parkinson-White syndrome (p. 936). Vaginal delivery seems preferable in most cases. In the absence of cyanosis, heart failure, or significant arrhythmias, affected women usually tolerate pregnancy well (Safi, 2016).

■ Pregnancy after Surgical Repair

Transposition of the Great Vessels

Pregnancy following *arterial switch operation* for transposition is associated with good outcomes. A major concern is fatal arrhythmias that usually are precipitated by exercise (Lin, 2017). Earlier studies cited a relatively high rate of heart failure and arrhythmias, but more recent studies have favorable pregnancy outcomes (Trigas, 2014). In one study of 20 pregnancies, there were three cases of heart failure (Horiuchi, 2019). Stoll and coworkers (2018) reported no adverse cardiac events in 25 pregnancies.

Of other defects, repaired *truncus arteriosus* and *double-outlet right ventricle* with subsequent successful, although eventful, pregnancies have been described (Drenthen, 2008; Hoendermis, 2008). Ironically, preconceptional counseling did little to dissuade these women from childbearing (Cauldwell, 2016).

Single Functional Ventricle

With *hypoplastic left heart syndrome*, most affected women are now expected to survive into adulthood (Davis, 2018). Frequently, these women become pregnant, and those who have undergone a *Fontan repair* carry a particularly higher risk for complications. In brief, this procedure involves diverting blood via a surgical anastomosis from the vena cava to the pulmonary artery without passing through the right ventricle. Blood flows passively to the pulmonary vasculature. Preload drives circulation in the Fontan circuit, and thus patients are sensitive to volume changes (Moroney, 2018).

From their review of 255 pregnancies in 133 women, Garcia-Ropero and colleagues (2018) reported 115 miscarriages (45 percent) and 19 elective terminations (7 percent). Cardiac complications included arrhythmias in 8 percent and heart failure in 4 percent of pregnancies. Among 133 live births, there were 68 preterm births (59 percent) and 7 perinatal deaths (6 percent). Postpartum venous thromboembolism also is common (Moroney, 2020).

Similar complications attend a maternal *systemic right ventricle*, that is, one in which the right ventricle rather than the left pumps blood to the systemic circulation (Khan, 2015).

■ Eisenmenger Syndrome

This describes secondary pulmonary hypertension that arises from any cardiac lesion. The most common underlying defects are ASD, VSD, and persistent ductus arteriosus (Fig. 52-5).

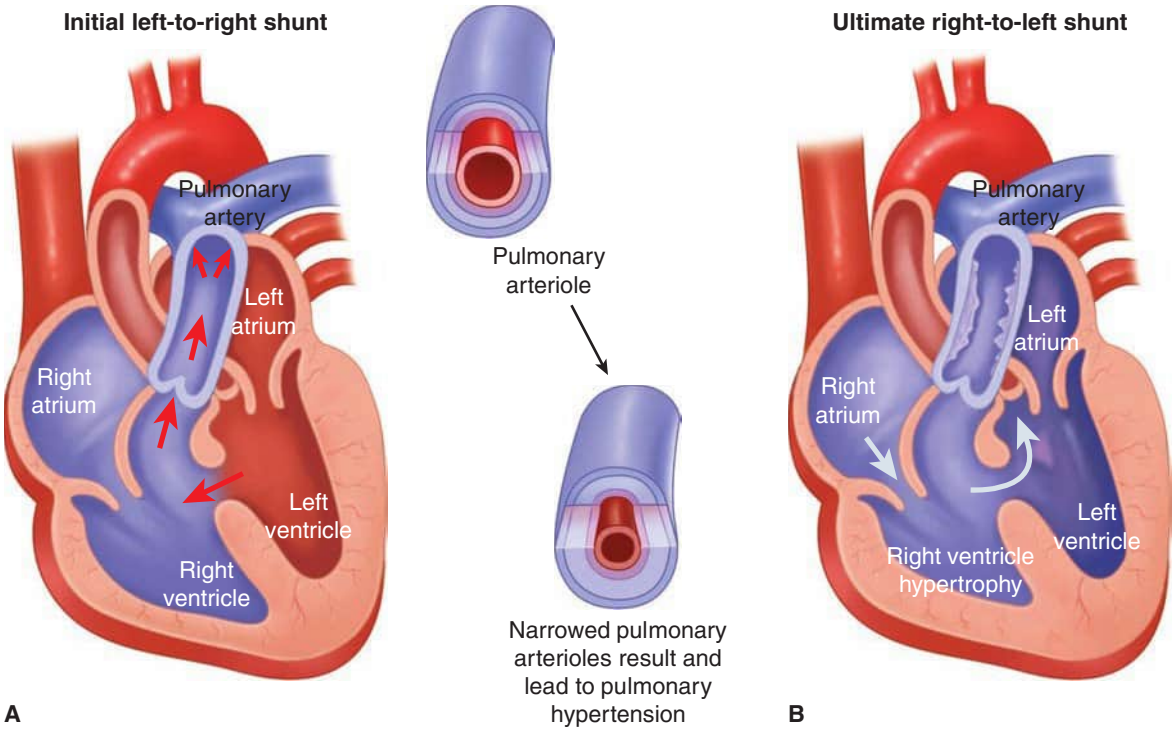

FIGURE 52-5 Eisenmenger syndrome due to a ventricular septal defect (VSD). **A.** Substantial left-to-right shunting through the VSD leads to morphological changes in the smaller pulmonary arteries and arterioles. Specifically, medial hypertrophy, intimal cellular proliferations, and fibrosis lead to narrowing or closure of the vessel lumen. These vascular changes create pulmonary hypertension and a resultant reversal of the intracardiac shunt **(B)**. With sustained pulmonary hypertension, extensive atherosclerosis and calcification often develop in the large pulmonary arteries. Although a VSD is shown here, Eisenmenger syndrome may also develop in association with a large atrial septal defect or persistent ductus arteriosus.

The syndrome develops when pulmonary vascular resistance exceeds systemic resistance and leads to concomitant right-to-left shunting. Patients are asymptomatic for years, but eventually pulmonary hypertension becomes severe enough to cause this shunting.

Pregnant women with Eisenmenger syndrome tolerate hypotension poorly, and death usually is caused by right ventricular failure with cardiogenic shock. In a review of 73 pregnancies, Weiss and associates (1998) cited a 36-percent maternal death rate. Three of 26 deaths were antepartum, and the remainder of women died intrapartum or within a month of delivery. In another study of 13 gravidas, one mother died 17 days after delivery, and there were five perinatal deaths (Wang, 2011). Last, in a series of 11 pregnancies in China, four mothers died (Duan, 2016). *Given such poor outcomes for both mother and fetus, Eisenmenger syndrome is considered to be an absolute contraindication to pregnancy* (American College of Obstetricians and Gynecologists, 2019; Foeller, 2018; Meng, 2017).

PULMONARY HYPERTENSION

Normal resting mean pulmonary artery pressure is 12 to 16 mm Hg. Most define *pulmonary hypertension* in nonpregnant individuals as a resting mean pulmonary pressure >25 mm Hg (Franco, 2019). Pulmonary vascular resistance in late normal pregnancy approximates 80 dyne/sec/cm^{-5}, which is 34-percent less than the nonpregnant value of 120 dyne/sec/cm^{-5} (Clark, 1989).

Physiologically, pregnancy is associated increased cardiac output, and in healthy gravidas, pulmonary vascular resistance decreases to help accommodate this (Clark, 1989). With pulmonary hypertension, the stiff pulmonary vasculature does not allow the normal fall in pulmonary vascular resistance. Thus, the normal increased cardiac output actually leads to further pulmonary artery pressure elevation and then eventually to right heart failure. With failure, the interventricular septum bulges leftward to impair left ventricular diastolic filling, which compromises cardiac output (Gei, 2014; Pieper, 2011).

The current clinical classification system, shown in Table 52-8, contains five groups of disorders that cause pulmonary hypertension (Galiè, 2016). Important prognostic and therapeutic distinctions separate group 1 pulmonary arterial hypertension and the other groups. Group 1, which is more common in nonpregnant women, indicates that a specific disease affects pulmonary arterioles. It includes idiopathic or primary pulmonary arterial hypertension as well as those cases secondary to a known cause such as connective tissue disease. For example, approximately a third of women with scleroderma and 10 percent with systemic lupus erythematosus have pulmonary arterial hypertension (Franco, 2019). Other causes in young women are human immunodeficiency virus (HIV) infection, sickle-cell disease, and thyrotoxicosis.

In pregnant women, group 2 disorders are the most common. These are secondary to pulmonary *venous* hypertension caused by left-sided atrial, ventricular, or valvular disorders. A typical example is mitral stenosis discussed earlier (p. 924). In contrast, groups 3 through 5 are seen infrequently in young otherwise healthy women.

Diagnosis and Prognosis

Symptoms may be vague, and dyspnea with exertion is the most frequent. With group 2 disorders, orthopnea and nocturnal dyspnea are also usually present. Angina and syncope occur when right ventricular output is fixed, and they suggest advanced disease. Chest radiography often shows enlarged pulmonary hilar arteries and attenuated peripheral markings. It may also disclose parenchymal causes of hypertension. Noninvasive echocardiography can provide an estimate of pulmonary artery pressures, although cardiac catheterization remains the standard for measurement. In studies of pregnant women who underwent both echocardiography and cardiac catheterization, pulmonary artery pressures were significantly overestimated by echocardiography in approximately a third of cases (Herrera, 2020; Wylie, 2007).

Regardless of the etiology, the final common pathway of pulmonary hypertension is right heart failure and death. The average survival length after diagnosis is <4 years (Krexi, 2015). That said, longevity depends on the severity and cause of pulmonary hypertension at discovery. As discussed later, some disorders respond to medical interventions, which may improve quality of life. Preconceptional and contraceptive counseling are imperative (American College of Obstetricians and Gynecologists, 2019).

Pregnancy

The maternal mortality rate is appreciable in affected women, and this is especially so with idiopathic pulmonary arterial hypertension (Martin, 2019). In the past, the ability to accurately identify causes and assess disease severity were often poor. Thus, although most severe cases of idiopathic pulmonary arterial hypertension had the worst prognosis, it was erroneously assumed that all types of pulmonary hypertension were equally dangerous. With widespread use of echocardiography, less-severe lesions with a better prognosis are now discernible. The maternal mortality rate for pulmonary hypertension has improved. In one study, it was 25 percent during the decade ending in 2007 compared with 38 percent for the decade ending in 1996 (Bédard, 2009). Importantly, almost 80 percent of the deaths were during the first month postpartum. Meng and associates (2017) reported mortality rates of 23 percent with group 1 and 5 percent with the other groups. Mortality risk correlates positively with advancing pulmonary hypertension severity, which is characterized by Eisenmenger syndrome, severe hypertension, and higher NYHA class (Keepanasseril, 2019; Sun, 2018). In an audit of 47 pregnancies in women with pulmonary hypertension at Parkland Hospital, the maternal mortality rate was 9 percent (Herrera, 2020). Of four deaths, three women had severe hypertension. A striking example of right ventricular hypertrophy in one of these women who died is shown in Figure 52-6.

Pregnancy is contraindicated with severe disease. This is especially true in women with pulmonary arterial changes, which develop in most group 1 cases. With milder disease from other causes—group 2 being the most common—the prognosis is better. With the more frequent use of echocardiography and pulmonary artery catheterization in young women with

TABLE 52-8. Comprehensive Clinical Classification of Pulmonary Hypertension of the European Society of Cardiology and the European Respiratory Society

1. Pulmonary arterial hypertension
- Idiopathic
- Heritable
- Drug and toxin induced
- Associated with connective tissue disease, HIV infections, portal hypertension, congenital heart diseases, schistosomiasis

1′ Pulmonary venoocclusive disease and/or pulmonary capillary hemangiomatosis
- Idiopathic
- Heritable
- Drugs, toxins and radiation induced
- Associated with connective tissue disease, HIV infection

1″ Persistent pulmonary hypertension of the newborn

2. Pulmonary hypertension due to left heart disease
- Left ventricular systolic dysfunction
- Left ventricular diastolic dysfunction
- Valvular disease
- Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies
- Congenital/acquired pulmonary vein stenosis

3. Pulmonary hypertension due to lung diseases and/or hypoxia
- Chronic obstructive pulmonary disease
- Interstitial lung disease
- Other pulmonary diseases with mixed restrictive and obstructive pattern
- Sleep-disoriented breathing
- Alveolar hypoventilation disorder
- Chronic exposure to high altitude
- Developmental lung diseases

4. Chronic thromboembolic pulmonary hypertension/other pulmonary artery obstructions
- Chronic thromboembolic pulmonary hypertension
- Other pulmonary artery obstructions, i.e., tumors, arteritis, pulmonary stenosis, parasites

5. Pulmonary hypertension with unclear and/or multifactorial mechanisms
- Hematological disorders: chronic hemolysis, myeloproliferative disorders, splenectomy
- Systemic disorders: sarcoidosis, pulmonary histiocytosis, neurofibromatosis
- Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
- Others: fibrosing mediastinitis, chronic renal failure

HIV = human immunodeficiency virus.
Adapted from Galiè, 2016.

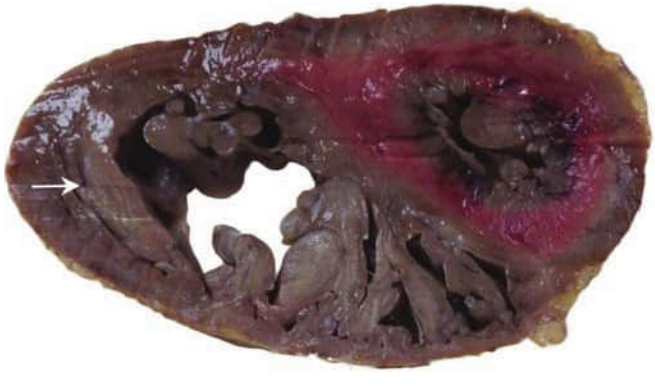

FIGURE 52-6 Cross-sectional display of right cardiac dysmorphology in a pregnant woman who died from undiagnosed primary pulmonary hypertension. There is prominent dilation of the right ventricle with right ventricular hypertrophy (*arrow*).

heart disease, we have identified women with mild to moderate pulmonary hypertension who tolerate pregnancy, labor, and delivery well (Herrera, 2020).

■ Management

Treatment of symptomatic pregnant women includes limiting activity and avoiding supine position later in gestation. Diuretics, supplemental oxygen, and pulmonary vasodilator drugs are standard therapy for symptoms. Some recommend anticoagulation. Several reports describe the successful use of intravenous pulmonary artery vasodilators (Foeller, 2018; Franco, 2019). Prostacyclin analogues that can be administered parenterally include epoprostenol (Flolan) and treprostinil (Remodulin), whereas iloprost (Ventavis) is inhaled. Each has been used in pregnancy. Inhaled nitric oxide is an option that has been

employed in cases of acute cardiopulmonary decompensation. As reviewed by Običan and Cleary (2014), phosphodiesterase-5 inhibitors, such as sildenafil (Viagra), cause vasodilation of both the pulmonary and systemic vascular beds and have an inotropic effect on the hypertrophic right ventricle. This also has been used to advantage during pregnancy (Meng, 2017). Bosentan—an endothelin-receptor antagonist, and riociguat—a soluble guanylate cyclase stimulator, are teratogenic in mice and contraindicated in pregnancy (Franco, 2019).

During labor and delivery, supplemental oxygen is given to maintain >90 percent saturation. These women are at greatest risk when venous return and right ventricular filling are diminished. To avoid hypotension, assiduous attention is given to epidural analgesia induction, fluid therapy, and blood loss prevention and treatment at delivery (Martin, 2019; Meng, 2017).

CARDIOMYOPATHIES

The American Heart Association defines these as a heterogeneous group of myocardial diseases associated with mechanical and/or electrical dysfunction (Narula, 2017). Affected women usually have inappropriate ventricular hypertrophy or dilation. Cardiomyopathies stem from varied causes, and the most frequent is genetic. Of the two major divisions, *primary cardiomyopathies* are solely or predominantly confined to the heart muscle. Examples are hypertrophic cardiomyopathy, dilated cardiomyopathies, and peripartum cardiomyopathy. *Secondary cardiomyopathies* result from generalized systemic disorders that produce pathological myocardial involvement. Diabetes, systemic lupus erythematosus, chronic hypertension, and thyroid disorders are representative conditions.

Hypertrophic Cardiomyopathy

This disorder affects approximately 1 in 500 adults (Herrey, 2014). Characterized by cardiac hypertrophy, myocyte disarray, and interstitial fibrosis, the condition in up to 60 percent of affected patients is caused by mutations in genes that encode cardiac sarcomere proteins. In such cases, inheritance is autosomal dominant, and genetic screening is complex (Cirino, 2019; Elliott, 2014). Other genetic and nongenetic etiologies underlie 5 to 10 percent of cases, and the cause is unknown in approximately 25 percent. The resulting myocardial muscle abnormality is typified by left ventricular myocardial hypertrophy with a pressure gradient against left ventricular outflow. Diagnosis is established by echocardiographic identification of a hypertrophied and nondilated left ventricle in the absence of other cardiovascular conditions.

Most affected women are asymptomatic, but dyspnea, anginal or atypical chest pain, syncope, and arrhythmias may develop. Complex arrhythmias may progress to sudden death, which is the most frequent cause of death. Asymptomatic patients with runs of ventricular tachycardia are especially prone to sudden death. Symptoms usually worsen with exercise.

Studies that include more than 700 pregnancies in 500 women indicate an overall relatively good prognosis (Schaufelberger, 2019). In a systematic review with 237 women with hypertrophic cardiomyopathy who had a combined 408 pregnancies, the maternal mortality rate was 0.5 percent (Schinkel, 2014). Worsening of symptoms or other complications developed in 29 percent, and 26 percent delivered preterm.

Management is similar to that for aortic stenosis (p. 926). Controlling heart rate and avoiding preload and afterload reduction are therapy basics. Strenuous exercise is prohibited during pregnancy. Abrupt positional changes are avoided to prevent reflex vasodilation and decreased preload. If symptoms develop, especially angina, β-adrenergic or calcium-channel blocking drugs are given. Drugs that evoke diuresis or reduce vascular resistance are generally not used because they decrease preload. But if these are necessary, women should be closely monitored. The delivery route is determined by obstetrical indications. Choice of anesthesia is controversial, and some consider general anesthesia the safest. Regional analgesia can be used with carefully titrated, adequate intravascular volume to maintain left ventricular filling pressure. Neonates rarely demonstrate inherited lesions at birth.

Dilated Cardiomyopathy

This is characterized by left and/or right ventricular enlargement and reduced systolic function in the absence of coronary, valvular, congenital, or systemic disease known to cause myocardial dysfunction. Although there are many known inherited and acquired causes of dilated cardiomyopathy, the etiology remains undefined in approximately half of cases (Schaufelberger, 2019). Some result from viral infections, including myocarditis and HIV. Other causes, which are potentially reversible, include alcoholism, cocaine abuse, coronavirus disease 2019 (COVID-19), and thyroid disease.

In affected gravidas, the rate of major adverse cardiovascular events in pregnancy ranges from 25 to 40 percent (American College of Obstetricians and Gynecologists, 2019; Grewal, 2009). Heart failure and arrhythmias are the most common, and women with preexisting moderate or severe left ventricular dysfunction or NYHA functional class III or IV are at greatest risk. Dilated cardiomyopathy is managed with therapy for standard heart failure and for the specific underlying etiology (Bozkurt, 2016).

Peripartum Cardiomyopathy

This disorder is similar to other forms of nonischemic dilated cardiomyopathy except for its unique relationship with pregnancy. Peripartum cardiomyopathy shares a genetic predisposition with both familial and sporadic idiopathic dilated cardiomyopathy (Cunningham, 2019; Ware, 2016). It is a diagnosis of exclusion following a concurrent evaluation for peripartum heart failure.

Although the term *peripartum cardiomyopathy* has been used widely, until recently, little evidence supported a unique pregnancy-induced cardiomyopathy. Pearson (2000) reported findings of a workshop of the National Heart, Lung, and Blood Institute that established the following diagnostic criteria:

Development of cardiac failure in the last month of pregnancy or within 5 months after delivery (Fig. 52-7),

- Absence of an identifiable cause for the cardiac failure,
- Absence of recognizable heart disease prior to the last month of pregnancy, and

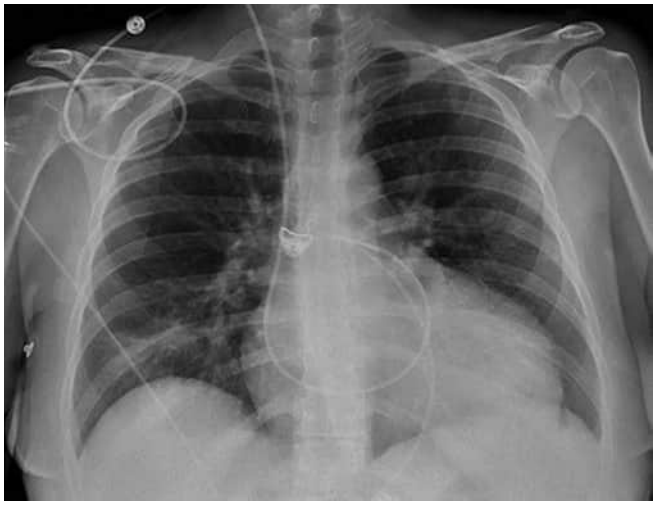

FIGURE 52-7 Peripartum cardiomyopathy with mild pulmonary edema. Chest radiograph of a woman with an abnormally enlarged heart and mild perihilar opacification consistent with dilated cardiomyopathy.

- Left ventricular systolic dysfunction demonstrated by classic echocardiographic criteria. These include depressed ejection fraction or fractional shortening along with a dilated left ventricle.

The incidence of peripartum cardiomyopathy varies considerably and depends on the population studied and the diligence of the search for a cause. The average frequency in the United States is 1 per 1000 to 4000 births (Cruz, 2018; Cunningham, 2019).

The etiology of peripartum cardiomyopathy remains unknown, and proposed causes include viral myocarditis, abnormal immune response to pregnancy, aberrant response to the greater hemodynamic burden of pregnancy, hormonal interactions, malnutrition, inflammation, and apoptosis. The current theory regarding pathophysiology is that of a "two-hit hypothesis" (Cruz, 2018; Ricke-Hoch, 2020). In this regard, peripartum cardiomyopathy affects genetically susceptible women who have one of several cardiac gene mutations to include *TTNC1*, *TTN*, and *STAT3*. Pregnancy at term is further characterized by prodigious secretion of prolactin by the maternal pituitary. At the same time, the placenta secretes high levels of the antiangiogenic molecule *soluble fms-like tyrosine kinase (sFlt-1)*. Although a number of putative triggering events have been hypothesized, a 16-kDa prolactin fragment—*vasoinhibin*—acts to cause myocardial damage with clinically apparent ventricular dysfunction. This is made worse by high levels of sFlt-1, which is superabundant in women with preeclampsia, multifetal pregnancy, or both. Bromocriptine therapy has been evaluated because it inhibits prolactin secretion, and preliminary studies support its use (Haghikia, 2019). For the same reason, it is also reasonable to proscribe breastfeeding.

Hypertensive disorders frequently coexist with peripartum cardiomyopathy, and another proposed mechanism links peripartum cardiomyopathy to preeclampsia (Cunningham, 2019). Antiangiogenic factors are known to be associated with preeclampsia and can induce peripartum cardiomyopathy in susceptible mice. Thus, cardiomyopathy may be precipitated by antiangiogenic factors in a genetically predisposed host because of insufficient proangiogenic factors.

Ntusi and coworkers (2015) analyzed the clinical features of women with peripartum cardiomyopathy compared with those with hypertensive heart failure. All women with peripartum cardiomyopathy became symptomatic in the postpartum period, whereas 85 percent of women with hypertensive heart failure developed symptoms antepartum. Peripartum cardiomyopathy was significantly linked with twin gestation, smoking, and echocardiographic abnormalities. In contrast, hypertensive heart failure patients more often had a family history of hypertension, hypertension and preeclampsia in a prior pregnancy, and left ventricular hypertrophy.

Management

Management of peripartum cardiomyopathy is the same as that of heart failure, and described earlier (p. 922). Therapy is aimed at volume overload, afterload reduction, rhythm control, and inotropic support (Davis, 2020). In addition, β-blocker therapy is used to decrease mortality rates. Anticoagulation with LMWH is considered when the ejection fraction reaches 30 to 35 percent because of the increased risk for left ventricular thrombi (Bauersachs, 2016; Bozkurt, 2016).

In one pilot study, bromocriptine resulted in higher rates of left ventricular recovery at 6 months and lower mortality rates (Sliwa, 2010). A larger study of 115 women showed no difference in full restoration of left ventricular function between those treated and untreated with bromocriptine (Haghikia, 2013). Another investigation of 63 women showed no difference in left ventricular function improvement with short-term versus long-term bromocriptine therapy (Hilfiker-Kleiner, 2017). The use of bromocriptine as adjuvant therapy is considered experimental at this time.

Prognosis

Approximately half of women suffering from peripartum cardiomyopathy recover baseline ventricular function within 6 months of delivery. This rate is lower in obese women (Davis, 2018). In a group of 100 women with newly diagnosed peripartum cardiomyopathy, 72 percent had a left ventricular ejection fraction ≥50 percent at 1 year postpartum (McNamara, 2015). Recovery to this level occurred in almost 90 percent of women whose baseline ejection fraction was at least 30 percent. This is compared with <40 percent in women whose baseline ventricular ejection fraction was <30 percent. Recovery was also related to the baseline left ventricular end-diastolic diameter. Event-free survival at 1 year occurred in 93 percent. Six women experienced nine major events that included four deaths, four left ventricular assist device implantations, and one heart transplantation. Li and colleagues (2016) also found that a baseline left ventricular ejection fraction <34 percent and a BNP level >1860 pg/mL were associated with an approximately threefold greater risk of persistent left ventricular systolic dysfunction. The mortality rate approaches 5 to 10 percent at 1 year in women with persistent cardiac failure (American College of Obstetricians and Gynecologists, 2019).

Long-term follow-up was reported in 28 women with a median surveillance of 91 months (Ersbøll, 2018). Although

most women were asymptomatic, compared with controls, they had lower ejection fractions, less maximal exercise capacity, and subtle diastolic dysfunction.

Subsequent Pregnancy

From the largest studies on the topic, approximately a third of women with a history of peripartum cardiomyopathy will suffer relapse with worsening of symptoms and deterioration of left ventricular function during another pregnancy (Elkayam, 2014a). The risk of relapse in women with persistent left ventricular dysfunction is substantially higher than in those who have recovered normal ventricular function before a subsequent pregnancy (Hilfiker-Kleiner, 2017). However, normalization of left ventricular function does not guarantee an uncomplicated pregnancy, because approximately 20 percent of these women are at risk for deterioration in that function (Codsi, 2018).

■ Other Cardiomyopathy Types

Arrhythmogenic right ventricular dysplasia is a unique cardiomyopathy defined histologically by progressive replacement of right ventricular myocardium with adipose and fibrous tissue. It has an estimated population prevalence of 1 in 5000, predisposes to ventricular tachyarrhythmias, and is a cause of sudden death, particularly in younger individuals (Agir, 2014). Studies of pregnancies in affected women reported symptoms, including heart failure, in 18 to 33 percent of pregnancies (Schaufelberger, 2019). Based on their systematic review, Krul and coworkers (2011) counsel against pregnancy.

Restrictive cardiomyopathy is probably the least common type. This inherited cardiomyopathy is characterized by a ventricular filling pattern in which worsening myocardial stiffness raises ventricular pressure precipitously and allows only a small filling volume (Elliott, 2008). Pregnancy is not advised because of the severe clinical course and poor prognosis in general.

Takotsubo cardiomyopathy is a rare form of acute reversible left ventricular apical wall ballooning (Kraft, 2017). It is considered to be "stress induced" and appears to be more common with preeclampsia and cesarean delivery. Myocardial infarction must be excluded (Oindi, 2019).

INFECTIVE ENDOCARDITIS

Persons at greatest risk for endocarditis are those with congenital heart lesions, intravenous drug use, degenerative valve disease, and intracardiac devices (Karchmer, 2018). *Subacute bacterial endocarditis* usually stems from a low-virulence bacterial infection superimposed on an underlying structural lesion. These are usually native valve infections. Organisms that cause indolent endocarditis are most often viridans-group streptococci or *Staphylococcus* or *Enterococcus* species. Among intravenous drug abusers and those with catheter-related infections, *Staphylococcus aureus* predominates. With prosthetic valve infections, *Staphylococcus epidermidis* is a frequent cause. *Streptococcus pneumoniae* and *Neisseria gonorrhoeae* may occasionally cause acute, fulminating disease. Others have reported other *Neisseria* species, group B streptococcus, and *Escherichia coli* endocarditis during pregnancy or peripartum.

■ Diagnosis and Management

Infective endocarditis symptoms vary and often develop insidiously. Fever, often with chills, is seen in 80 to 90 percent of cases; a murmur is heard in up to 85 percent; and anorexia, fatigue, and other constitutional symptoms are common (Karchmer, 2018). Clinical clues are anemia, proteinuria, and manifestations of embolic lesions that include petechiae, focal neurological changes, chest or abdominal pain, and extremity ischemia. In some cases, heart failure develops. Symptoms may persist for several weeks before the diagnosis is found, and a high index of suspicion is necessary.

Diagnosis is made using the *Duke-Li classification*, which combines microbiology and imaging criteria with five minor criteria (Iung, 2019). Echocardiography may be diagnostic, but lesions <2 mm or those on the tricuspid valve may be missed. If uncertain, transesophageal echocardiography is accurate and informative. Importantly, a negative echocardiographic study does not exclude endocarditis.

Treatment is primarily medical, and ascertainment of the infecting organism and its sensitivities is imperative for antimicrobial selection. Guidelines for appropriate antibiotic treatment are published by professional societies and updated regularly (Habib, 2015; Karchmer, 2018). Recalcitrant bacteremia and heart failure due to valvular dysfunction are a few reasons for which persistent infection may require valve replacement (Iung, 2019).

■ Pregnancy

Infective endocarditis is uncommon during pregnancy and the puerperium. In an earlier period, the incidence of endocarditis at Parkland Hospital approximated 1 in 16,000 births (Cox, 1988). With the current opioid use disorder epidemic, endocarditis may become more frequent (Prasad, 2019). Associated maternal and fetal mortality rates are from 25 to 35 percent (Dagher, 2021; Habib, 2015). In one review, risk factors were intravenous drug use (14 percent), congenital heart disease (12 percent), and rheumatic heart disease (12 percent). The most common pathogens were streptococcal (43 percent) and staphylococcal (26 percent) species. Among 51 pregnancies, the maternal mortality rate was 11 percent (Kebed, 2014).

■ Endocarditis Prophylaxis

For years, patients with any heart valve problem were given periprocedural antibiotics for endocarditis prophylaxis. Currently, however, recommendations are more stringent. The American Heart Association recommends prophylaxis for dental procedures in those with: (1) a prosthetic valve or prosthetic material used in a valve repair, (2) prior endocarditis, (3) unrepaired cyanotic heart defect or repaired lesion with residual defect at prosthetic sites, and (4) valvulopathy after heart transplantation (Nishimura, 2017). In the absence of pelvic infection, the American College of Obstetricians and Gynecologists (2018b) does not recommend endocarditis prophylaxis for either vaginal or cesarean delivery, except with the lesions cited above.

Pregnant women at highest risk for endocarditis are those with cyanotic cardiac disease, prosthetic valves, or both.

TABLE 52-9. Single-Dose Antibiotic Prophylaxis for Infective Endocarditis in High-Risk Patients

American College of Obstetricians and Gynecologists (2018b)
Standard (IV): ampicillin 2 g ***or*** cefazolin or ceftriaxone 1 g
Penicillin-allergic (IV): cefazolin or ceftriaxone 1 g ***or*** clindamycin 600 mg
Oral: amoxicillin 2 g
American Heart Association/European Society of Cardiology (Karchmer, 2018)
Standard: amoxicillin 2 g PO ***or*** ampicillin 2 g IV or IM
Penicillin-allergic: clarithromycin or azithromycin 500 mg PO; cephalexin 2 g PO; clindamycin 600 mg PO, IV, or IM; ***or*** cefazolin or ceftriaxone 1 g IV or IM

IM = intramuscularly; IV = intravenously; PO = per os (orally).
Cefazolin or ceftriaxone given 30 minutes, and all others given 1 hour prior to procedure.

Table 52-9 shows prophylactic regimens for women not already receiving intrapartum antimicrobial therapy for another indication that would also provide coverage against endocarditis. These are administered as close to 30 to 60 minutes before the anticipated delivery time as is feasible.

ARRHYTHMIAS

Both preexisting and new-onset cardiac arrhythmias are often encountered during pregnancy, labor, delivery, and the puerperium. They are usually benign and their incidence in pregnancy appears to be increasing (MacIntyre, 2018). The mechanism(s) responsible for the higher incidence are not clear. From some studies, estradiol and progesterone are proarrhythmic. Estrogen augments the number of adrenergic receptors in the myocardium, and adrenergic responsiveness seems to be greater in pregnancy (Enriquez, 2014). Perhaps the normal but mild hypokalemia of pregnancy and/or the physiological rise in heart rate serves to induce arrhythmias. Alternatively, detection of arrhythmias may be greater because of the frequent visits in routine prenatal care.

Bradyarrhythmias

Slow heart rhythms, including complete heart block, are compatible with a successful pregnancy outcome (Keepanasseril, 2015). Some women with complete heart block have syncope during labor and delivery, and occasionally temporary cardiac pacing is necessary. In our experiences and from others, women with permanent artificial pacemakers usually tolerate pregnancy well (Hidaka, 2011). With fixed-rate devices, cardiac output apparently is increased by augmented stroke volume.

Patients with pacemakers or other electrical implants require special precautions during surgery. Stray current may be interpreted as an intracardiac signal by the implanted device and lead to pacing changes. In addition, myocardial burns may result from conduction of electrosurgical current to the pacing electrode rather than to the grounding pad. With these devices, preventive steps include cardiology consultation; bipolar electrosurgery or Harmonic scalpel use rather than monopolar current; if needed, minimal monopolar settings; continuous cardiac and pulse oximetry monitoring; contingency plans for arrhythmias; and close proximity of active (electrosurgical pencil) and return (electrosurgical grounding pad) electrodes (Crossley, 2011).

Supraventricular Tachycardias

The most common arrhythmia seen in reproductive-aged women is *paroxysmal supraventricular tachycardia (SVT)*. The prevalence during pregnancy is 24 cases per 100,000 hospital admissions, and approximately 20 percent will experience symptomatic exacerbations during pregnancy (Enriquez, 2014). Interestingly, the mean heart rate of pregnant women with paroxysmal SVT is 184 bpm compared with 166 bpm in nonpregnant affected women (Yu, 2015). In one study, approximately half of women with paroxysmal SVT had an initial onset during pregnancy (Bánhidy, 2015). Notably, maternal paroxysmal SVT was associated with a twofold higher risk of septal cardiac defects, particularly secundum atrial septal defects, in their offspring.

For acute SVT treatment, vagal maneuvers, which include Valsalva maneuver, carotid sinus massage, bearing down, and immersion of the face in ice water, raise vagal tone and block the atrioventricular node. Intravenous adenosine is a short-acting endogenous nucleotide that also blocks AV nodal conduction. Our experiences are similar to those of others in that adenosine is safe and effective for cardioversion in hemodynamically stable gravidas (Page, 2015). Transient fetal bradycardia has been described with adenosine (Dunn, 2000).

If pharmacological therapy is ineffective or contraindicated, the American College of Cardiology and the American Heart Association recommend synchronized cardioversion in pregnant women with hemodynamically unstable SVT (Page, 2015). Although electrical cardioversion with standard energy settings is not contraindicated in pregnancy, vigilance is important. Barnes and colleagues (2002) described a case in which direct current cardioversion led to a sustained uterine contraction and fetal bradycardia. As an aside, pregnancy has no effect on the operation of implantable cardioverter-defibrillator devices (Boulé, 2014).

If cardioversion fails or is unsafe because of concurrent thrombus, then long-term anticoagulation and heart rate control with medication are necessary (DiCarlo-Meacham, 2011). Other treatment options recommended by the American College of Cardiology and the American Heart Association (Page, 2015) include:

- Intravenous metoprolol or propranolol when adenosine is ineffective or contraindicated,

- Intravenous verapamil when adenosine and β-blocking agents are ineffective or contraindicated,
- Intravenous procainamide,
- Intravenous amiodarone for potentially life-threatening SVT and when other therapies are ineffective or contraindicated.

Atrial fibrillation and *atrial flutter* rarely present for the first time during pregnancy. A new-onset atrial fibrillation should prompt a search for underlying etiologies that include cardiac anomalies, hyperthyroidism, pulmonary embolism, drug toxicity, and electrolyte disturbances (MacIntyre, 2018). Major complications include embolic stroke. When associated with mitral stenosis, pulmonary edema may develop in later pregnancy if the ventricular rate is increased. Unstable patients are treated with cardioversion and rate control.

Pregnancy may predispose otherwise asymptomatic women with *Wolff-Parkinson-White (WPW) syndrome* to exhibit arrhythmias. In a study of women with asymptomatic or mildly symptomatic disease, half developed SVT for the first time, and the other half experienced an increase in their attack rate (Kounis, 1995). In some patients, accessory pathway ablation may be indicated. Patients with Ebstein anomaly are prone to have WPW syndrome. Driver and associates (2015) have provided a review.

Ventricular Tachycardia

This form of arrhythmia is uncommon but potentially fatal in healthy young women without underlying heart disease. Brodsky and coworkers (1992) described seven pregnant women with new-onset ventricular tachycardia and reviewed 23 reports. Most of these women were not found to have structural heart disease. In 14 cases, tachycardia was precipitated by physical exercise or psychological stress. Abnormalities found included two cases of myocardial infarction, two of prolonged QT interval, and one of anesthesia-provoked tachycardia. They concluded that pregnancy events precipitated the tachycardia and recommended β-blocking agents for control. As previously discussed (p. 934), *arrhythmogenic right ventricular dysplasia* will result occasionally in ventricular tachyarrhythmias. If unstable, emergency cardioversion is indicated, and standard adult energy settings are adequate (Lin, 2015).

Prolonged QT-Interval

The *long QT syndrome* is the most frequent inherited channelopathy (MacIntyre, 2018). This conduction anomaly may predispose individuals to a potentially fatal ventricular arrhythmia known as *torsades de pointes*. Two studies comprised of 502 pregnant women with long QT syndrome both reported a significant rise in cardiac events postpartum but not during pregnancy (Rashba, 1998; Seth, 2007). The normal elevation in heart rate during pregnancy may be partially protective. Paradoxically, β-blocking agents—preferably propranolol—lower the risk of torsades de pointes in patients with long QT syndrome and should be continued throughout pregnancy and the puerperium (Ishibashi, 2017). Importantly, many medications, including some used during pregnancy, such as the erythromycins and many antiemetics, may predispose to QT prolongation. For opioid-addicted women, the use of methadone to treat withdrawal symptoms may be problematic (Bogen, 2017). Last, Cuneo and colleagues (2020) observed an eightfold risk for stillbirth in women with long QT syndrome (Chap. 35, p. 624).

DISEASES OF THE AORTA

Aortic Dissection

Marfan syndrome and coarctation are two aortic diseases that place the pregnant woman at greater risk for aortic dissection (Russo, 2017). Indeed, half of dissection cases in young women are related to pregnancy (O'Gara, 2004). Other risk factors are bicuspid aortic valve and Turner, Noonan, Loeys-Dietz, or Ehlers-Danlos syndrome (Cauldwell, 2019b; Russo, 2018). Pregnancy-related cardiac guidance for women with Turner syndrome is outlined in Chapter 3 (p. 37). Although the mechanism(s) involved are unclear, the initiating event is a tear in the intimal layer of the aorta, followed by hemorrhage into the media, and finally rupture.

In most cases, aortic dissection presents with severe chest pain described as ripping, tearing, or stabbing. Diminution or loss of peripheral pulses coupled with a recently acquired aortic insufficiency murmur is an important physical finding. The differential diagnosis of aortic dissection in pregnancy includes myocardial infarction, pulmonary embolism, pneumothorax, aortic valve rupture, and obstetrical catastrophes such as placental abruption and uterine rupture.

More than 90 percent of patients with aortic dissection have an abnormal chest radiograph. Aortic angiography is the most definitive method for diagnosis confirmation. However, sonography, computed tomography, and MR imaging are used more frequently depending on the clinical urgency.

Initial medical treatment is given to lower blood pressure. Proximal dissections most often need to be resected, and the aortic valve replaced if necessary. Distal dissections are more complex, and many may be treated medically. Among *nonpregnant* patients with abdominal aortic aneurysms <5.5 cm, survival is not improved by immediate elective repair compared with surveillance and delayed repair. Karthikesalingam and associates (2016) suggest that the size threshold for aneurysm repair should be revisited.

Marfan Syndrome

This autosomal dominant connective tissue disorder has an incidence of 1 per 3000 to 5000 individuals and is without racial or ethnic predilection (Azizad-Pinto, 2017). As discussed in Chapter 62 (p. 1121), Marfan syndrome is caused by any of more than 1000 mutations in the fibrillin (*FBN1*) gene. It is characterized by generalized tissue weakness that can result in dangerous cardiovascular complications. All tissues are involved, and other frequent defects include joint laxity and scoliosis. Progressive aortic dilation causes aortic valve insufficiency, and infective endocarditis or mitral valve prolapse with insufficiency may be comorbid. Aortic dilation and dissecting aneurysm are the most serious abnormalities. Early death is due to either a dissecting aneurysm or to valvular insufficiency and heart failure.

During pregnancy, the primary concern with Marfan syndrome is aortic dissection (Curry, 2014; Russo, 2017). A study using the Nationwide Inpatient Sample from 2003 to 2010 described 339 deliveries in women with Marfan syndrome. There was one maternal death and six (1.8 percent) aortic dissections (Hassan, 2015). From the United Kingdom, Cauldwell and colleagues (2019a) described 258 pregnancies in 151 affected women. Although no women died, 1.9 percent had an aortic dissection.

The aortic root usually measures approximately 2 cm, and during normal pregnancy, it expands slightly. With Marfan syndrome, aortic root repair is recommended at diameters of 4.0 to 4.5 cm (Azizad-Pinto, 2017). The guidelines of the American College of Cardiology, the American Heart Association, and the American Association of Thoracic Surgeons advise prophylactic aortic repair in women considering pregnancy if the diameter of the ascending aorta exceeds 4 cm (Hiratzka, 2010). The guidelines of the European Society of Cardiology advise repair of the aorta at diameters >4.5 cm (Regitz-Zagrosek, 2018). Surgical repair is also considered using a formula indexed to height because shorter patients have dissection at a smaller diameter (Bradley, 2014).

For pregnant women with known thoracic aortic root or ascending aortic dilation, monthly or bimonthly echocardiographic measurements of the ascending aortic dimensions are recommended to detect expansion (American College of Obstetricians and Gynecologists, 2019). Prophylactic β-blocking agents have become standard for gravidas with Marfan syndrome because they reduce hemodynamic stress on the ascending aorta and slow the dilation rate. Ideally, pregnant women with aortic aneurysms are delivered at facilities in which cardiothoracic surgery is available. Vaginal delivery with regional analgesia and an assisted second stage seem safe for women with an aortic root diameter <4 cm.

Cesarean delivery may be considered for values between 4.0 and 4.5 cm. When the aortic root measures >4.5 cm, elective cesarean delivery is recommended, and direct replacement of the proximal aorta with a prosthetic graft can be considered (Regitz-Zagrosek, 2018). Successful aortic root replacement during pregnancy has been described, but the surgery has also been associated with fetal hypoxic-ischemic encephalopathy (Seeburger, 2007). Several case reports describe emergency cesarean deliveries in women with acute type A dissections that were repaired successfully at the time of delivery (Guo, 2011; Haas, 2011; Papatsonis, 2009).

To evaluate obstetrical outcomes, investigators for one study of 63 women with Marfan syndrome analyzed their 142 pregnancies. Of 111 pregnancies progressing past 20 weeks' gestation, 15 percent delivered preterm, and 5 percent had preterm prematurely ruptured membranes (Meijboom, 2006). There were eight perinatal deaths, and half of the neonatal survivors were subsequently diagnosed with Marfan syndrome.

Aortic Coarctation

In this relatively rare lesion, the aorta is abnormally narrowed and is often accompanied by abnormalities of other large arteries. A fourth of affected patients have a bicuspid aortic valve, and another 10 percent have cerebral artery aneurysms. Other associated lesions are persistent ductus arteriosus, septal defects, and Turner syndrome. The collateral circulation arising above the coarctation remodels and expands, often strikingly, to cause localized erosion of rib margins by hypertrophied intercostal arteries. Typical findings include hypertension in the upper extremities but normal or decreased pressures in the lower extremities. Some have described diagnosis during pregnancy using MR imaging (Sherer, 2002; Zwiers, 2006). Jimenez-Juan and associates (2014) found that aortic diameter measured by MR imaging and the risk of adverse events during pregnancy were inversely correlated. Of note, no adverse outcomes occurred if the minimum diameter at the coarctation exceeded 15 mm.

Major complications with aortic coarctation include congestive heart failure after long-standing severe hypertension, bacterial endocarditis of an associated bicuspid aortic valve, and aortic rupture. Antihypertensive therapy using β-blocking drugs is usually required because hypertension may worsen in pregnancy. Aortic rupture is more likely late in pregnancy or early puerperium. Cerebral hemorrhage from *circle of Willis aneurysms* also may occur. According to the World Health Organization, severe coarctation should preclude pregnancy (Foeller, 2018).

In one study of outcomes from 188 pregnancies, a third of women had hypertension that was related to significant coarctation gradients, and one woman died from dissection at 36 weeks' gestation (Beauchesne, 2001). In 700 deliveries complicated with coarctation, hypertensive complications of pregnancy were increased three- to fourfold (Krieger, 2011). Importantly, almost 5 percent of women with coarctation had an adverse cardiovascular outcome—maternal death, heart failure, arrhythmia, cerebrovascular or other embolic event—compared with only 0.3 percent of controls. Of women with coarctation, 41 percent underwent cesarean delivery compared with 26 percent of controls.

Congestive heart failure demands vigorous efforts to improve cardiac function and may warrant pregnancy interruption. In this setting, some authors recommend that resection of the coarctation be undertaken to protect against the possibility of a dissecting aneurysm and aortic rupture. This poses significant perfusion risk, especially for the fetus, because all the arterial collaterals must be clamped for variable periods.

ISCHEMIC HEART DISEASE

Pregnant women with coronary artery disease commonly have the classic risk factors of family history, diabetes, smoking, hypertension, hyperlipidemia, and obesity (Tripathi, 2019). The rate of ischemic heart disease is estimated to be 10 cases per 100,000 pregnancy and postpartum hospitalizations (Smilowitz, 2018; Tripathi, 2019). Although relatively rare, the risk of acute myocardial infarction is approximately threefold higher in pregnant women compared with nonpregnant women of similar age (Elkayam, 2014b).

Acute Coronary Syndrome

Myocardial infarction (MI) is the end result of an acute coronary syndrome. It can result from coronary artery atherosclerosis,

dissection, embolism, spasm, or arteritis (American College of Obstetricians and Gynecologists, 2019; Cauldwell, 2020). The mortality rate with MI in pregnancy is higher compared with age-matched nonpregnant women. In a Nationwide Inpatient Sample study totaling 859 pregnancies complicated by acute MI, the death rate was 5.1 percent (James, 2006). Women who sustain an infarction <2 weeks before delivery are at especially high risk of death due to the greater myocardial demand of labor and delivery (Esplin, 1999).

In a systematic review of 150 cases, most women developed an acute MI during the third trimester or postpartum (Elkayam, 2014b). Approximately three fourths presented with ST segment-elevation MI (STEMI). The leading mechanisms of acute infarction included *spontaneous coronary dissection* (43 percent) and *atherosclerotic disease* (27 percent). Significant complications included heart failure (38 percent), recurrent angina or infarction (19 percent), and ventricular arrhythmias (12 percent). The maternal and fetal mortality rates were 7 and 5 percent, respectively.

Diagnosis of acute coronary syndrome during pregnancy does not differ from that in nonpregnant patients and is based on clinical presentation, characteristic ECG changes, and evidence of myocardial necrosis reflected by elevated serum high-sensitivity troponin I levels (Pacheco, 2014). Consider that troponin I levels are greater, however, in preeclamptic and hypertensive women compared with normotensive gravidas (Ravichandran, 2019).

With spontaneous coronary artery dissection, establishing the diagnosis requires an increased index of suspicion in the women presenting with chest pain (Codsi, 2016). For this condition, coronary angiography is considered the diagnostic gold standard and should be expeditiously performed if acute coronary syndrome—either MI or unstable angina—is present (Hayes, 2018).

Treatment of acute MI is similar to that for nonpregnant patients (Pacheco, 2014). Several reports describe successful percutaneous transluminal coronary angioplasty and stent placement during pregnancy (American College of Obstetricians and Gynecologists, 2019). Cardiopulmonary resuscitation may be required, as described in Chapter 50 (p. 897). If the infarct has healed sufficiently, cesarean delivery is reserved for obstetrical indications, and epidural analgesia is ideal for labor.

■ Pregnancy with Prior Ischemic Heart Disease

Ischemic heart disease is characteristically progressive, and because it is usually associated with hypertension or diabetes, pregnancy in most of these women seems inadvisable. In an earlier review of 30 pregnancies in women who had sustained an *infarction remote from pregnancy*, none of the women died, four had congestive heart failure, and four had worsening angina during pregnancy (Vinatier, 1994). Pombar and coworkers (1995) evaluated outcomes of women with diabetes-associated ischemic heart disease and infarction. Three had undergone coronary artery bypass grafting before pregnancy. Of 17 women, eight died during pregnancy. Certainly, pregnancy raises cardiac workload, and these investigators concluded that ventricular performance should be assessed using ventriculography, radionuclide studies, echocardiography, or coronary angiography before conception. Without significant ventricular dysfunction, pregnancy will likely be tolerated. For the woman who becomes pregnant before these studies are performed, echocardiography is done. Exercise tolerance testing may be indicated, and radionuclide ventriculography exposes the fetus to minimal radiation (Chap. 49, p. 875).

COMMON OBSTETRICAL MEDICATIONS

Common medications used in pregnancy require special consideration in women with cardiac conditions. Terbutaline causes vasodilation and tachycardia, which can be dangerous in patients with mitral and aortic stenosis. Nifedipine for hypertension control or tocolysis results in hypotension that can have negative consequences for patients with aortic stenosis, pulmonary hypertension, and Eisenmenger syndrome. Postpartum hemorrhage should be managed aggressively, and methylergonovine generally is a safe choice. Prostaglandin $F_{2\alpha}$ may cause pulmonary shunting and bronchospasm, which results in elevation of pulmonary artery pressure. Consideration is given to the vasodilatory effects of hydralazine in conditions such as hypertrophic cardiomyopathy. Hydralazine also causes tachycardia. The β-blocking agent labetalol is a safe choice unless there is ventricular failure. In general, oxytocin and magnesium sulfate have minimal cardiac effects.

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CHAPTER 53

Chronic Hypertension

In reproductive-aged women, the prevalence of hypertension approximates 6 percent (Centers for Disease Control and Prevention, 2017). Thus, not surprisingly, chronic hypertension is one of the most common serious complications encountered during pregnancy. In one study of more than 56 million births, the incidence was 1.8 percent (Bateman, 2012). Chronic hypertension complicated 2.3 percent of pregnancies in data from the Medicaid Analytic Extract (Bateman, 2015). Despite an increasing prevalence from 1970 to 2010, optimal management has not been well studied (Ananth, 2019).

Chronic hypertension usually improves during early pregnancy. This is followed by variable behavior later in pregnancy and may include development of superimposed preeclampsia. The latter carries significant risks for maternal and perinatal morbidity and mortality.

GENERAL CONSIDERATIONS

Blood pressure is a polygenic biological variant that differs between populations. Numerous epigenetic factors also influence penetrance differences between individuals. Moreover, clinical features such as increasing age and weight correlate positively with rising pressures. Last, resting blood pressure measurements do not reflect daily activities. Therefore, adults have a broad range of normal blood pressure values, which makes defining hypertension difficult.

Definition and Classification

Chronic hypertension would logically be defined as some level of sustained resting blood pressure that is associated with acute or long-term adverse effects. Most consider 140/90 mm Hg as the upper limit of normal. In the United States, these values were derived primarily from life insurance actuarial tables constructed using data from white adult males. These "norms" disregard ethnicity, gender, and other covariants. The importance of race is emphasized by Kotchen (2018), who cites the incidence of hypertension—defined as blood pressure >140/90 mm Hg—to be 34 percent in blacks, 29 percent in whites, and 21 percent in Mexican Americans.

For many years, the Joint National Committee promulgated guidelines for diagnosis, classification, and management of chronic hypertension. Recently, a coalition led by the American College of Cardiology and the American Heart Association published criteria for the diagnosis of hypertension (Table 53-1) (Whelton, 2018).

TABLE 53-1. Criteria for Diagnosis of Hypertension

Blood Pressure (mm Hg)			Nonpregnant ACC/AHA	Pregnant ACOG
SBP		DBP		
<120	and	<80	Normal	Normal
120–129	and	<80	Elevated	Normal
130–139	or	80–89	Stage 1 HTN	Normal
140–159	or	≥90	Stage 2 HTN	Mild to moderate HTN
≥160	or	≥110	Stage 2 HTN	Severe HTN

ACC = American College of Cardiology; ACOG = American College of Obstetricians and Gynecologists; AHA = American Heart Association; DBP = diastolic blood pressure; HTN = hypertension; SBP = systolic blood pressure.

Treatment and Benefits for Nonpregnant Adults

Chronic hypertension accounts for nearly 15 percent of deaths worldwide (Kotchen, 2018). Long term, hypertension raises substantively the risk of cardiovascular disease, coronary heart disease, congestive heart failure, stroke, renal failure, peripheral arterial disease, and mortality. These risks decline with treatment of otherwise normal adults who have sustained hypertension.

Based on these benefits, current guidelines recommend antihypertensive therapy for stage 1 hypertension in nonpregnant adults with risk factors for current or future cardiovascular disease. However, given the different diagnostic criteria in pregnancy (see Table 53-1), the best management for women being treated and contemplating pregnancy, for those undergoing treatment who become pregnant, or for those first identified to have chronic hypertension during pregnancy is unknown (American College of Obstetricians and Gynecologists, 2018a; August, 2015). In these women, the benefits and safety of instituting antihypertensive therapy are less clear, as subsequently discussed.

Preconceptional Counseling

Women with chronic hypertension ideally undergo counseling before pregnancy (American College of Obstetricians and Gynecologists, 2018b). Initial questions ascertain hypertension duration, degree of blood pressure control, and current therapy. Home measurement devices are checked for accuracy. General health, daily activities, and dietary habits also are assessed (Table 53-2). Women who require multiple medications for control or who have poorly controlled pressures carry greater risk for adverse pregnancy outcomes. Patient counseling should disclose maternal and fetal risks, which are detailed in later sections (pp. 946 and 948).

For hypertensive women with disease exceeding 5 years or with comorbid diabetes, cardiovascular and renal function are assessed (August, 2015; Chahine, 2019). Renal function is evaluated by serum creatinine measurement and urine spot protein/creatinine ratio measurement. If the ratio is abnormally high (>0.3), proteinuria can be further quantified with a 24-hour urine collection (Kuper, 2016; Morgan, 2016a).

Women with evidence of organ dysfunction or those with prior adverse events such as a stroke, myocardial infarction, arrhythmias, or ventricular failure carry markedly higher risks for a recurrence or worsening dysfunction during pregnancy. Specific preconceptional guidance for these conditions is found in Chapters 63 (p. 1132) and 52 (p. 918), respectively. Although poorly controlled hypertension is considered a contraindication for pregnancy by some, there is no consensus. Women who maintain persistent systolic pressures ≥160 mm Hg or diastolic pressures ≥110 mm Hg despite therapy; require multiple antihypertensive agents; have a serum creatinine level >2 mg/dL; or have a history of prior stroke, myocardial infarction, or cardiac failure must be counseled regarding the marked risks to themselves and to their fetus. These are described in the next sections.

PREGNANCY CONSIDERATIONS

Diagnosis and Evaluation

Chronic hypertension is diagnosed if it precedes pregnancy or if it is identified before 20 weeks' gestation. Prior to this gestational age, preeclampsia is rarely seen (Chap 40, p. 690). The American College of Obstetricians and Gynecologists (2018a, 2020) defines hypertension as a systolic pressure ≥140 mm Hg or a diastolic pressure ≥90 mm Hg (see Table 53-1). In suspected

TABLE 53-2. Lifestyle Modifications for Hypertensive Patients

Weight reduction: BMI ≤25 kg/m^2
Consume a dietary pattern that emphasizes intake of vegetables, fruits, and whole grains; includes low-fat dairy products, poultry, fish, legumes, nontropical vegetable oils, and nuts; and limits sweets and red meats. Examples are DASH, USDA Food Pattern, or the AHA Diet
Lower sodium intake: consume no more than 2400 mg/d; 1500 mg/d desirable
Engage in aerobic physical activity three to four sessions per week, lasting on average 40 minutes per session, and involving moderate- to vigorous-intensity physical activity
Moderation of alcohol consumption: ≤1 drink daily (none when pregnant)

AHA = American Heart Association; DASH = Dietary Approaches to Stop Hypertension; USDA = United States Department of Agriculture.
Summarized from Kotchen, 2018; Whelton, 2018.

cases of "white-coat" hypertension, serial ambulatory monitoring can be considered. In some women without overt chronic hypertension, a history of repeated pregnancies complicated by gestational hypertension, with or without preeclampsia, may be elicited. Either is a risk factor for latent chronic hypertension. This is especially true for prior preeclampsia and particularly for early-onset preeclampsia (van Eerden, 2018). In many ways, gestational hypertension is analogous to gestational diabetes. Women with the former have a *chronic hypertensive diathesis*, in which heredity and epigenetics play a major role.

Although uncommon, secondary causes of hypertension are always a possibility in affected women. Thus, chronic renal disease, obstructive sleep apnea, connective tissue disease, primary aldosteronism, Cushing syndrome, pheochromocytoma, and myriad other causes are considered during evaluation (American College of Obstetricians and Gynecologists, 2018a). That said, most pregnant women with antecedent hypertension will have otherwise uncomplicated disease. The hypertensive disorders that uniquely complicate pregnancy are discussed in Chapter 40.

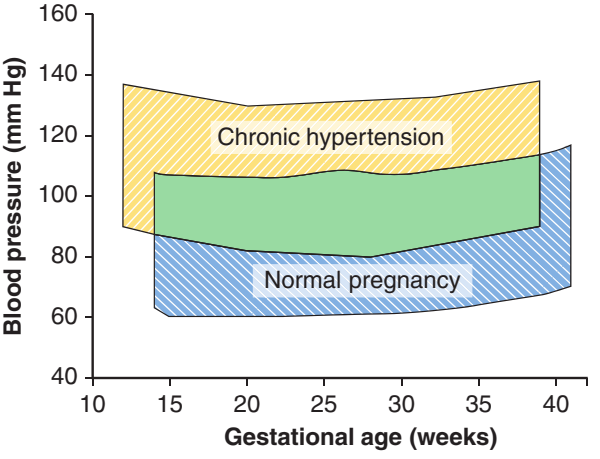

FIGURE 53-1 Mean systolic and diastolic blood pressures across pregnancy in 107 untreated chronically hypertensive women (*yellow*) compared with blood pressures across pregnancy in 4589 healthy nulliparas (*blue*). (Data from August, 2015; Levine, 1997; Sibai, 1990.)

■ Risk Factors

Several factors increase the likelihood that pregnant women will have chronic hypertension. Three of those most frequently cited are ethnicity, obesity, and diabetes. As previously noted, black women are more commonly affected. Related to this, hundreds of blood pressure–related phenotypes and genomic regions have been identified (Ward, 2015). Obesity may raise the prevalence of chronic hypertension tenfold (Chap. 51, p. 904). In addition, obese women are more likely to develop superimposed preeclampsia (Ornaghi, 2018).

The *metabolic syndrome* is a clinical cluster that includes hypertension, high blood sugar, excess fat at the waist, and abnormal cholesterol or triglyceride levels. This constellation is a risk marker for superimposed preeclampsia and for persistent postpartum hypertension (Jeyabalan, 2015). Diabetes is also prevalent in chronically hypertensive women, and its interplay with obesity and preeclampsia is prominent (Leon, 2016). The most frequent comorbidities associated with chronic hypertension are pregestational diabetes—6.6 percent, thyroid disorders—4.1 percent, and collagen vascular disease—0.6 percent (Bateman, 2012).

■ Physiological Effects of Chronic Hypertension

Blood pressure decreases in the first trimester due to a 30-percent drop in systemic vascular resistance. In most women with chronic hypertension, this decline is followed by a rise in blood pressure during the third trimester (Fig. 53-1). Women with chronic hypertension have persistently elevated vascular resistance and possibly reduced intravascular volume expansion (Tihtonen, 2007). Moreover, in women with superimposed preeclampsia, arterial mechanical properties are most marked (Hibbard, 2015).

ADVERSE PREGNANCY EFFECTS

Chronic hypertension is associated with adverse maternal and perinatal outcomes listed in Table 53-3. Rates of these complications positively correlate with the severity and duration of prepregnancy hypertension. Elevated blood pressure defined by criteria in Table 53-1 may herald adverse outcomes similar to those in women with chronic hypertension defined by criteria of the American College of Obstetricians and Gynecologists (Keene, 2019; Sutton, 2018). Development of superimposed preeclampsia, particularly early-onset disease, is especially dangerous.

■ Maternal Morbidity and Mortality

Most women with satisfactorily controlled hypertension and no end-organ damage will do well in pregnancy. Complications are more likely with severe baseline hypertension and documented end-organ damage, especially ventricular hypertrophy and hypertensive glomerulosclerosis (Ambia, 2018, 2019; Morgan, 2016b). Women with chronic hypertension have higher rates of stroke, pulmonary edema, and renal failure (Gilbert, 2007; Zofkie, 2018). These observations were verified in the report from the Nationwide Patient Sample (Bateman, 2012).

TABLE 53-3. Some Adverse Effects of Chronic Hypertension on Maternal and Perinatal Outcomes

Maternal	Perinatal
Superimposed preeclampsia	Stillbirth
HELLP syndrome	Fetal-growth restriction
Placental abruption	Preterm delivery
Pulmonary edema	Neonatal death
Stroke	Neonatal morbidity
Acute kidney injury	Congenital anomalies
Heart failure	
Hypertensive cardiomyopathy	
Myocardial infarction	
Maternal death	

HELLP = hemolysis, elevated liver enzyme levels, low platelet count.

In this study, hypertension complications included pulmonary edema—1.5 per 1000, stroke—2.7 per 1000, mechanical ventilation—3.8 per 1000, acute kidney injury—5.9 per 1000, and maternal mortality—0.4 per 1000. In another report, the maternal mortality rate was greater in women with severe hypertension (Akbar, 2019). Peripartum cardiomyopathy is another associated risk (Cunningham, 2019).

Dangerous blood pressure elevation can develop with chronic hypertension. Systolic pressure ≥160 mm Hg or diastolic pressure ≥110 mm Hg will rapidly cause renal or cardiopulmonary dysfunction or cerebral hemorrhage (Clark, 2012). In addition to hypertensive heart failure mentioned above, coronary artery and aortic dissection have been described (Faden, 2016; Weissman-Brenner, 2004). With superimposed preeclampsia or eclampsia, the maternal prognosis is poor unless the pregnancy is ended (Becker, 2018). Placental abruption is a common and serious complication (p. 946).

Chronic hypertension is associated with a fivefold higher risk for maternal death (Gilbert, 2007). In the United States from 2011 to 2013, hypertensive disorders, including chronic hypertension and preeclampsia syndrome, accounted for 7.4 percent of 2009 pregnancy-related deaths (Creanga, 2017). Undoubtedly related were other causes of death such as cardiovascular conditions—15.5 percent, cerebrovascular accidents—6.6 percent, and cardiomyopathy—11 percent. Moodley (2007) reported similar findings in 3406 maternal deaths from South Africa.

Superimposed Preeclampsia

The reported incidence of superimposed preeclampsia varies from 20 to 50 percent because it is not precisely defined (American College of Obstetricians and Gynecologists, 2018a, 2020; Bramham, 2016; Moussa, 2017). In a Maternal-Fetal Medicine Units Network trial, superimposed preeclampsia was diagnosed in 25 percent of hypertensive gravidas (Caritis, 1998). August and colleagues (2015) hypothesize that this predilection may stem from similar genetic, biochemical, and metabolic abnormalities.

The risk for superimposed preeclampsia positively correlates with the severity of baseline hypertension and the need for antihypertensive therapy (Ankumah, 2014; Morgan, 2016a). Preliminary observations indicate that pregnant women with initial blood pressures ≥130/80 mm Hg early in pregnancy have excessive rates of preeclampsia (Greiner, 2020; Keene, 2019; Roman, 2020). Moreover, compared with women who do not develop preeclampsia, these pressures nadir earlier in gestation (Fig. 53-2) (Morgan, 2016a). The preeclampsia risk is even greater if end-organ damage, such as baseline proteinuria, is present.

Prediction

Thus far, individual predictive tests for superimposed preeclampsia have been disappointing (Conde-Agudelo, 2015; Correa, 2016). First-trimester serum markers used for aneuploidy screening are one group (Chap. 17, p. 338). Of these, inhibin A levels are reduced in patients destined to develop preeclampsia, but its low sensitivity makes it clinically unuseful (Sibai, 2008; Zeeman, 2003). Similarly, maternal serum pregnancy-associated plasma protein-A (PAPP-A) levels are decreased in the first trimester of pregnancies that are later complicated by preeclampsia (Tan, 2018). Of angiogenic and antiangiogenic factors, low plasma levels of placental growth factor (PlGF) and high levels of soluble fms-like tyrosine kinase-1 (sFlt-1) have been associated with superimposed preeclampsia development (Binder 2020; Nzelu, 2020). Last, the umbilical artery pulsatility index appears to be elevated in the first trimester of these pregnancies (O'Gorman, 2016). Combining all these factors may be useful in predicting superimposed preeclampsia (O'Gorman, 2016; Stepan, 2020).

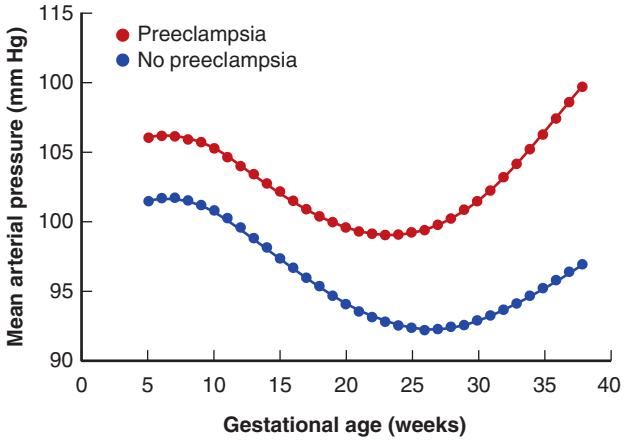

FIGURE 53-2 Blood pressure trends in treated, chronically hypertensive women with and without superimposed preeclampsia. Mean maternal pressures (MAPs) at entry ($p = 0.002$) and throughout gestation ($p < 0.001$) are significantly different for each group. MAP nadir at 23.3 weeks (95% CI, 22.5–24.1) for superimposed preeclampsia versus 26.4 weeks (95% CI, 22.5–27.6) for those without preeclampsia is significant (3.1 weeks, 95% CI, 2.3–4.3).

Prevention

Trials using various medications to prevent preeclampsia in women with chronic hypertension show little or no benefit. Low-dose aspirin has been evaluated most frequently (Mol, 2016; Staff, 2015). The U.S. Preventive Services Task Force concluded with "moderate certainty" that treatment with low-dose aspirin for chronically hypertensive women at high risk for preeclampsia is beneficial (Henderson, 2014). The American College of Obstetricians and Gynecologists (2018a) subsequently recommended initiating 81 mg between 12 and 28 weeks' gestation and continuing therapy until delivery for these at-risk gravidas.

Antioxidants to prevent preeclampsia have been studied. Spinnato and coworkers (2007) randomly assigned 311 women with chronic hypertension to treatment with vitamins C and E or with a placebo. A similar number in both groups developed preeclampsia—17 versus 20 percent, respectively.

Placental Abruption

Chronic hypertension increases the risk two- to threefold for premature placental separation. This event's harms are detailed in Chapter 43 (p. 753). The general obstetrical population risk is 1 abruption in 200 to 300 pregnancies, and in women with

chronic hypertension, this rises to 1 in 60 to 120 pregnancies (Ankumah, 2014; Cruz, 2011; Magee, 2015). Most abruptions affect women with worsening hypertension or superimposed preeclampsia. Vigil-De Gracia and associates (2004) reported an 8.4-percent risk in women with severe hypertension.

Perinatal Morbidity and Mortality

Rates of almost all adverse perinatal outcomes are greater in women with chronic hypertension than in normotensive gravidas. Those who develop preeclampsia have substantially higher adverse outcome rates. As shown in Figure 53-3, adverse outcome rates rise incrementally with increasing blood pressures (Ankumah, 2014). There is evidence to suggest that chronic hypertension—treated or untreated—is associated with congenital anomalies (Battarbee, 2020). Data from untreated women help tease away drug effects on organogenesis. Bateman and coworkers (2015) found an odds ratio of 1.5 for cardiac defects. A systematic review noted a comparable risk ratio of 1.4 (Ramakrishnan, 2015). From one large birth defect study, five cases of fetal esophageal atresia were found in those with untreated hypertension and yielded an adjusted odds ratio of 3.2 (van Gelder, 2015).

The stillbirth frequency with chronic hypertension is substantively greater, and common etiologies include superimposed severe preeclampsia, abruption, and fetal-growth restriction. Rates range from 15 to 24 deaths per 1000 births (Ahmad, 2012; Ankumah, 2014; Bateman, 2012). Low-birthweight neonates also are common and result from fetal-growth restriction, indicated preterm delivery, or both (see Fig. 53-3).

The incidence of fetal-growth restriction averages 20 percent. Zetterström and colleagues (2006) reported a 2.5-fold risk for fetal-growth restriction in 2754 chronically hypertensive Swedish women compared with the risk in normotensive gravidas. Another study of 1609 Dutch nulliparas showed a 1.3-fold greater risk (Broekhuijsen, 2012). As with other complications, fetal-growth dysfunction is more likely in those who develop superimposed preeclampsia. In one study, the incidence of growth-restricted fetuses born to women with superimposed preeclampsia was almost 50 percent compared with only 21 percent in chronically hypertensive women without preeclampsia

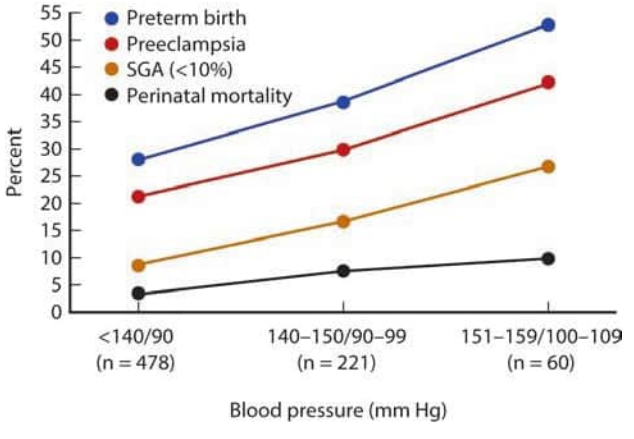

FIGURE 53-3 Frequency of selected adverse maternal and perinatal outcomes by blood pressure stratification in women with mild chronic hypertension. SGA = small for gestational age.

(Chappell, 2008). Last, women with chronic hypertension severe enough to warrant treatment had an 11-percent incidence of fetal-growth restriction sufficiently severe to yield birthweights ≤3rd percentile (Morgan, 2016a). Thus, neonates born to these women have a correspondingly high rate of intensive-care unit (ICU) admission.

All of these adverse perinatal effects of chronic hypertension contribute to the greater perinatal mortality rate, which is two- to fourfold higher than the rate in nonaffected gravidas (American College of Obstetricians and Gynecologists, 2018a). Stratified by severity, the perinatal death rate was 31 per 1000 births in those with mild hypertension, 72 per 1000 births with moderate disease, and 100 per 1000 births in women with severe chronic hypertension (Ankumah, 2014). In a study from Parkland Hospital, the perinatal mortality rate was 32 per 1000 births in women with hypertension severe enough to require treatment (Morgan, 2016a). As expected, the highest rates are in women who develop superimposed preeclampsia, for whom the risk doubles (Al Khalaf, 2021; Grover, 2021).

If diabetes coexists with chronic hypertension, preterm delivery, fetal-growth restriction, and perinatal mortality rates are increased even more (Yanit, 2012). Last, children born to women with chronic hypertension have long-term endocrine and metabolic morbidities, specifically obesity (Imterat, 2020). This epigenetic effect of hypertension and of other maternal chronic diseases is detailed in Chapter 47 (p. 831).

MANAGEMENT DURING PREGNANCY

Chronic hypertension management aims to prevent moderate or severe hypertension, to delay or dampen superimposed preeclampsia, and to reduce rates of adverse maternal or perinatal outcomes. Blood pressure self-monitoring is encouraged, but for accuracy, automated devices must be properly calibrated (Whelton, 2018). Dietary counseling and reduction of behaviors such as tobacco, alcohol, cocaine, or other substance use serve as early interventions. A low-sodium diet and low-dose aspirin are others (Battarbee, 2020; Chaemsaithong, 2020). Last, pharmacologic therapy is instituted to maintain blood pressures within suitable ranges, which are outlined later (p. 951).

Some women—especially those with long-term or untreated hypertension—have complications that raise the risk of adverse pregnancy events. Concentric ventricular hypertrophy and proteinuria are concerns in these women. (Ambia, 2017, 2019; Kim, 2016; Morgan, 2016a,b). Thus, early in prenatal care, cardiovascular and renal baseline functions are assessed with echocardiogram and a 24-hour urine collection for protein measurement.

Antihypertensive Drugs

Treatment of hypertension during pregnancy has included every drug class, but information is still limited regarding safety and efficacy (American College of Obstetricians and Gynecologists 2013, 2018a). Some commonly used drugs are listed in Table 53-4 and the following summary is abstracted from several sources, including the 2020 Prescribers' Digital Reference. Possible fetal effects of many of these drugs are also discussed in Chapter 8.

TABLE 53-4. Some Antihypertensive Drugs Used for Treatment of Chronic Hypertension During Pregnancy[a]

Drug	Comment
Adrenergic-receptor agents[b]	
β-blockers: propranolol, metoprolol	Avoid with asthma, decompensated heart function
α/β-blocker: labetalol	
α-agonist: methyldopa	Less effective for severe hypertension; sedative side effects
Calcium-channel blocking agents[b]	
Nifedipine, amlodipine, verapamil	Avoid with tachycardia
Diuretic[c]	
Hydrochlorothiazide	Begin before 20 weeks' gestation
Vasodilating agent[c]	
Hydralazine	Hypertension complicated by cardiac or renal dysfunction; less effective with severe hypertension

[a]Drugs compatible with pregnancy (Briggs, 2022).
[b]First-line agents.
[c]Second-line agents.

Adrenergic Receptor–Blocking Agents

Peripherally acting β-adrenergic-receptor blockers cause a generalized decline in sympathetic tone and lower cardiac output. Examples are propranolol (Inderal) and metoprolol (Lopressor, Toprol). Atenolol is not recommended because of its link with fetal-growth restriction (Bello, 2021). Labetalol (Normodyne) is an α/β-adrenergic blocker that is considered safe. Clonidine (Catapres) and α-methyldopa (Aldomet) act *centrally* by reducing sympathetic outflow to effect a generalized decreased vascular tone. Drugs in this class most frequently used in pregnancy are methyldopa and labetalol (American College of Obstetricians and Gynecologists, 2018a).

Calcium Channel–Blocking Agents

These drugs are divided into three subclasses based on their calcium-channel actions. Common agents include nifedipine (Procardia, Adalat)—a dihydropyridine—and verapamil (Calan)—a phenylalkyl amine derivative. These agents have negative inotropic effects and thus worsen ventricular dysfunction and congestive heart failure. Theoretically, they may potentiate the vasoactive actions of magnesium sulfate administered for eclampsia neuroprophylaxis. Webster and coworkers (2017) found nifedipine equally effective as labetalol for treatment of chronic hypertension in pregnancy. However, those treated with nifedipine advantageously had less blood pressure variation than those treated with labetalol (Shawkat, 2018). Although data are limited, calcium channel–blocking agents appear to be safe therapy for chronic hypertension during pregnancy (American College of Obstetricians and Gynecologists, 2018a; Briggs, 2022).

Diuretics

Thiazide diuretics are sulfonamides, and these were the first drug group used to successfully treat chronic hypertension. These agents and loop-acting diuretics such as furosemide (Lasix) are commonly used in nonpregnant patients. Short term, they provide sodium and water diuresis with volume depletion. Over time, there is *sodium escape,* and volume depletion partially corrects. Some aspect of lowered peripheral vascular resistance likely contributes to their effectiveness in reducing long-term morbidity (Umans, 2015).

Thiazide drugs may be mildly diabetogenic, and the normal expected volume expansion of pregnancy may be curtailed (Sibai, 1984). Although rates of adverse perinatal outcomes are not greater with diuretic use, concerns have curtailed diuretic use as first-line therapy for chronic hypertension in pregnancy and particularly after 20 weeks' gestation (Working Group Report, 2000). Overall, thiazide diuretics are considered safe in pregnancy (Briggs, 2022).

Vasodilators

Hydralazine (Apresoline) relaxes arterial smooth muscle and has been used parenterally for decades to safely treat severe peripartum hypertension (Chap. 41, p. 722). However, oral hydralazine monotherapy for chronic hypertension is not generally used because of its weak antihypertensive effects and resultant tachycardia. It is employed as an effective vasodilator adjunct for long-term use with other antihypertensives in women with chronic renal insufficiency or ventricular dysfunction.

Angiotensin-Converting Enzyme Inhibitors

These drugs inhibit the conversion of angiotensin-I to the potent vasoconstrictor angiotensin-II. They can cause severe fetal malformations when given in the second and third trimesters. These include oligohydramnios, hypocalvaria, and renal dysfunction (Chap. 8, p. 150). Some preliminary studies also suggest teratogenic effects (Hoeltzenbein, 2018). They are not recommended at any time during pregnancy (Briggs, 2022).

Angiotensin-receptor blockers act in a similar manner. However, instead of blocking the production of angiotensin-II, they inhibit binding to its receptor. They are presumed to have the same adverse fetal effects as angiotensin-converting enzyme inhibitors and also are contraindicated in pregnancy.

Antihypertensive Treatment in Pregnancy

Mild or Moderate Hypertension

Initiating or continuing prepregnancy antihypertensive treatment during pregnancy is debatable for women with mild or moderate hypertension (see Table 53-1). In older observational reports, most pregnancy outcomes were generally good in women with untreated mild to moderate hypertension. However, these studies were relatively small and had widely varying inclusion and outcome criteria. More recently, a Cochrane review of approximately 5000 women with mild to moderate hypertension reported that the risk for severe hypertension in these individuals with initially milder hypertension declined with therapy (Abalos, 2018). The frequencies of superimposed preeclampsia, preterm birth, small-for-gestational age newborns, and perinatal mortality, however, did not differ.

Lowering blood pressure can theoretically decrease uteroplacental perfusion and lead to small-for-gestational age neonates. von Dadelszen and coworkers (2000) found that the decline in mean arterial pressure associated with antihypertensive therapy was linked to a higher frequency of small-for-gestational age newborns. Other studies both confirm and refute these findings (Mitchell, 2019; Morgan, 2020). In two of the larger randomized trials, the incidence of growth restriction was not higher in women randomly assigned to treatment (Gruppo di Studio Ipertensione in Gravidanza, 1998; Sibai, 1990). Conversely, worsening blood pressure itself is associated with abnormal fetal growth. Also, some suggest that the drugs have a direct fetal action (Umans, 2015). Therefore, the question regarding treatment of mild to moderate chronic hypertension in pregnancy is yet to be resolved.

Severe Chronic Hypertension

As classified by the American College of Obstetricians and Gynecologists (2018a), severe hypertension includes a systolic pressure ≥160 mm Hg or a diastolic pressure ≥110 mm Hg. Treatment should be initiated for persistent severe hypertension to reduce maternal morbidity and mortality risks (Akbar, 2019). In women with cardiovascular or renal end-organ damage, treatment may be instituted at systolic pressures ≥140 to 150 mm Hg or diastolic pressures ≥90 to 100 mm Hg in an attempt to mitigate further damage.

Women whose hypertension is severe enough to require antihypertensive therapy or cause end-organ damage carry an increased risk for superimposed preeclampsia. In an older study, Sibai and coworkers (1986) described outcomes from 44 pregnancies in women whose blood pressure at 6 to 11 weeks' gestation was ≥170/110 mm Hg. All were given oral treatment with α-methyldopa and hydralazine to maintain pressures <160/110 mm Hg. Half of these women developed superimposed preeclampsia, and all adverse perinatal outcomes were in this group. Conversely, those women with severe chronic hypertension who did not develop superimposed preeclampsia had reasonably good outcomes. Morgan and colleagues (2016a) confirmed these findings in their study of 447 women requiring treatment for chronic hypertension prior to 20 weeks.

Cardiac abnormalities and renal insufficiency resulting from uncontrolled hypertension raise the risk for adverse pregnancy outcomes. Women with baseline proteinuria >300 mg/d have higher rates of superimposed preeclampsia, preterm birth, and small-for-gestational age neonates compared with those whose 24-hour protein excretion is <300 mg/d (Table 53-5) (Morgan, 2016b). Abnormal cardiac remodeling and left ventricular hypertrophy also are associated with superimposed preeclampsia, preterm birth, and neonatal ICU admission (Ambia, 2018, 2019).

"Tight Control"

During the past decade, the concept of *tight control* of blood pressure has been advocated to optimize maternal and perinatal outcomes. Such control is analogous to that of glycemic control for diabetes management. The observational study by

TABLE 53-5. Selected Pregnancy Outcomes in Women with Chronic Hypertension with and without Baseline Proteinuria[a] and Who Were Treated During Pregnancy

Outcome	Baseline Proteinuria[a]	No Proteinuria	*p* value
Superimposed preeclampsia	79%	49%	<0.001
Abruption	0	1%	0.45
EGA at delivery (mean)[b]	35.1 ± 4.3 wk	37.2 ± 3.3 wk	<0.001
≤30 weeks	18%	6%	0.001
≤34 weeks	34%	17%	0.005
≤37 weeks	48%	26%	0.002
Birthweight (mean)[b]	2379 ± 1028 g	2814 ± 807 g	<0.001
≤3rd percentile	20%	9%	0.01
≤10th percentile	41%	22%	<0.001
Perinatal mortality	36/1000	31/1000	0.47

[a]Defined as ≥300 mg/d protein excretion before 20 weeks' gestation.
[b]Mean ± standard deviations.
EGA = estimated gestational age.

Ankumah and colleagues (2014) noted earlier lends credence to tighter blood pressure control. They showed that the adverse pregnancy outcome risk was lower when blood pressures before 20 weeks' gestation were <140 mm Hg compared with higher-pressure categories and increasing blood pressures.

Unfortunately, those observations were not confirmed. Magee and associates (2015) randomized 987 women to either less-tight or tight control of hypertension. Except for a lower rate of severe hypertension in the tightly controlled group, other outcomes between these two groups did not differ (Table 53-6). Analyzing the same cohort, no gestational age was identified at which tight control was preferable (Pels, 2018). A systematic review reported similar results (Panaitesc, 2017). At this time, no proven benefits or risks are attributed to "tight"—target diastolic pressure <85 mm Hg—versus "less-tight"—target diastolic pressure <100 mm Hg—control of chronic hypertension during pregnancy (American College of Obstetricians and Gynecologists (2018a). A randomized trial—Project CHAP—is ongoing to help address this question (U.S. National Library of Medicine, 2020).

Recommendations for Therapy

Until the treatment of uncomplicated mild to moderate chronic hypertension in pregnancy is confirmed to have benefits, it seems reasonable to follow the guidelines of the American College of Obstetricians and Gynecologists (2018a) and the Society for Maternal-Fetal Medicine (2015). Thus, pregnant women with *severe hypertension* must be treated for maternal neuro-, cardio-, and renoprotection. Treatment is also mandatory for women with prior adverse outcomes such as a stroke, myocardial infarction, and evidence for cardiac or renal dysfunction.

Many find it reasonable to begin antihypertensive treatment in otherwise healthy pregnant women with persistent systolic pressures >150 mm Hg or diastolic pressures >95 to 100 mm Hg (August, 2015; Webster, 2017). Drugs commonly used are listed in Table 53-4. At Parkland Hospital, we initiate treatment with antihypertensive agents at blood pressures ≥150/100 mm Hg. Our preferred regimens include monotherapy with a β-blocking drug such as labetalol or a calcium channel–blocking agent such as nifedipine or amlodipine (Norvasc). Adjunct therapy with a thiazide diuretic seems reasonable for women in the first half of pregnancy. This is more beneficial in black women, in whom the prevalence of salt-sensitive chronic hypertension is high.

Controversy surrounds women who present early in pregnancy and who are already taking antihypertensive drugs (Rezk, 2016). According to the American College of Obstetricians and Gynecologists (2018a) and the Society for Maternal-Fetal Medicine (2015), for women with mild to moderate hypertension, it is *reasonable* to discontinue medications during the first trimester and to restart them if blood pressures approach the severe range. At Parkland Hospital, we continue treatment if the woman is already taking medications when she presents for prenatal care. As exceptions, angiotensin-converting enzyme inhibitors and angiotensin-receptor blockers are stopped.

Some women will have persistently worrisome hypertension despite usual therapy. In these women, development of superimposed preeclampsia becomes a primary concern and is detailed next. Other possibilities include inaccurate blood pressure measurements, suboptimal treatment, illicit drug use, and antagonizing substances such as chronic ingestion of nonsteroidal antiinflammatory drugs (NSAIDs) (Moser, 2006; Sowers, 2005).

TABLE 53-6. Selected Maternal and Perinatal Outcomes in Pregnant Women with Chronic Hypertension According to Less-Tight versus Tight Control

Outcome	Less-Tight Control	Tight Control
Maternal		
Placental abruption	2.2%	2.3%
Severe hypertension[a]	41%	28%
Preeclampsia	49%	46%
HELLP syndrome	1.8%	0.4%
Perinatal		
Deaths	28/1000	23/1000
Weight <10th percentile	16%	20%
Weight <3rd percentile	4.7%	5.3%
Respiratory problem	17%	14%

[a]p <0.001, all other comparisons p >0.05.
HELLP = hemolysis, elevated liver enzyme levels, low platelet count.

Superimposed Preeclampsia

As discussed in Chapter 40 (p. 690), conditions that support the diagnosis of superimposed preeclampsia include worsening hypertension, new-onset proteinuria, neurological symptoms such as severe headaches and visual disturbances, generalized edema, oliguria, and certainly, convulsions or pulmonary edema. These same criteria apply to women with chronic hypertension.

However, preeclampsia can be difficult to diagnose in a chronically hypertensive woman. First, blood pressures may increase during pregnancy in women with chronic hypertension alone and without superimposed preeclampsia. This is most commonly encountered near the end of the second trimester. In the absence of other supporting criteria for superimposed preeclampsia, this likely represents the higher end of the normal blood-pressure curve shown in Figure 53-1. In such women, if preeclampsia is excluded, it is reasonable to begin or to increase the dose of antihypertensive therapy.

As a second diagnostic obstacle, many chronically hypertensive patients have preexisting end-organ damage and laboratory values that mimic preeclampsia. New-onset proteinuria is consistent with the diagnosis of superimposed preeclampsia. However, this is not applicable to women who have underlying renal disease with chronic proteinuria (Cunningham, 1990; Morgan, 2016b). In these women, diagnosing superimposed preeclampsia based on worsening proteinuria is problematic. Laboratory abnormalities that support preeclampsia include rising serum creatinine or hepatic transaminase levels, thrombocytopenia, or any of the facets of HELLP (hemolysis, elevated liver enzyme levels, low platelet count) syndrome. For women with chronic

hypertension and superimposed preeclampsia with severe features, magnesium sulfate for maternal neuroprophylaxis is recommended (Chap. 41, p. 719).

Expectant Management of Early-Onset Preeclampsia

Given that 40 to 50 percent of cases of superimposed preeclampsia develop early and before 37 weeks, considerations for expectant management to allow fetal maturation may be reasonable (Harper, 2016). However, most maternal outcomes are better when women with superimposed preeclampsia are delivered, even when the fetus is markedly preterm. Increased risk for placental abruption, cerebral hemorrhage, and peripartum heart failure attend delivery delays (Cunningham, 1986, 2005; Martin, 2005). And prolonged expectant management is associated with an increased risk of maternal cardiac disease in the ensuing years (Rosenbloom, 2020). In a study from Magee-Women's Hospital, 42 of 68 carefully selected women with a median gestational age of 31.6 weeks were expectantly managed (Samuel, 2011). Despite liberal criteria to mandate delivery, 17 percent of these mothers developed either placental abruption or pulmonary edema. The latency period was extended by a mean of 10 days. There were no perinatal deaths, however, neonatal outcomes were no better than those in the group delivered immediately. Women with superimposed preeclampsia before 34 weeks' gestation may be candidates for expectant management at facilities with adequate maternal and neonatal ICU resources (American College of Obstetricians and Gynecologists, 2018a). At Parkland Hospital, we pursue delivery when superimposed preeclampsia is diagnosed.

Fetal Assessment

Because of greater stillbirth and fetal-growth restriction risks, antepartum fetal surveillance is recommended for women with chronic hypertension. However, data are limited regarding which subpopulations with chronic hypertension benefit most. The ideal test, testing interval, and gestational age of initiation are other unknowns (American College of Obstetricians and Gynecologists, 2018a; Freeman, 2008).

All women with chronic hypertension should undergo a sonographic fetal-growth assessment in the third trimester. Additionally, Chahine and colleagues (2019) recommend that women with low-risk disease undergo weekly antepartum testing. They defined low-risk by four criteria: (1) women ≤35 years of age, (2) mild- to moderate-range blood pressures not requiring medication, (3) no prior hypertension-related adverse pregnancy outcomes, and (4) no end-organ damage. For antepartum testing, a nonstress test or a biophysical profile is suitable (Chap. 20, p. 392).

Women with high-risk disease fail to meet these four criteria. For them, sonography and antepartum testing are considered earlier, and the value of these tools to assess fetal-growth restriction is detailed in Chapter 47 (p. 830). One surveillance algorithm for suspected fetal-growth restriction is outlined in Figure 47-6 (p. 829).

Delivery Timing

For women with mild to moderate chronic hypertension who have an otherwise uncomplicated pregnancy, the American College of Obstetricians and Gynecologists (2018a) recommends waiting for delivery until 37 to 38 weeks' gestation. Women taking antihypertensive drugs are not delivered before $37^{0/7}$ weeks, and those not receiving drug treatment are delivered no earlier than $38^{0/7}$ weeks. A nationally convened consensus committee recommended consideration for delivery at 38 to 39 weeks, that is, ≥37 completed weeks (Spong, 2011). A large population-based Canadian study showed similar results (Ram, 2018). Expectant management beyond 39 weeks' gestation is associated with an increasing incidence of severe preeclampsia, and planned delivery before 37 weeks was associated with a rise in rates of adverse neonatal outcomes (Harper, 206).

For women who have fetal-growth restriction, the decision to deliver incorporates clinical judgment. Maternal health is balanced against estimated fetal weight, gestational age, and chance of neonatal survival.

Intrapartum Considerations

For women with chronic hypertension, obstetrical factors dictate delivery route. Magnesium sulfate is not given unless there is superimposed severe preeclampsia. Epidural analgesia is ideal but does not substantively lower blood pressure. A trial of labor induction is preferable, and many of these women will deliver vaginally (Alexander, 1999; Atkinson, 1995). Similarly, for the growth-restricted fetus, delivery route is based on obstetrical factors. However, many fetuses with growth restriction exhibit nonreassuring fetal heart rate patterns and require cesarean delivery (McKinney, 2016).

For women with superimposed preeclampsia, intrapartum management mirrors that described in Chapter 41 (p. 719). These women may have a longer first-stage labor (Bregand-White, 2017). Epidural analgesia for labor and delivery is optimal, but it is not provided with the intent to treat hypertension (Lucas, 2001). That said, women with superimposed preeclampsia are more sensitive to the acute hypotensive effects of epidural analgesia (Vricella, 2012). Magnesium sulfate neuroprophylaxis is initiated for eclampsia prevention. Severe hypertension—diastolic blood pressure ≥110 mm Hg or systolic pressure ≥160 mm Hg—is treated with either intravenous hydralazine, intravenous labetalol, or oral nifedipine. Some prefer to treat women when the diastolic pressure reaches 100 to 105 mm Hg. Vigil-De Gracia and coworkers (2006) randomly assigned 200 gravidas to receive intravenous hydralazine or labetalol to acutely lower severe high blood pressure. Outcomes were similar except for significantly higher rates of maternal palpitations and tachycardia with hydralazine and significantly greater rates of neonatal hypotension and bradycardia with labetalol.

Postpartum Care

Prevention and management of adverse postpartum complications is similar in women with severe chronic hypertension and in those with severe preeclampsia–eclampsia. For persistent severe hypertension, consideration is given to causes such as pheochromocytoma or Cushing disease (Sibai, 2012). In women with chronic end-organ damage, certain complications

are more common. These include cerebral or pulmonary edema, heart failure, renal dysfunction, or cerebral hemorrhage, especially within the first 48 hours after delivery. These frequently are preceded by sudden elevations of mean arterial blood pressure, especially of the systolic component (Cunningham, 2000, 2005; Martin, 2005).

Following delivery, as maternal peripheral resistance rises, left ventricular workload also grows. This elevation is further aggravated by appreciable and pathological amounts of interstitial fluid that are mobilized to be excreted as endothelial disruption from preeclampsia resolves. In these women, sudden hypertension—either moderate or severe—may exacerbate diastolic dysfunction, cause systolic dysfunction, and lead to pulmonary edema (Cunningham, 1986; Gandhi, 2001). Prompt hypertension control, along with furosemide-evoked diuresis, usually quickly resolves pulmonary edema.

The antihypertensive regimen given antepartum may be continued in the puerperium. In untreated women, labetalol or nifedipine can also be used for persistent hypertension (Sharma, 2017). It also is possible in many women to forestall postpartum hypertension by administering intravenous or oral furosemide to augment normal postpartum diuresis. In one study, 20 mg oral furosemide given daily for 5 days to postpartum women with severe preeclampsia aided blood pressure control (Ascarelli, 2005). A recent randomized trial showed that daily furosemide decreased the need for antihypertensive therapy at hospital discharge (Perdigao, 2020). Daily weights are helpful in this regard. On average, a woman should weigh 15 pounds less immediately after delivery. Excessive extracellular fluid can then be estimated by comparing her last prenatal weight plus 15 pounds against the puerpera's current weight.

Some evidence supports that *chronic* ingestion of NSAIDs in the puerperium elevates blood pressure in women with severe preeclampsia (Vigil-De Gracia, 2017). This may not be problematic if these drugs are given only intermittently and as needed (Blue, 2018). Postpartum admission rates for severe hypertension approximate 1.5 percent (Chornock, 2021).

Discussion of postpartum contraception may begin prior to delivery. As described in Chapter 38 (p. 672), certain methods are less ideal or contraindicated for some women with chronic hypertension. Moreover, for puerpera at highest risk for future pregnancy complications, the Society for Maternal–Fetal Medicine (2019) encourages immediate postpartum long-acting reversible contraceptive (LARC) insertion for suitable candidates.

Long-Term Prognosis

Women with chronic hypertension are at high risk for lifetime cardiovascular complications, especially when accompanied by diabetes, obesity, and the metabolic syndrome. Persistent hypertension 3 years after severe preeclampsia was associated with a thicker left-ventricular septum compared with women who became normotensive (Vaught, 2019). The lifetime cardiovascular morbidity and mortality risks associated with hypertensive disorders of pregnancy are discussed in Chapter 41 (p. 726) (Wu, 2021).

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CHAPTER 54

Pulmonary Disorders

During pregnancy, pulmonary disorders are frequently encountered. In one study, asthma and community-acquired pneumonia accounted for almost 10 percent of nonobstetrical antepartum hospitalizations (Gazmararian, 2002). Pregnant women, especially those in the last trimester, tolerate lung disease poorly because of important pregnancy-induced changes in ventilatory physiology (Han, 2018). Lung volumes and capacities are significantly altered. In turn, these shift gas concentrations and acid-base values in blood. These important and sometimes marked changes are reviewed in Chapter 4 (p. 66), and normal values for blood gas can be found in the Appendix (p. 1232). Some of these can be summarized as follows:

1. *Vital capacity* and *inspiratory capacity* increase by approximately 20 percent by late pregnancy.
2. *Expiratory reserve volume* declines from 1300 mL to approximately 1100 mL.
3. Progesterone-driven respiratory stimulation raises *tidal volume* approximately 40 percent.
4. *Minute ventilation* increases 30 to 40 percent due to higher tidal volume. As a result, arterial partial pressure of oxygen (Pao_2) rises from 100 to 105 mm Hg.
5. Expanded metabolic demands cause a 30-percent increase in *carbon dioxide (CO_2) production*. But, because of its concomitantly greater diffusion capacity and hyperventilation, the $Paco_2$ is reduced from 40 to 32 mm Hg.
6. *Residual volume* diminishes approximately 20 percent from 1500 mL to 1200 mL.
7. An expanding uterus and higher intraabdominal pressure lower *chest wall compliance* by one third. This causes a 10- to 25-percent reduction in *functional residual capacity*—the sum of expiratory reserve and residual volumes.

Beginning at 14 to 16 weeks' gestation *forced vital capacity* and *peak expiratory flow* progressively increase (Grindheim, 2012). The result of these pregnancy-induced changes is substantively greater ventilation due to deeper but not more frequent breathing. This is thought to be stimulated by basal oxygen consumption, which incrementally rises from 20 to 40 mL/min in the second half of pregnancy.

ASTHMA

Pathophysiology

Asthma is a chronic inflammatory airway syndrome with a major hereditary component. Polymorphism genes on chromosome 5q that include cytokine gene clusters, β-adrenergic and glucocorticoid receptor genes, and the T-cell antigen receptor gene are associated with greater airway responsiveness and persistent subacute inflammation (Barnes, 2018). Racial differences are seen, and morbidity rates are disproportionately higher in black compared with white women (Kodadhala,

2018). Asthma is etiologically and clinically heterogeneous, and an environmental allergic stimulant such as influenza or cigarette smoke serves as a promoter for susceptible individuals.

The hallmarks of asthma are reversible airway obstruction from bronchial smooth muscle contraction, vascular congestion, tenacious mucus, and mucosal edema. Stimuli cause acute infiltration of eosinophils, mast cells, and T lymphocytes. Inflammatory mediators produced by these and other cells include histamine, leukotrienes, prostaglandins, cytokines, immunoglobulin E (IgE), and many others. F-series prostaglandins and ergonovine exacerbate asthma, and these commonly used uterotonics are avoided if possible.

Clinical Course

Asthma manifestations range from mild wheezing to severe bronchoconstriction, which obstructs airways and decreases airflow. This lowers the forced expiratory volume in 1 second/forced vital capacity (FEV_1/FVC) ratio and the peak expiratory flow rate (PEFR). The work of breathing progressively increases, and patients note chest tightness, wheezing, or breathlessness. Subsequent worsening of oxygenation primarily reflects ventilation–perfusion mismatching. This results from an uneven distribution of airway narrowing.

Varied manifestations of asthma have led to a classification system that considers severity, onset, and duration of symptoms (Table 54-1). With persistent or worsening bronchial obstruction, clinical stages progress as shown in Figure 54-1. Hypoxia initially is mitigated by hyperventilation, which maintains the Pao_2 within a normal range but lowers $Paco_2$, creating respiratory alkalosis. As airway narrowing worsens, the degree of ventilation–perfusion defects is accentuated, and arterial hypoxemia ensues. With severe obstruction, fatigue causes early CO_2 retention and impairs ventilation. Because of hyperventilation, this may only be seen initially as the $Paco_2$ returning to the normal range. With continuing obstruction, respiratory failure follows.

These changes are generally reversible and well tolerated by the healthy nonpregnant individual. However, even early asthma stages may be dangerous for the pregnant woman and her fetus. This is because diminished functional residual capacity and greater pulmonary shunting render the gravida more susceptible to hypoxia and hypoxemia.

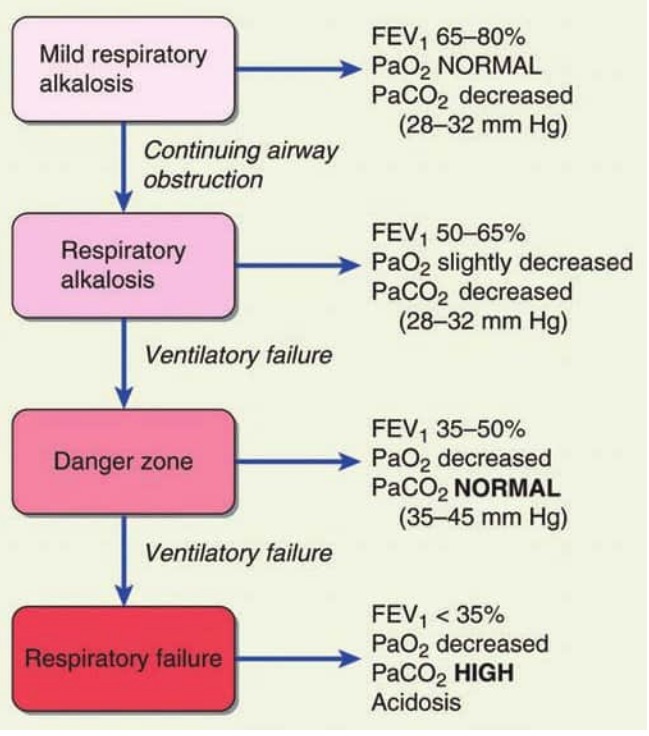

FIGURE 54-1 Clinical stages of asthma. FEV_1 = forced expiratory volume in 1 second.

Effects of Pregnancy on Asthma

Chronic asthma or an acute exacerbation affects up to 8 percent of gravidas (Baghlaf, 2019; Flores, 2020; Mazurek, 2018). Pulmonary function changes in pregnancy are more pronounced in asthmatics compared with healthy women (Zairina, 2015). Despite this, pregnancy has an unpredictable effect on underlying asthma. In a review of more than

TABLE 54-1. Classification of Asthma Severity

	Severity			
		Persistent		
Component	Intermittent	Mild	Moderate	Severe
Symptoms	≤2 d/wk	>2 d/wk, not daily	Daily	Throughout day
Nocturnal awakenings	≤2×/mo	3–4×/mo	>1×/wk, not nightly	Often 7×/wk
Short-acting β-agonist for symptoms	≤2 d/wk	≥2 d/wk, but not >1×/d	Daily	Several times daily
Interference with normal activity	None	Minor limitation	Some limitation	Extremely limited
Lung function	Normal between exacerbations			
FEV_1	>80% predicted	≥80% predicted	60–80% predicted	<60% predicted
FEV_1/FVC	Normal	Normal	Reduced 5%	Reduced >5%

FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity.
From National Heart, Lung, and Blood Institute, 2007.

2000 gravidas, approximately a third each improved, remained unchanged, or clearly worsened (Gluck, 2006). Exacerbations are more common with severe disease (Ali, 2013). In a study by Schatz and associates (2003), baseline severity correlated with asthma morbidity during pregnancy. With mild disease, 13 percent of women had an exacerbation and 2.3 percent required admission; with moderate disease, these numbers were 26 and 7 percent; and for severe asthma, 52 and 27 percent. Others have reported similar findings (Charlton, 2013; Hendler, 2006).

Intrapartum exacerbation rates are controversial. In one study, 20 percent of women with mild or moderate asthma had an intrapartum exacerbation (Schatz, 2003). Mabie and coworkers (1992) reported an 18-fold greater exacerbation risk following cesarean versus vaginal delivery. Conversely, Wendel and colleagues (1996) reported exacerbations at the time of delivery in only 1 percent of asthmatics.

Pregnancy Outcome

Asthma remains a potential risk factor for worse pregnancy outcomes despite continued improvements in treatment. Data from two large studies are shown in Table 54-2. The incidences of small-for-gestational-age neonates and perinatal mortality also are significantly greater in women with asthma (Kemppainen, 2018). However, these findings are not consistent among all studies. A study of approximately 3000 pregnancies complicated by asthma showed higher rates of maternal pneumonia and cesarean delivery but not of perinatal mortality (Shaked, 2019). In a European report of 37,585 pregnancies of women with asthma, the risks for most obstetrical complications were not increased (Tata, 2007). Blais and associates (2013) noted that the incidence of spontaneous abortion may be slightly greater in women with asthma.

TABLE 54-2. Maternal and Perinatal Outcomes in Women with Asthma

Asthmatics[a]	Odds Ratio (95% CI)
Maternal outcomes	
Hemorrhage	1.09 (1.03–1.16)
Gestational diabetes	1.10 (1.03–1.19)
Chorioamnionitis	1.12 (1.09–1.15)
Preeclampsia	1.14 (1.06–1.22)
Placental abruption	1.22 (1.09–1.36)
Placenta previa	1.30 (1.08–1.56)
ICU admission	1.34 (1.04–1.72)
Pulmonary embolism	1.71 (1.05–2.79)
Perinatal outcomes	
SGA neonates	1.10 (1.05–1.16)
Preterm delivery	1.17 (1.12–1.23)
Preterm PROM	1.18 (1.07–1.30)
Anomalies	1.48 (1.04–2.09)

[a]Compared with outcomes in 206,468 nonasthmatic women.
CI = confidence interval; ICU = intensive care unit; PROM = premature rupture of membranes; SGA = small for gestational age.
Data from Baghlaf, 2019; Mendola, 2013, 2014.

Some evidence suggests that severe disease, poor control, or both is linked to higher morbidity rates. In a study by the Maternal-Fetal Medicine Units (MFMU) Network, delivery before 37 weeks' gestation was not more frequent in pregnancies of women with asthma compared with controls (Dombrowski, 2004). However, for women with severe asthma, the rate was approximately twofold higher. The MFMU Network study suggests also a direct relationship of baseline pregnancy FEV_1 with birthweight and an inverse relationship with rates of gestational hypertension and preterm delivery (Schatz, 2006). Kemppainen and coworkers (2018) found that women requiring treatment for asthma during pregnancy are at greater risk for adverse perinatal outcomes.

Maternal morbidity rises markedly with status asthmaticus and includes life-threatening complications such as muscle fatigue with respiratory arrest, pneumothorax, pneumomediastinum, acute cor pulmonale, and cardiac arrhythmias. Not surprisingly, maternal and perinatal mortality rates rise substantively when mechanical ventilation is required.

Fetal Effects

Animal and human studies suggest that development of maternal respiratory alkalosis leads to fetal hypoxemia well before the alkalosis compromises maternal oxygenation (Rolston, 1974). Theories hypothesize that the fetus is jeopardized by decreased uterine blood flow, reduced maternal venous return, and an alkaline-induced leftward shift of the oxyhemoglobin dissociation curve (Chap. 50, p. 886). The fetal response to maternal hypoxemia is lower umbilical blood flow, higher systemic and pulmonary vascular resistance, and decreased cardiac output. Several studies cited above confirm that fetal-growth restriction rates rise with asthma severity. Because the fetus may be seriously compromised, aggressive management is necessary. Monitoring the fetal response is, in effect, an indicator of maternal status. A return of moderate variability or accelerations in the fetal heart rate is an indicator of improving maternal oxygen status.

Possible teratogenic or adverse fetal effects of drugs given to control asthma are a concern. Several reports show a slightly greater risk for abnormalities such as cleft lip and palate and autism spectrum disorders, but further verification is necessary (Eltonsy, 2016; Gidaya, 2016; Murphy, 2013b; Wang, 2014). It is worrisome that up to half of women discontinue essential treatment between 5- and 13-weeks' gestation (Enriquez, 2006).

■ Clinical Evaluation

The subjective severity of asthma frequently does not correlate with objective measures of airway function or ventilation. Clinical examination also can be an inaccurate predictor, but useful signs include labored breathing, tachycardia, pulsus paradoxus, prolonged expiration, and use of accessory muscles. Signs of a potentially fatal exacerbation include central cyanosis and altered consciousness.

Pulmonary function testing should be routine in the management of asthma. Sequential measurement of the FEV_1 or of the PEFR is the best measure of severity (see Table 54-1).

An FEV_1 <1 L, or <20 percent of predicted value, correlates with severe disease defined by hypoxia, poor response to therapy, and a high relapse rate. The PEFR correlates well with the FEV_1, and it can be measured reliably with inexpensive portable meters. It is advantageous for each woman to determine her own baseline when asymptomatic to compare with values when symptomatic.

Management of Chronic Asthma

Asthma management by an experienced team produces better outcomes (Lim, 2014; Wendel, 1996). Management guidelines include:

1. Patient education about general asthma management and its effect on pregnancy (Bonham, 2018; Robijn, 2019).
2. Avoidance or control of precipitating environmental factors. Viral infections that include the common cold are frequent triggers (Ali, 2013; Murphy, 2013a). Influenza and pneumococcal vaccination is encouraged.
3. Objective assessment of pulmonary function with PEFR or FEV_1 and of fetal status with serial growth ultrasound and antepartum testing if indicated (Chap. 20, p. 392).
4. Pharmacological therapy with appropriate combinations and doses to provide baseline control and treat exacerbations. Periodic medication reviews are helpful to avoid noncompliance (Robijn, 2019).
5. Treatment of related disorders including smoking, depression, rhinitis, and gastroesophageal reflux (Bonham, 2018).

In general, women with moderate to severe asthma ideally measure and record either their FEV_1 or PEFR twice daily. The FEV_1 ideally is >80 percent of predicted. For PEFR, predicted values range from 380 to 550 L/min. Each woman has her own baseline value, and therapeutic adjustments can be made using this (American College of Obstetricians and Gynecologists, 2019). Another described method is a management algorithm using fractional exhaled nitric oxide (FeNO) as a noninvasive marker of airway inflammation (Powell, 2011). Asthma exacerbations were reduced by 50 percent with this approach (Clifton, 2019).

Agents for Chronic Treatment

Selection depends on disease severity. No therapeutic regimen for management of asthma in pregnancy is universally accepted (Bain, 2014). β-agonists help abate bronchospasm, and corticosteroids treat inflammation. Stepwise regimens recommended for outpatient management are listed in Figure 54-2.

For mild intermittent asthma, short-acting inhaled β-agonists as needed are usually sufficient. Table 54-3 lists suitable agents.

For persistent asthma, most inhaled corticosteroids (ICS) are administered twice daily. The goal is to reduce β-agonists use for symptomatic relief. Initial low-dose ICS may be augmented to medium-ranging dosing if the moderate or severe symptoms shown in Table 54-1 persist. A case-control study from Canada with a cohort of more than 15,600 nonpregnant women with asthma showed that ICS reduced hospitalizations by 80 percent (Blais, 1998). At Parkland Hospital, Wendel and colleagues (1996) achieved a 55-percent reduction in readmissions when severe exacerbations were treated with ICS. In one study of nonpregnant subjects with mild asthma, as-needed budesonide-formoterol, which is an aerosol ICS and β-agonist combination, was superior to albuterol alone to prevent exacerbations (Beasley, 2019). This is incorporated in new guidelines (Cloutier, 2020).

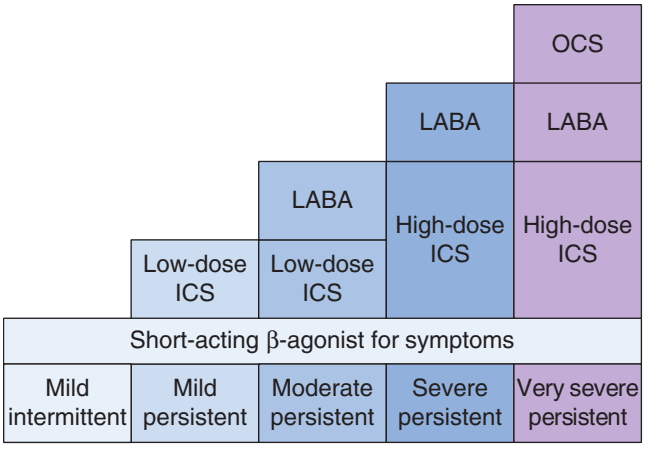

FIGURE 54-2 Stepwise approach to asthma treatment. ICS = inhaled corticosteroids; LABA = long-acting β-agonists; OCS = oral corticosteroids. (Barnes, 2018; National Heart, Lung, and Blood Institute, 2007.)

Theophylline has been used less frequently since ICS became available. Minimal benefit is gained with these compounds, and they have a high rate of side effects. However, some theophylline derivatives are considered useful for oral maintenance therapy if the initial response to ICS and β-agonists is not optimal (Barnes, 2018).

Of other agents, antileukotrienes inhibit leukotriene synthesis and include zileuton, zafirlukast, and montelukast. These drugs are given orally or by inhalation for prevention, but they are ineffective for acute disease (Barnes, 2018). For maintenance, they are used in conjunction with ICS to allow minimal corticosteroid dosing. Approximately half of individuals with asthma will improve with these drugs. However, they are less effective than ICS, and experience with their use in pregnancy is limited (Fanta, 2009). Last, cromones, which are mast cell degranulation inhibitors, are ineffective for acute asthma. They are used primarily to treat childhood asthma.

Vitamin D

Epidemiological data support an association between vitamin D insufficiency and asthma severity. The proposed mechanism is modulation of immunological pathways that diminish inflammatory responses (Pfeffer, 2018). Jensen and coworkers (2019) reported that pregnant women with asthma have low vitamin D levels. One systematic review suggested that increasing maternal vitamin D intake might prevent childhood asthma (Shi, 2021). Adams and colleagues (2021) reported an association between decreased maternal vitamin D levels and childhood wheezing. However, a randomized trial with antenatal vitamin D supplementation showed no lowering of childhood asthma risks at 6 years of age (Brustad, 2019).

TABLE 54-3. Chronic Asthma Treatment

Agent[a]	Brand Name	Available Doses per Puff	Dosage		
SABA Inhaler					
Albuterol	Proventil HFA, Ventolin HFA, ProAir HFA	90 μg	1-2 puffs every 4–6 hr		
Levalbuterol	Xopenex HFA	45 μg	1–2 puffs every 4–6 hr		
ICS Inhaler[b]			**Daily Corticosteroid Dosing**		
			Low	**Medium**	**High**
Beclomethasone HFA	QVAR	40, 80 μg	80–240 μg	>240–480 μg	>480 μg
Budesonide DPI	Pulmicort	90, 180, 200 μg	180–600 μg	>600–1200 μg	>1200 μg
Ciclesonide HFA	Alvesco	80, 160 μg	80–160 μg	>160–320 μg	>320 μg
Flunisolide HFA	Aerospan	80 μg	320 μg	>320–640 μg	>640 μg
Fluticasone furoate DPI	Arnuity Ellipta	100, 200 μg daily	100 μg	NA	200 μg
Fluticasone propionate DPI	Flovent Diskus	50, 100, 250 μg	100–300 μg	>300–500 μg	>500 μg
Fluticasone propionate HFA	Flovent HFA	44, 110, 220 μg	88–264 μg	>264–440 μg	>440 μg
Mometasone DPI	Asmanex	110, 220 μg	110–220 μg	330–440 μg	>440 μg
Mometasone HFA	Asmanex HFA	100, 200 μg	200 μg	400 μg	>400 μg
LABA /ICS Inhaler[b]					
Budesonide/formoterol	Symbicort	80/4.5, 160/4.5 μg	320/18 μg	>320/18–640/18 μg	>640/18 μg
Fluticasone/salmeterol DPI	Advair Diskus	100/50, 250/50, 500/50 μg	100/50–350/100 μg	350/100–500/100 μg	>500/50 μg
Fluticasone/salmeterol HFA	Advair HFA	45/21, 115/21, 230/21 μg	100/50–250/50 μg	300/50–500/50 μg	>500/50 μg
Fluticasone/salmeterol DPI	AirDuo Respiclick	55/14, 113/14, 232/14 μg	110/28 μg	226/28 μg	464/28 μg
Fluticasone/vilanterol	Breo Ellipta	100/25, 200/25 μg daily	100/25 μg	NA	200/25 μg
Mometasone/formoterol	Dulera	110/5, 200/5 μg	NA	400/20 μg	800/20 μg

[a]Agents in each group are arranged alphabetically.
[b]Twice daily dosing unless otherwise stated.
DPI = dry powder inhaler; HFA = hydrofluoroalkane (an aerosol propellant); hr = hour; ICS = inhaled corticosteroid; LABA = long-acting beta agonist; NA = not applicable; SABA = short-acting beta agonist.
American Academy of Allergy Asthma & Immunology, 2020; National Heart, Lung, and Blood Institute, 2007; Therapeutic Research Center, 2017.

Management of Acute Asthma

Early Treatment

Treatment of acute asthma during pregnancy is similar to that for the nonpregnant patient (Figure 54-3). Importantly, the threshold for hospitalization is significantly lower. Intravenous (IV) hydration may help clear pulmonary secretions, and supplemental oxygen is given by mask. The therapeutic aim is to maintain the Pao_2 >60 mm Hg, and preferably normal, along with 90- to 95-percent oxygen saturation. Baseline pulmonary function testing includes FEV_1 or PEFR. Continuous pulse oximetry and electronic fetal monitoring, depending on gestational age, may provide useful information. Arterial blood gas analysis aides in assessing the severity of an acute attack by providing objective assessment of maternal oxygenation, ventilation, and acid-base status (see Fig. 54-1). However, Wendel and associates (1996) found that *routine* arterial blood gas analysis did not help to manage most pregnant women who required admission for asthma control. If used, the results must be interpreted in relation to normal values for pregnancy. For example, a $Paco_2$ >35 mm Hg with a pH <7.35 is consistent with hyperventilation and CO_2 retention in a pregnant woman. Antibiotics are not given unless pneumonitis is comorbid (p. 962) (Terraneo, 2014).

First-line therapy for acute asthma includes a short-acting β-adrenergic agonist, such as terbutaline, albuterol, isoetharine, epinephrine, isoproterenol, or metaproterenol, which are given subcutaneously, taken orally, or inhaled. In severely ill women, these drugs can be given intravenously (Barnes, 2018).

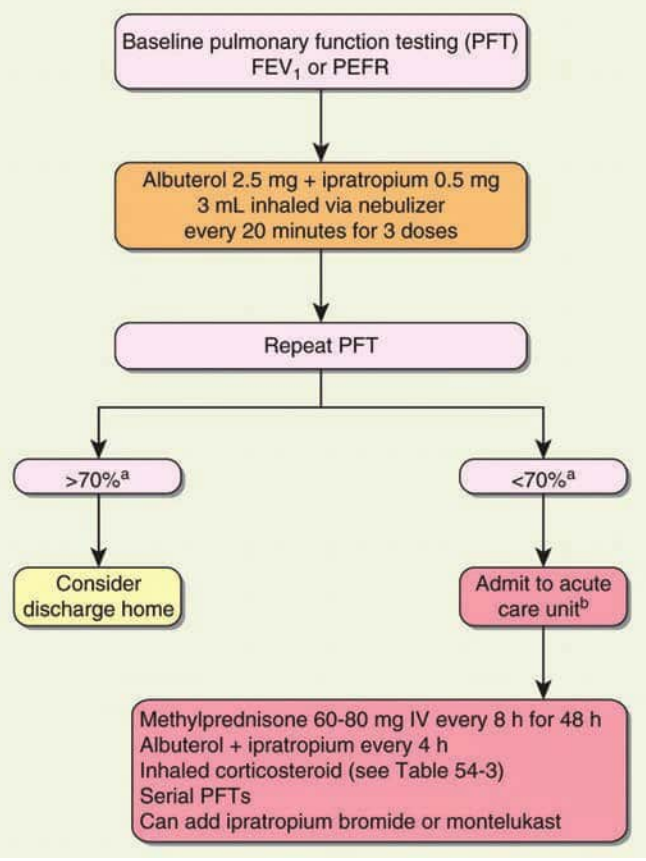

FIGURE 54-3 Protocol for management of acute asthma at Parkland Hospital. [a]Of predicted value. [b]Labor & delivery unit, recovery area, or intensive care unit. FEV_1 = forced expiratory volume at 1 second; PEFR = peak expiratory flow rate (liters per minute).

Systemic corticosteroids are given early to all patients with severe acute asthma. One regimen is oral prednisone or prednisolone or IV methylprednisolone in a dose of 30 to 45 mg daily for 5 to 10 days without tapering (Barnes, 2018). At Parkland Hospital, we use a higher daily IV dose (see Figure 54-3). Because their onset of action is several hours, corticosteroids are given initially along with β-agonists for severe acute asthma. If the response is unsatisfactory, a nebulized anticholinergic drug may be added. These drugs act to relax smooth muscle and diminish mucus. By nebulizer, a 0.5-mg dose of ipratropium bromide is provided every 20 minutes as needed for three consecutive doses. Additional doses every 6 to 8 hours can be used (National Heart, Lung, and Blood Institute, 2007). Also, for severe exacerbations, IV magnesium sulfate or theophylline may prove efficacious.

Further management depends on the severity and response to therapy. If initial therapy with a β-agonist is associated with FEV_1 or PEFR improvement to a level >70 percent of baseline, discharge can be considered. For the woman with obvious respiratory distress or with an FEV_1 or PEFR <70 percent of predicted after three doses of a β-agonist, admission is usually advisable (Lazarus, 2010). Intensive therapy is continued with short-acting inhaled β-agonists, IV corticosteroids, inhaled anticholinergics, and close observation for worsening respiratory distress or fatigue in breathing (Racusin, 2013). The woman is cared for in the delivery unit or an intermediate or intensive care unit (ICU) (Dombrowski, 2006; Zeeman, 2003).

Status Asthmaticus and Respiratory Failure

Severe asthma of any type not responding after 30 to 60 minutes of intensive therapy is termed *status asthmaticus*. Generally, management of nonpregnant patients with status asthmaticus in an intensive care setting results in a good outcome. In pregnant women, consideration should be given to early intubation when maternal respiratory status worsens despite aggressive treatment (see Fig. 54-1). Fatigue, CO_2 retention, and hypoxemia are indications for mechanical ventilation (Chan, 2015). In refractory cases, venovenous extracorporeal membrane oxygenation (ECMO) has been successfully used for status asthmaticus during pregnancy (Clifford, 2018; Steinack, 2017).

■ Labor and Delivery

For the laboring patient who has symptomatic asthma, the PEFR or FEV_1 is determined on admission, and serial measurements are taken. Maintenance medications are continued through delivery, and stress-dose corticosteroids are not necessary (Sylvester-Armstrong, 2020).

Oxytocin or prostaglandins E_1 or E_2 can be used for cervical ripening and induction. A non-histamine-releasing narcotic such as fentanyl may be preferable to meperidine for labor, and epidural analgesia is ideal. For surgical delivery, conduction analgesia is preferred because tracheal intubation can trigger severe bronchospasm. Postpartum hemorrhage is treated with oxytocin or prostaglandin E_1 (misoprostol) or E_2 (dinoprostone [Prostin]). Prostaglandin $F_{2\alpha}$ (Hemabate) is contraindicated because it may cause significant bronchospasm.

ACUTE BRONCHITIS

Large airway infection is manifest by cough without pneumonitis. It is common in adults, especially in winter months. Infections are usually caused by viruses, and of these, influenza A and B, parainfluenza, respiratory syncytial, coronavirus, adenovirus, and rhinovirus are frequent isolates (Irwin, 2018). Bacterial agents causing community-acquired pneumonia are rarely implicated. The cough of acute bronchitis persists for 10 to 20 days and occasionally lasts for a month or longer. Evidence supporting the benefits of antimicrobial therapy is limited (Smith, 2017). As supportive care, cough suppressants containing dextromethorphan and expectorants with guaifenesin appear safe in pregnancy (Briggs, 2022).

PNEUMONIA

Infection of the lungs is a leading cause of death in the United States (Heron, 2017). Current classification includes *community-acquired pneumonia (CAP),* which is typically encountered in healthy young women, including gravidas. Patients in outpatient care facilities develop an infection that more closely resembles *hospital-acquired pneumonia (HAP)* (Mandell, 2018).

In most cases of CAP, the offending pathogen is not identified. In a study from the Centers for Disease Control and Prevention (CDC), pathogens were identified in only 38 percent of nearly 2500 adults with pneumonia (Jain, 2015). These

included viruses in 23 percent, bacteria in 11 percent, both in 3 percent, and fungi or protozoa in 1 percent. These percentages changed in 2020 due to the COVID-19 pandemic (p. 964). Half of bacterial isolates were *Streptococcus pneumoniae*.

Pneumonia in pregnant women is relatively common (Brito, 2011; Sheffield, 2009). Gazmararian and coworkers (2002) reported that pneumonia accounts for 4.2 percent of antepartum admissions for nonobstetrical complications. Pneumonia is also a frequent indication for postpartum readmission (Belfort, 2010). Admission rates for respiratory illnesses during influenza season are higher than rates in the remaining months.

Regardless of etiology, mortality from pneumonia is infrequent in young women. However, during pregnancy, severe pneumonitis with appreciable loss of ventilatory capacity is less well tolerated (Callaghan, 2015; Rogers, 2010). Hypoxemia and acidosis are also poorly accommodated by the fetus, and they may stimulate preterm labor after midpregnancy. Because many cases of pneumonia follow viral upper respiratory illnesses, worsening or persistence of symptoms may represent developing pneumonia. Any gravida suspected of having pneumonia should undergo chest radiography.

Bacterial Pneumonia

Many bacteria that cause CAP, such as *S pneumoniae*, are part of the normal flora. Some factors that perturb the symbiotic relationship between colonizing bacteria and mucosal phagocytic defenses include acquisition of a virulent strain or bacterial infections following a viral infection. Cigarette smoking and chronic bronchitis favor colonization with *S pneumoniae*, *Haemophilus influenzae*, and *Legionella* species. Other risk factors include asthma, binge drinking, and human immunodeficiency virus (HIV) infection (Mandell, 2018).

Incidence and Causes

Pregnancy itself does not appear to predispose to pneumonia. Jin and associates (2003) reported the antepartum hospitalization rate for pneumonia to be 1.5 per 1000 deliveries—almost identical to the rate of 1.47 per 1000 for nonpregnant women. Similarly, among 75,000 pregnancies at Parkland Hospital, the incidence was 1.5 per 1000 (Yost, 2000). As discussed, at least half are caused by viruses—influenza A and B, metapneumovirus, adenovirus, and respiratory syncytial virus (Mandell, 2018). A fourth are bacterial, and *S pneumoniae* causes half of these. Community-acquired methicillin-resistant *Staphylococcus aureus* (CA-MRSA) has emerged as a common pathogen that may cause necrotizing pneumonia (Moran, 2013). Occasionally, Legionnaires disease is encountered (Close, 2016).

Diagnosis

Typical symptoms of pneumonia include cough, dyspnea, sputum production, and pleuritic chest pain. Mild upper respiratory symptoms and malaise precede these symptoms, and mild leukocytosis is usually present. Chest radiography is essential for diagnosis (Fig. 54-4). Radiographical findings do not accurately predict the etiology, and as discussed, the responsible pathogen is often not identified. Tests to identify a specific agent are optional (Mandell, 2018). Sputum cultures, polymerase chain reaction (PCR) tests, serological testing, cold agglutinin identification, and tests for bacterial antigens are not routinely recommended. Exceptions are rapid PCR testing of nasal swab samples for influenza A and B and for COVID-19. An assay to screen for all three is available. Determination of serum procalcitonin levels did not improve diagnostic efficacy (Huang, 2018).

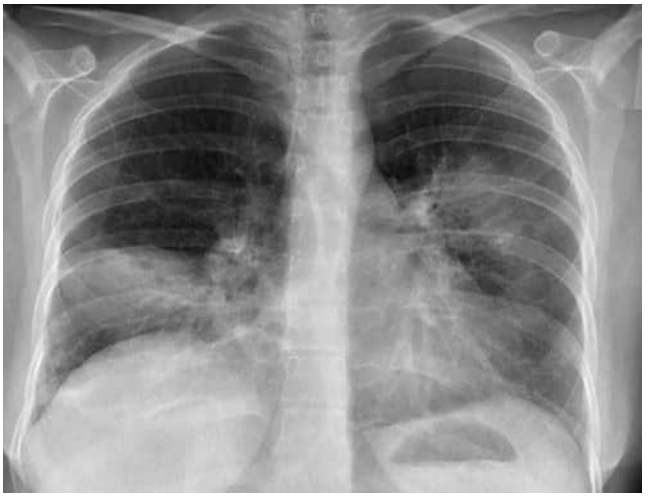

FIGURE 54-4 Chest radiograph in a pregnant woman with right middle lobe and left upper lobe pneumonia. Rounded right middle lobe and left apical infiltrates are consistent with the diagnosis.

Management

Many healthy young adults can be safely treated as outpatients, and the pneumonia severity index (PSI) and the CURB-65 scoring system are guides to admission (Mandell, 2018). Neither has been studied in pregnancy, and at Parkland Hospital, we hospitalize all gravidas with radiographically proven pneumonia. Outpatient therapy or 23-hour observation with optimal follow-up are reasonable options. Table 54-4 displays risk factors that should prompt consideration for hospitalization (Mandel, 2018).

With severe disease, admission to an ICU or intermediate care unit is advisable. Approximately 20 percent of pregnant women with pneumonia admitted to Parkland Hospital require this level of care (Zeeman, 2003). Severe pneumonia is a relatively common cause of acute respiratory distress syndrome (ARDS) during pregnancy, and mechanical ventilation may become necessary (Chap. 50, p. 885). In a review of 51 gravidas who required mechanical ventilation, 12 percent had pneumonia (Jenkins, 2003). Still, their mortality rate is lower than that for other causes of ARDS (Rush, 2017).

TABLE 54-4. Risk Factors for Early Deterioration in Community-Acquired Pneumonia

Respiratory rate ≥30/min
Arterial O_2 saturation <90%
Hypothermia: core temperature <36°C
Hypotension requiring aggressive fluid resuscitation
Multilobular infiltrates
Leukopenia: <4000/μL
Thrombocytopenia: <100,000/μL
Confusion/disorientation

TABLE 54-5. Empirical Inpatient Antimicrobial Treatment for Community-Acquired Pneumonia in Pregnancy[a]

Uncomplicated, otherwise healthy[b,c]

Macrolides[c]: clarithromycin, 500 mg twice daily or azithromycin, 500 mg daily. Both have IV and oral forms

Plus

Oseltamivir, 75 mg orally twice daily for 5 d for suspected influenza A infection

Severe pneumonia[d]

Respiratory fluoroquinolones: moxifloxacin, 400 mg daily or levofloxacin, 750 mg daily. Both have IV and oral forms

or

β-lactams: ampicillin/sulbactam, 3 g IV every 6 hr; ceftriaxone, 1–2 g daily; ceftaroline, 600 mg IV every 12 hr; or cefotaxime, 1–2 g every 8 hr. The β-lactam should be coupled with a macrolide above

Plus

Oseltamivir, as above, for suspected influenza A infection

[a]Antibiotics are discontinued after 5 to 7 days in those afebrile for 48 to 72 hours.
[b]Use as inpatient or outpatient regimen.
[c]Doxycycline may be given instead if postpartum.
[d]See Table 54-4 for criteria.
ER = extended release; IV = intravenous.

Initial antimicrobial and antiviral treatment is empirical (Mandell, 2018). In most otherwise healthy pregnant women, bacterial pneumonias are caused by pneumococci, *Mycoplasma*, or *Chlamydophila*. Monotherapy initially is with a macrolide (Table 54-5). Yost and colleagues (2000) reported that erythromycin monotherapy, given intravenously and then orally, was effective in all but one of 99 pregnant women with uncomplicated pneumonia. During influenza season, we routinely administer oseltamivir (Tamiflu) along with empirical therapy for bacterial pneumonia.

For women with more severe disease according to criteria in Table 54-4, Mandell and Wunderink (2018) recommend: (1) a respiratory fluoroquinolone or (2) a macrolide plus a preferred β-lactam (see Table 54-5). Resistance of pneumococcal isolates to macrolides will favor fluoroquinolone regimens. The teratogenicity risk of fluoroquinolones is low, and these should be given if indicated (Briggs, 2022). If MRSA is suspected, IV vancomycin, 15 mg/kg every 12 hours, or linezolid, 600 mg every 12 hours, is added (Metlay, 2019).

Clinical improvement is usually evident in 48 to 72 hours with resolution of fever in 2 to 4 days. With improvement, patients can be transitioned to oral forms. Treatment of uncomplicated pneumonia is recommended for 5 to 7 days total (Musher, 2014). Patients should be afebrile for 48 to 72 hours and demonstrate signs of clinical stability before therapy is discontinued. Radiographic abnormalities may take up to 6 weeks to completely resolve (Torres, 2008).

Worsening disease is a poor prognostic feature, and serial radiography is recommended if fever persists. Even with improvement, however, approximately 20 percent of women develop a pleural effusion. Treatment failure may occur in up to 15 percent of cases, and a wider antimicrobial regimen and more extensive diagnostic testing is warranted. For example, in some cases, computed tomography of the chest may be necessary to identify empyema that requires drainage.

Pregnancy Outcome

Maternal and perinatal morbidity and mortality rates from pneumonia remain formidable. In five studies with a total of 632 women published after 1990, almost 7 percent required intubation and mechanical ventilation, and the maternal mortality rate was 0.8 percent.

In up to a third of cases of acute lung infection, prematurely ruptured membranes and preterm delivery are frequent complications (Getahun, 2007; Shariatzadeh, 2006). Likely related to these, older studies report a twofold increase in rates of low-birthweight neonates (Sheffield, 2009). In one population-based study from Taiwan of nearly 219,000 births, incidences of preterm and growth-restricted newborns and of preeclampsia and cesarean delivery were significantly higher (Chen, 2012).

Prevention

Two pneumococcal vaccines are available—a 23-serotype preparation (PPSV23 [Pneumovax]) and a newer 13-serotype vaccine (PCV13 [Prevnar 13]). PPSV23 is 60- to 70-percent protective, and its use lowers emergence of drug-resistant pneumococci. Neither vaccine is recommended for healthy pregnant women. However, for gravidas with chronic diabetes mellitus or with chronic heart, lung, or liver disease, one lifetime dose of PPSV23 is suggested, if not previously provided. Moreover, for women with chronic immunocompromise, generalized malignancy, chronic renal disease, cochlear implant, or asplenia, such as with sickle-cell disease, one lifetime PCV13 dose is followed by one PPSV23 dose at least 8 weeks later and then again 5 years later if not provided previously (Freedman, 2021).

■ Influenza Pneumonia

Influenza A and B are RNA viruses that cause potentially epidemic respiratory infection, including pneumonitis, in the

winter months. The virus is spread by aerosolized droplets and quickly infects ciliated columnar epithelium, alveolar cells, mucus gland cells, and macrophages.

Clinical Presentation

Each year, 10 percent of pregnant women develop influenza (Cantu, 2013). Disease onset follows 1 to 4 days after exposure, and common symptoms include fever, cough, myalgia, and chills (Wright, 2018). In most healthy adults, infection is self-limited. Pneumonia is the most frequent complication and mimics bacterial pneumonia. According to the CDC, infected pregnant women are more likely to be hospitalized and admitted to an ICU (Lindley, 2019). Others have corroborated these observations (Mertz, 2019; Prasad, 2019). At Parkland Hospital during the 2003–2004 influenza season, pneumonia developed in 12 percent of pregnant women with influenza (Rogers, 2010).

The 2009–2010 pandemic with the influenza (A/H1N1) pdm09 strain was particularly severe (Rasmussen, 2014). In an MFMU Network study, 10 percent of pregnant or postpartum women admitted with H1N1 influenza were cared for in an ICU, and 11 percent of these patients died (Varner, 2011). Risk factors included advanced pregnancy, smoking, and chronic hypertension. Overall, influenza accounted for 12 percent of pregnancy-related deaths during the 2009–2010 pandemic (Callaghan, 2015). During the 2013–2014 influenza season, a fourth of pregnant women admitted to California ICUs died (Louie, 2015). ECMO may be lifesaving (Anselmi, 2015; Saad, 2016).

Rapid PCR testing of nasal swab samples for influenza A and B is available. Primary influenza pneumonitis is characterized by sparse sputum production and radiographic interstitial infiltrates (Wright, 2018). More commonly, secondary or mixed pneumonia develop from bacterial superinfection by streptococci or staphylococci after 2 to 3 days of initial clinical improvement. The CDC (2007) reported several cases in which CA-MRSA caused influenza-associated pneumonitis with a case-fatality rate of 25 percent.

Management

Supportive treatment is recommended for uncomplicated influenza, and early antiviral therapy is effective (Oboho, 2016; Wright, 2018). The American College of Obstetricians and Gynecologists (2018a) recommends treatment of all pregnant women with suspected or proven influenza. This is regardless of rapid influenza testing, which can have false-negative results (Datkhaeva, 2019). Hospitalization is considered for severely ill women and for those with pneumonia. Influenza hospitalization rates for those with advanced pregnancy are higher compared with nonpregnant women (Dodds, 2007; Schanzer, 2007).

Treatment is with neuraminidase inhibitors, which interfere with release of progeny virus from infected host cells and thus prevent infection of new host cells. The preferred agent is oseltamivir (Tamiflu), which is given orally, 75 mg twice daily. An alternative is zanamivir (Relenza), which is given by inhalation, 10 mg twice daily. Recommended treatment duration with either is 5 days. Last, peramivir (Rapivab) may be given as a 600-mg IV dose over 15 to 30 minutes. All shorten the course of illness by 1 to 2 days, and they probably reduce the risk for pneumonitis (Belgi, 2014; Muthuri, 2014). Few data guide use of these agents in pregnant women, but the drugs are not teratogenic in animal studies and are considered low risk (Briggs, 2022). Recently, the endonuclease inhibitor baloxavir marboxil (Xofluza) was approved for use in nonpregnant individuals but is not recommended for pregnant women.

Prevention

Vaccination against influenza A is recommended by the American College of Obstetricians and Gynecologists (2018b) and the Centers for Disease Control and Prevention (2019a). During the 2018–2019 flu season, the CDC reported that only half of pregnant women received the influenza vaccine (Lindley, 2019). In a recent survey, however, O'Leary and colleagues (2019) reported a 10-percent vaccine refusal rate in office practices.

Any inactivated influenza vaccines (IIV) or recombinant influenza vaccine (RIV) may be used and is given once each flu season. Live attenuated influenza vaccine (LAIV) should not be used in pregnancy (Freedman, 2021). Prenatal vaccination affords some temporary protection for infants (Madhi, 2014; Munoz, 2019; Tita, 2016). The vaccine has not been linked with birth defects or adverse childhood health effects at 5 years of age (Briggs, 2022; Conlin, 2018; Walsh, 2019). In one case-control study, an association with vaccination and miscarriage was found (Donahue, 2017). However, the observations were not definite and should not alter clinical practice (Rasmussen, 2019; Sperling, 2018). Effects on pregnancy outcomes are discussed in more detail in Chapter 67 (p. 1187).

A second coronavirus—Middle East Respiratory Syndrome (MERS-CoV)—originated in Saudi Arabia in 2013. Fortunately, the epidemic was contained and short lived.

Coronavirus

The first coronaviral infection in China in 2002 that caused severe acute respiratory syndrome (SARS) was termed SARS-CoV. It caused atypical pneumonitis with a case-fatality rate of approximately 10 percent (Dolin, 2012). SARS in pregnancy had a case-fatality rate of up to 40 percent (Maxwell, 2017). Ng and associates (2006) reported that the placentas from 7 of 19 cases showed abnormal intervillous or subchorionic fibrin deposition in three, and extensive fetal thrombotic vasculopathy in two.

In the winter of 2019–2020, a second worldwide outbreak of a genetically similar virus originated in China. This was Coronavirus 2 (SARS-CoV2) known as COVID-19. Illness severity ranges from mild common-cold symptoms to severe pneumonia or acute respiratory distress syndrome (Rasmussen, 2020). From 18 affected pregnancies, the clinical course of COVID-19 is similar to that seen in nonpregnant women. However, preterm labor appears to be an associated risk (Chen, 2020; Zhu, 2020).

To minimize transmission of COVID-19, inpatient guidelines recommend caring for an affected patient in a negative-pressure airborne infection isolation room (AIIR) or transfer to an equipped facility. The potential for vertical transmission (mother–to–newborn) transmission is currently unclear Breslin, 2020). Neonates are suspected to have infection. Thus, isolation of the newborn from other neonates is recommended.

A newborn may room in with its mother, who practices hand hygiene and wears a mask (American College of Obstetricians and Gynecologists, 2021; Centers for Disease Control and Prevention, 2020).

Varicella Pneumonia

Infection with varicella-zoster virus, the same agent responsible for chickenpox, results in pneumonitis in 5 percent of gravidas (Harger, 2002). Diagnosis and management are considered in Chapter 67 (p. 1186).

Pneumocystis Pneumonia

Fungal and yeast infections are usually of greatest consequence in immunocompromised hosts, especially in women with acquired immunodeficiency syndrome (AIDS). Of these, lung infection with *Pneumocystis jirovecii*, formerly called *Pneumocystis carinii*, is a common complication. The opportunistic yeast-like fungus causes interstitial pneumonia characterized by dry cough, tachypnea, dyspnea, and diffuse radiographic infiltrates. This organism is identified by polymerase chain reaction testing of bronchoalveolar lavage secretions or, when necessary, tissue staining of biopsy specimens (Morris, 2018). More common in HIV-infected persons, its incidence has risen in other immunocompromised groups (Rego de Figueiredo, 2019).

In a report from the AIDS Clinical Trials Centers, pneumocystis pneumonia was the most frequent HIV-related disorder in pregnant women (Stratton, 1992). Ahmad and associates (2001) reviewed 22 cases during pregnancy and cited a 50-percent mortality rate. Treatment is with trimethoprim-sulfamethoxazole for 14 to 21 days. Alternative agents include sulfadiazine plus pyrimethamine. Glucocorticoids also improve survival rates. Echinocandins have been used successfully in nonpregnant patients (Huang, 2019). Tracheal intubation and mechanical ventilation may be required in some cases.

For prophylaxis, several international health agencies recommend one double-strength trimethoprim-sulfamethoxazole tablet orally daily for certain groups of HIV-infected pregnant women. These include women with $CD4^+$ T-lymphocyte counts $<200/\mu L$, those whose $CD4^+$ T lymphocytes constitute <14 percent, or if there is an AIDS-defining illness, particularly oropharyngeal candidiasis (Centers for Disease Control and Prevention, 2021).

Fungal Pneumonia

Any of several fungi can cause pneumonia. In pregnancy, this is usually seen in women with HIV infection or other sources of immunocompromise. In uncompromised women, infection is usually mild and self-limited. It is characterized initially by cough and fever, and dissemination is infrequent (Mansour, 2015).

Histoplasmosis and *blastomycosis* do not appear to be more frequent or more severe during pregnancy (Youssef, 2013). Data concerning *coccidioidomycosis* are conflicting (Bercovitch, 2011; Patel, 2013). In a case-control study from an endemic area, pregnancy was a significant risk factor for disseminated disease (Rosenstein, 2001). In another study, however, Caldwell and coworkers (2000) identified 32 serologically confirmed cases during pregnancy and documented dissemination in only three. Women with associated erythema nodosum have a better prognosis, whereas mediastinal lymphadenopathy may more likely reflect disseminated disease (Mayer, 2013). Last, Crum and Ballon-Landa (2006) reviewed 80 cases of antepartum coccidioidomycosis and found that almost all women diagnosed in the third trimester had disseminated disease. Although the overall maternal mortality rate was 40 percent, it was 20 percent for 29 cases reported since 1973. Spinello (2007) and Bercovitch (2011) with their colleagues provide reviews of coccidioidomycosis in pregnancy.

Most cases of *cryptococcosis* reported during pregnancy manifest as meningitis. Otherwise healthy pregnant women occasionally have cryptococcal pneumonia (Asadi Gharabaghi, 2014). Diagnosis is difficult because clinical presentation is similar to that of other community-acquired pneumonias.

Itraconazole is the preferred therapy for most disseminated fungal infections (Edwards, 2018). Pregnant women have also been given IV amphotericin B or ketoconazole (Lewis, 2018; Paranyuk, 2006; Pilmis, 2015). Amphotericin B has been used extensively in pregnancy with no embryofetal effects. Early in pregnancy, fluconazole and ketoconazole may be embryotoxic in large doses. In the first trimester, these two and itraconazole are ideally avoided if possible (Briggs, 2022).

Three echinocandin derivatives—*caspofungin*, *micafungin*, and *anidulafungin*—are effective for invasive candidiasis (Edwards, 2018). They are embryotoxic and teratogenic in laboratory animals and use in human pregnancies has not been reported (Briggs, 2022).

TUBERCULOSIS

It is estimated that a third of the world population is infected with *Mycobacterium tuberculosis* (Getahun, 2015). In the United States, it is uncommon and is a disease of the elderly, the urban poor, minority groups, and patients with HIV infection (Raviglione, 2018). According to the CDC (2019b), the incidence of *active tuberculosis* in this country has plateaued since 2000, and immigrants account for more than half of active cases. Individuals born in the United States have newly acquired infection, whereas foreign-born persons usually have reactivation of latent infection.

Infection begins with inhalation of mycobacteria, which incites a granulomatous pulmonary reaction. In >90 percent of patients, infection is contained and is dormant for long periods (Getahun, 2015). In those who are immunocompromised, tuberculosis becomes reactivated to cause clinical disease. Active disease manifests usually as cough with minimal sputum production, low-grade fever, hemoptysis, and weight loss. Various infiltrative patterns are seen on chest radiograph, and cavitation or mediastinal lymphadenopathy may be associated. Stained smears of sputum reveal acid-fast bacilli (AFB) in approximately two thirds of culture-positive individuals. Forms of extrapulmonary tuberculosis include lymphadenitis, pleural, genitourinary, skeletal, meningeal, gastrointestinal, and miliary or disseminated (Raviglione, 2018). Silent endometrial tuberculosis can cause tubal infertility (Levison, 2010).

Tuberculosis and Pregnancy

The considerable influx of women into the United States from Asia, Africa, Mexico, and Central America has been accompanied by an increased frequency of tuberculosis in pregnancy. The prevalence of tuberculosis was 7.1 cases per 100,000 pregnancy-related hospitalizations (Dennis, 2018). Sackoff and associates (2006) reported positive tuberculin test results in half of 678 foreign-born women attending prenatal clinics in New York City. At Jackson Memorial Hospital in Miami, 21 percent of 207 pregnant women with HIV infection had a positive skin test result (Schulte, 2002).

One review of 3384 pregnant women showed that 72 percent of active disease is pulmonary (Sobhy, 2017). It also confirmed earlier studies that showed greater adverse maternal and perinatal outcomes (Table 54-6). Others have found similar untoward effects (Dennis, 2018; El-Messidi, 2016). From her review, Efferen (2007) cited twofold greater rates of low birthweight, preterm delivery, and preeclampsia. The perinatal mortality rate was almost tenfold higher. Conversely, treated tuberculosis is usually associated with good pregnancy outcomes (Moro, 2018; Taylor, 2013).

Extrapulmonary tuberculosis is less common, although its incidence appears to be rising (El-Messidi, 2016). Llewelyn and colleagues (2000) reported that 9 of 13 pregnant women with extrapulmonary disease had delayed diagnoses. In the review cited above, 5.8 percent of women had extrapulmonary infections, and they had worse outcomes (Sobhy, 2017). Jana and coworkers (1999) described outcomes in 33 pregnant women with renal, intestinal, and skeletal tuberculosis, and a third had low-birthweight newborns. Prevost and Fung Kee Fung (1999) reviewed 56 cases of tuberculous meningitis in which a third of mothers died. Spinal tuberculosis may cause paraplegia, but vertebral fusion may prevent it from becoming permanent (Badve, 2011). Psoas abscess develops in 5 percent of those with spinal infections (Nigam, 2013). Other presentations include widespread intraperitoneal tuberculosis simulating ovarian carcinomatosis or degenerating leiomyoma, and hyperemesis gravidarum stemming from tubercular meningitis (Kutlu, 2007; Moore, 2008; Sherer, 2005).

TABLE 54-6. Adverse Maternal and Perinatal Outcomes in 3384 Pregnancies Complicated by Active Tuberculosis

Outcomes	Odds Ratio[a](95% CI)
Maternal	
Cesarean delivery	2.1 (1.17–3.79)
ARDS	2.8 (1.35–6.10)
Anemia	3.8 (2.21–6.71)
Pneumonia	8.4 (5.8–12.3)
Miscarriage	9.0 (4.93–16.7)
Prenatal Admission	9.6 (2.3–40.6)
Perinatal	
Preterm birth	1.6 (1.2–2.4)
Low birthweight	1.7 (1.2–2.4)
Anomalies	1.8 (1.24–2.62)
Fetal distress	2.3 (1.2–4.5)
Mortality	4.2 (4.9–11.8)

[a]Compared with women without tuberculosis.
ARDS = acute respiratory distress syndrome.
Data from El-Messidi, 2016; Sobhy, 2017.

Diagnosis

For latent tuberculosis, two testing types are used. One is the time-honored *tuberculin skin test (TST),* and the others are *interferon-gamma release assays (IGRAs),* which are becoming preferred (Lewinsohn, 2017; Sosa, 2019). IGRAs are blood tests that measure interferon-gamma release in response to antigens present in *M tuberculosis* but not in *bacille Calmette-Guérin (BCG)* vaccine.

The alternative is skin testing, for which the preferred antigen is *purified protein derivative (PPD)* of intermediate strength of 5 tuberculin units. If the intracutaneously applied test result is negative, no further evaluation is needed. A positive skin test result measures ≥5 mm in diameter and requires evaluation for active disease, including a chest radiograph. For active infection, nucleic acid amplification testing and mycobacterial culture is recommended (Raviglione, 2018).

Clinicians should promptly contact their state health department for cases of suspected or confirmed active tuberculosis. Health departments can assist in providing patient and public health management. This often includes *directly observed therapy (DOT)* to ensure regimen compliance (Centers for Disease Control and Prevention, 2013a). Each state's control office can be found at www.cdc.gov/tb/links/tboffices.htm.

Treatment

Latent Infection

In nonpregnant, tuberculin-positive patients younger than 35 years with no evidence of active disease, treatment is given to substantially reduce the risk that their latent infection will progress to active disease. The preferred therapy is one of three rifamycin-based regimens with or without isoniazid for 3 to 4 months duration (Sterling, 2020). Alternatively, isoniazid, 300 mg orally daily, is given for 6 to 9 months. Isoniazid has been used for decades, and it is considered safe in pregnancy (Briggs, 2022; Moro, 2018). However, for gravidas with latent infection, most recommend that isoniazid therapy be delayed until after delivery (Hill, 2019). Some even recommend withholding treatment until 3 to 6 months after delivery because of a possibly increased isoniazid-induced hepatitis risk in postpartum women. Serum levels of hepatic transaminases should be monitored with isoniazid therapy.

Compliance is a major problem with postpartum therapy. Only 10 to 18 percent of postpartum patients complete treatment (Cruz, 2005; Sackoff, 2006). One obvious disconnect is that care for tuberculosis is given in health systems apart from prenatal care (Zenner, 2012). In a decision model, Boggess and colleagues (2000) reported fewer cases of tuberculosis if treatment for a positive tuberculin skin test result occurred antepartum.

There are exceptions to delayed treatment for latent infection in pregnancy. Recent skin test convertors are treated antepartum because the incidence of active infection is 5 percent in the first year (Zumla, 2013). Skin-test-positive women exposed to active infection are also treated because the incidence of infection is 0.5 percent per year. Last, women with HIV infection are treated because they have an approximate 10-percent annual risk of active disease.

Active Infection

Regimens. Resistance to antituberculosis drugs has led to emergence of *multidrug-resistant tuberculosis (MDR-TB)* strains. The World Health Organization (2017) recommends isoniazid, rifampin, ethambutol, and pyrazinamide together for 6 months for nonpregnant persons. These are used until susceptibility studies are performed (Nahid, 2016). Pyridoxine is added to help prevent isoniazid-associated neuropathy. A newer 4-month isoniazid, rifapentine, moxifloxacin, and pyrazinamide regimen was not inferior to the standard one (Dorman, 2021).

During pregnancy, in the first 2-month *bactericidal phase*, isoniazid, rifampin, and ethambutol are given. This is followed by a 7-month *continuation phase* with isoniazid and rifampin (Raviglione, 2018). A few reports describe MDR-TB during pregnancy, and treatment options have been reviewed (Esmail, 2018). Treatment should be undertaken in consultation with infectious disease and the local health department. Breastfeeding is not prohibited during antituberculous therapy. If neonatal therapy is indicated, medication levels in breast milk are inadequate for this.

Treatment of active disease is of special concern in HIV-infected women who are antiretroviral naïve. In these circumstances, beginning concomitant therapy with antituberculosis and antiretroviral therapy can cause the *immune reconstitution inflammatory syndrome (IRIS)* with toxic drug effects (Lai, 2016). That said, some studies support administration of antiretroviral therapy 2 to 4 weeks after beginning antituberculosis therapy (Blanc, 2011; Havlir, 2011). Also, rifampin or rifabutin may be contraindicated if certain protease inhibitors or nonnucleoside reverse transcriptase inhibitors are used. If there is resistance to rifabutin or rifampin, then pyrazinamide therapy is given. Of the second-line regimens, the aminoglycosides—streptomycin, kanamycin, amikacin, and capreomycin—are ototoxic to the fetus and are contraindicated (Briggs, 2022).

Transmission Prevention. Inpatient airborne precautions should be initiated for any patient with suspected active pulmonary tuberculosis or for patients who remain infectious despite treatment. Precautions include rooming in a negative-pressure room. Patients are encouraged to wear surgical masks during interactions, and health-care workers should don personally fitted N95 respirator masks. Patients undergoing treatment can be considered noninfectious: (1) after 2 weeks of DOT treatment compliance, (2) after three consecutive AFB-negative sputum smears, or (3) after clinical improvement evidenced by absent fever and resolving cough (Centers for Disease Control and Prevention, 2013b).

Neonatal Tuberculosis

Tuberculous bacillemia can infect the placenta, but the fetus infrequently becomes infected. *Congenital tuberculosis* applies also to newborns who are infected by aspiration of infected secretions at delivery. Each route constitutes approximately half of the cases. Neonatal tuberculosis simulates other congenital infections and manifests with hepatosplenomegaly, respiratory distress, fever, and lymphadenopathy (Yeh, 2019).

Cantwell and colleagues (1994) reviewed 29 cases of congenital tuberculosis. Only 12 of the mothers had active infection, and tuberculosis was frequently demonstrated by postpartum endometrial biopsy. Adhikari and associates (1997) described 11 South African postpartum women whose endometrial biopsy was culture-positive. Six of their neonates had congenital tuberculosis.

Neonatal infection is unlikely if the mother with active disease is treated before delivery or if her sputum culture is negative. Most experts recommend isolation of the susceptible newborn from the mother suspected of having active disease. If the mother is infectious, 3 to 6 months of isoniazid prophylaxis is given to the newborn. In an older study, the risk of disease in the untreated infant born to a woman with active infection was 50 percent in the first year (Jacobs, 1988).

SARCOIDOSIS

This is a chronic, multisystem inflammatory disease of unknown etiology characterized by an accumulation of T-helper lymphocytes and phagocytes within noncaseating granulomas (Baughman, 2018; Spagnolo, 2018). Predisposition to the disease is genetically determined and characterized by an exaggerated response of helper T lymphocytes to environmental triggers. Pulmonary involvement is most common, followed by skin, eyes, lymph nodes, and then all other organ systems. The prevalence of sarcoid in the United States is 20 to 60 cases per 100,000, with equal sex distribution. It is more than 10 times more common for blacks than for whites. Most patients are between 20 and 40 years at disease presentation.

Pulmonary symptoms are dominant, and more than 90 percent of patients have an abnormal chest radiograph at some point. *Interstitial pneumonitis* is the hallmark of pulmonary involvement, and half of affected patients develop permanent radiological changes. *Lymphadenopathy*, especially of the mediastinum, is present in 75 to 90 percent of cases. A third each have uveitis and skin involvement, the latter usually manifest as *erythema nodosum*. In women, sarcoid causes approximately 10 percent of cases of erythema nodosum (Mert, 2007). Importantly, any other organ system may be involved. Confirmation of the diagnosis is with biopsy—preferably a lymph node. However, because the lung may be the only obviously involved organ, tissue acquisition is often difficult.

The overall prognosis for sarcoidosis is good, and it resolves without treatment in 50 percent of patients. Still, quality of life is diminished, and in 20 percent chronic organ dysfunction, albeit mild and nonprogressive, persists (Spagnolo, 2018). Approximately 5 percent die because of their disease.

Glucocorticoids are the most widely used treatment for symptomatic disease. Permanent organ derangement is seldom reversed by their use (Spagnolo, 2018). Thus, the decision to treat is based on symptoms, physical findings, chest radiograph,

TABLE 54-7. Maternal and Perinatal Adverse Outcomes in 678 Women with Sarcoidosis

Outcomes	Odds Ratio[a] (95% CI)
Preeclampsia	1.62 (1.18–2.22)
Preterm delivery	1.73 (1.40–2.15)
Deep-vein thrombosis	4.92 (1.58–15.33)
Eclampsia	5.27 (1.69–16.40)
Pulmonary embolism	6.68 (3.99–11.21)

[a]Compared with 7,094,000 women without sarcoidosis.
CI = confidence interval.

and pulmonary function tests. Unless respiratory symptoms are prominent, therapy is usually withheld for a several-month observation period. If inflammation does not subside, prednisone, 20 to 40 mg/d, is given daily and tapered to <10 mg by 6 months (Baughman, 2018). For those with an inadequate response, immunosuppressive or cytotoxic agents and cytokine modulators can be used.

Sarcoidosis and Pregnancy

Because it is uncommon and frequently benign, sarcoidosis is not often diagnosed in pregnancy. In a study of the Nationwide Inpatient Sample, the incidence was 9.6 cases per 100,000 births (Hadid, 2015). Meningitis, heart failure, and neurosarcoidosis complicating pregnancy have been described (Cardonick, 2000; Maisel, 1996; Wallmüller, 2012). Many small studies report benign associations between sarcoidosis and pregnancy. However, Table 54-7 displays the increased incidences of both maternal and fetal adverse outcomes found in a Nationwide Inpatient Sample study of 678 cases (Hadid, 2015). Risks for preeclampsia and preterm delivery were approximately twofold greater. Risks for eclampsia, deep-vein thrombosis, and pulmonary embolism were five- to sevenfold higher.

Active sarcoidosis is treated using the same guidelines as for nongravid women. Severe disease warrants serial pulmonary function determination. Symptomatic uveitis, constitutional symptoms, and pulmonary symptoms are treated with prednisone.

CYSTIC FIBROSIS

Pathophysiology

Cystic fibrosis is an autosomal recessive exocrinopathy and is one of the most common fatal genetic disorders in Caucasians. Cystic fibrosis is caused by one of more than 2000 mutations in a 230-kb gene on the long arm of chromosome 7 (Sorscher, 2018). The normal peptide gene product functions as a chloride channel and is termed the *cystic fibrosis transmembrane conductance regulator (CFTR)*. Mutations in the chloride channel alters epithelial transport of electrolytes in CFTR-secretory cells. Affected sites include the sinuses, lung, pancreas, liver, and reproductive tract.

Exocrine gland ductal obstruction develops from thick, viscid secretions. In the lung, submucosal glandular ducts are affected. Eccrine sweat gland abnormalities are the basis for the diagnostic *sweat test*, characterized by elevated sodium, potassium, and chloride levels in sweat.

Lung involvement is commonplace and is usually the cause of death. Bronchial gland hypertrophy with mucous plugging and small-airway obstruction leads to subsequent infection that ultimately causes chronic bronchitis and bronchiectasis. For complex and not completely explicable reasons, chronic inflammation is caused by *Pseudomonas aeruginosa*, *S aureus*, *and H influenzae*. Acute and chronic parenchymal inflammation ultimately causes extensive fibrosis, and along with airway obstruction, ventilation–perfusion mismatch develops. Pulmonary insufficiency is the end result. Currently, the median predicted survival is 37 years, and nearly 80 percent of females with cystic fibrosis now survive to adulthood (Patel, 2015).

As discussed in Chapter 17 (p. 342), phenotypes vary widely, even among homozygotes for the common Phe508del (ΔF508) mutation. Disease severity depends on which two alleles are inherited, and approximately 10 percent are disease-causing mutations (Sorscher, 2018). Homozygosity for ΔF508 is one of the most severe, and 90 percent of individuals with clinical disease carry at least one F508 allele.

Preconceptional Counseling

Women with clinical cystic fibrosis are subfertile because of tenacious cervical mucus. Traxler and colleagues (2019) recommend in-depth preconceptional counseling regarding contraception. Males have oligospermia or aspermia from associated *congenital bilateral absence of the vas deferens (CBAVD)*, and 98 percent are infertile (Ahmad, 2013). Despite this, the North American Cystic Fibrosis Foundation estimated that 4 percent of affected women become pregnant every year (Edenborough, 1995). The endometrium and tubes express some CFTR but are functionally normal, and the ovaries do not express the *CFTR* gene. Both intrauterine insemination and in vitro fertilization can be successful for affected women. Important factors are the long-term prognosis for the parent(s) and mutation transmission to their offspring.

Screening

The American College of Obstetricians and Gynecologists (2020) recommends that carrier screening be offered to *all* women, affected by cystic fibrosis or not, who are currently pregnant or considering conception (Chap. 17, p. 342). The CDC also added cystic fibrosis to newborn screening programs (Chap. 32, p. 594). The CFTR2 website (www.cftr2.org) helps delineate which gene variants have a clear disease-causing role and which are benign mutations.

Prenatal Care

Pregnancy outcome is inversely related to severity of lung dysfunction. Advanced chronic lung disease, hypoxia, and frequent infections may prove deleterious. At least in the past, *cor pulmonale* was common, but even that does not preclude successful pregnancy (Cameron, 2005). In some women, *pancreatic dysfunction* may cause malnutrition. Approximately 10 percent have pregestational diabetes (Reynaud, 2017). Otherwise normal pregnancy-induced insulin resistance frequently

results in gestational diabetes after midpregnancy. In one study of 48 pregnancies, half had pancreatic insufficiency, and a third required insulin (Thorpe-Beeston, 2013).

Cystic fibrosis is not affected by pregnancy. Early reports of a deleterious effect on the course of cystic fibrosis were related to severe disease (Olson, 1997). When matched with nonpregnant women by disease severity, some reports indicate no deleterious effects on long-term survival (Schechter, 2013).

Management

Prepregnancy counseling is imperative. Women who choose to become pregnant require close surveillance for development of superimposed infection, diabetes, and heart failure. Serial pulmonary function testing assists management and estimates prognosis. If the FEV_1 is at least 50 percent, women usually tolerate pregnancy well (Reynaud, 2020). Emphasis is placed on postural drainage, bronchodilator therapy, and infection control.

β-Adrenergic bronchodilators help control airway constriction. Inhaled recombinant human deoxyribonuclease I improves lung function by reducing sputum viscosity (Sorscher, 2018). Inhaled 7-percent saline produces short- and long-term benefits. Nutritional status is assessed, and appropriate dietary counseling given. Calcium and vitamin D are given for poor bone mineralization. Pancreatic insufficiency requires replacement of oral pancreatic enzymes. Promising new therapy to correct CFTR protein dysfunction has been recently described. Using a combination of "CFTR correctors" (tezacaftor–ivacaftor congeners), patients homozygous for the Phe508del mutation significantly benefitted (Davies, 2018; Keating, 2018). No reports of these drugs are available regarding pregnant women.

Infection is heralded by increasing cough and mucus production. Oral semisynthetic penicillins or cephalosporins usually suffice to treat staphylococcal infections. *Pseudomonas* infection is problematic, and inhaled tobramycin and colistin have been used successfully to control this organism. Serious pulmonary infections are treated with immediate hospitalization and aggressive therapy. The threshold for hospitalization with other complications is low. For labor and delivery, epidural analgesia is recommended (Deighan, 2014).

Pregnancy Outcome

Earlier reports chronicled the poor maternal and perinatal outcomes in affected women (Cohen, 1980; Kent, 1993). More recent reports describe better outcomes, but there still are serious complications (Schlüter, 2019). Disease severity is now quantified by pulmonary function studies, which are the best predictor of pregnancy and long-term maternal outcome. One report of 69 pregnancies found that if prepregnancy FEV_1 was <60 percent of predicted, the risk for preterm delivery, respiratory complications, and death of the mother within a few years of childbirth was substantive (Edenborough, 2000). Others report similar findings (Fitzsimmons, 1996; Thorpe-Beeston, 2013).

Of 75 pregnancies from the French Cystic Fibrosis Registry, almost 20 percent of newborns were delivered preterm, and 30 percent had growth restriction (Gillet, 2002). The one maternal death was due to *Pseudomonas* sepsis in a woman whose prepregnancy FEV_1 was 60 percent. Long-term, however, 17 percent of women died, and four infants had confirmed cystic fibrosis. Meconium peritonitis is found in 10 to 20 percent of affected fetuses (Boczar, 2015; Terlizzi, 2016). In a more recent report from the French registry, women with pregestational diabetes had outcomes similar to those without diabetes (Reynaud, 2017).

TABLE 54-8. Odds Ratios for Maternal Complications in 1119 Pregnant Women with Cystic Fibrosis Compared with Controls

Complication	Odds Ratio
Asthma	5
Thrombophilia	6
Diabetes	14
Acute kidney injury	16
Respiratory failure	30
Mechanical ventilation	32
Pneumonia	69
Death	125

Patel and associates (2015) queried the National Inpatient Sample database and reported that the prevalence of cystic fibrosis in pregnancy had a significant linear rise from 2000 to 2010. They analyzed 1119 affected women and reported a litany of risks (Table 54-8). In contrast, perinatal outcomes were surprisingly good.

Lung Transplantation

Cystic fibrosis is a common antecedent disease leading to lung transplantation. Gyi and coworkers (2006) reviewed 10 pregnancies in women following transplantation and reported nine liveborn neonates. Maternal outcomes were less favorable. Of the three gravidas who developed rejection during pregnancy, all had progressively declining pulmonary function and died of chronic rejection by 38 months after delivery. More recent international data show a median survival of 10.5 years in patients living beyond the first year (Yusen, 2015).

CARBON MONOXIDE POISONING

Carbon monoxide is a ubiquitous gas, and most nonsmoking adults have a carbon monoxyhemoglobin saturation of 1 to 3 percent. In cigarette smokers, levels may be 5 to 15 percent, and polycythemia is comorbid. Carbon monoxide is the most frequent cause of poisoning worldwide (Stoller, 2007). Toxic levels are often encountered in inadequately ventilated areas warmed by space heaters.

Carbon monoxide is particularly toxic because it is odorless and tasteless and has a high affinity for hemoglobin binding. Thus, it displaces oxygen and impedes its transfer with resultant hypoxia. Besides acute sequelae including death and anoxic encephalopathy, cognitive defects develop in as many as half of patients following loss of consciousness or in those with carbon monoxide levels >25 percent (Weaver, 2002). Hypoxic brain

damage has a predilection for the cerebral cortex and white matter and for the basal ganglia (Lo, 2007; Prockop, 2007). A Parkinson syndrome sometimes follows after recovery.

Pregnancy and Carbon Monoxide Poisoning

Through several physiological alterations, the rate of endogenous carbon monoxide production almost doubles in normal pregnancy (Longo, 1977). Although the pregnant woman is not more susceptible to carbon monoxide poisoning, the fetus does not tolerate excessive exposure (Friedman, 2015; Nowadly, 2018). With chronic exposure, maternal symptoms usually appear when the carboxyhemoglobin concentration is 5 to 20 percent. Symptoms include headache, weakness, dizziness, physical and visual impairment, palpitations, and nausea and vomiting. With acute exposure, concentrations of 30 to 50 percent produce symptoms of impending cardiovascular collapse. Levels >50 percent may be fatal for the mother.

Because hemoglobin F has an even higher affinity for carbon monoxide, fetal carboxyhemoglobin levels are 10 to 15 percent higher than those in the mother. This may be due to facilitated diffusion (Longo, 1977). Importantly, the half-life of carboxyhemoglobin is 2 hours in the mother but 7 hours in the fetus. Carbon monoxide is bound so tightly to hemoglobin F, the fetus may be hypoxic even before maternal carbon monoxide levels are appreciably elevated. Several anomalies are associated with embryonic exposure, and anoxic encephalopathy is the primary sequela of later fetal exposure (Alehan, 2007; Nowadly, 2018).

Treatment

For all victims, treatment of carbon monoxide poisoning is supportive along with immediate administration of 100-percent inspired oxygen. Indications for hyperbaric oxygen treatment in nonpregnant individuals are unclear (Kao, 2005). Weaver and associates (2002) reported that hyperbaric oxygen treatment minimized the incidence of cognitive defects in adults at both 6 weeks and 1 year compared with normobaric oxygen. Hyperbaric oxygen is generally recommended in pregnancy if carbon monoxide exposure has been "significant" (Aubard, 2000; Ernst, 1998). The problem is how to define significant exposure (Friedman, 2015). Although maternal carbon monoxide levels are not accurately predictive of those in the fetus, some clinicians recommend hyperbaric therapy if maternal levels exceed 15 to 20 percent. Towers and Corcoran (2009) described affected fetuses to have an elevated baseline heart rate, diminished variability, and absent accelerations and decelerations with fetal monitoring. Treatment of the affected newborn with hyperbaric oxygen also is controversial (Bar, 2007).

Elkharrat and coworkers (1991) described successful hyperbaric treatments in 44 pregnant women. In another report, a woman's abnormal neurological and cardiopulmonary findings abated in a parallel fashion with resolution of associated fetal heart rate variable decelerations (Silverman, 1997). Greingor and coworkers (2001) used 2.5-atm hyperbaric 100-percent oxygen for 90 minutes in a 21-week-pregnant woman who was delivered of a healthy neonate at term. The Undersea and Hyperbaric Medical Society (2021) has a list of accredited facilities.

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CHAPTER 55

Thromboembolic Disorders

During the past century, the frequency of venous thromboembolism (VTE) during the puerperium decreased remarkably as early ambulation became routine practice. Despite this and other advances in prevention and treatment, thromboembolism remains a leading cause of maternal morbidity and mortality (Abe, 2019). Thrombotic pulmonary embolism accounted for almost 10 percent of pregnancy-related deaths in the United States between 2011 and 2015 (Creanga, 2017; Petersen, 2019).

The absolute incidence of VTE during pregnancy is low—1 or 2 cases per 1000 pregnancies. However, the risk is approximately five times higher than that among women who are not pregnant (Greer, 2015). Approximately equal numbers of cases are identified antepartum and in the puerperium. But deep-vein thrombosis alone is more frequent antepartum, and pulmonary embolism is more common postpartum. During the first 6 weeks of the puerperium, the estimated incidence of a thromboembolic complication is 22 events per 100,000 deliveries. Although still elevated, the risk falls to approximately 3 cases per 100,000 deliveries during the second 6-week postpartum period (Kamei, 2014). As many as 2 percent of these women have postthrombotic syndrome (Govindappagari, 2020).

PATHOPHYSIOLOGY

Rudolf Virchow (1856) postulated that stasis, local trauma to the vessel wall, and hypercoagulability predisposed to venous thrombosis. During pregnancy, the risk for each of these rises. Compression of the pelvic veins and inferior vena cava by the enlarging uterus renders the lower extremity venous system particularly vulnerable to stasis. Marik and Plante (2008) cite a 50-percent reduction in venous flow velocity in the legs that lasts from the early third trimester until 6 weeks postpartum. This stasis is the most constant predisposing risk factor for venous thrombosis. Venous stasis, delivery, preeclampsia, and sepsis contribute to endothelial cell injury. Last, as listed in the Appendix (p. 1228), the synthesis of most clotting factors is markedly enhanced during pregnancy and favors coagulation.

Risk factors for developing VTE during pregnancy are shown in Table 55-1. The most important of these is a personal history of thrombosis. Specifically, 15 to 25 percent of all VTE cases during pregnancy are recurrent events (American College of Obstetricians and Gynecologists, 2020b). Another important individual risk factor is a genetically determined thrombophilia. An estimated 20 to 50 percent of women who develop a venous thrombosis during pregnancy or postpartum have an identifiable underlying procoagulant genetic disorder (American College of Obstetricians and Gynecologists, 2020a).

Calculated risks for thromboembolism are approximately doubled in women with multifetal gestation, anemia, hyperemesis, hemorrhage, cesarean delivery, obesity, preeclampsia, and postpartum infection (Waldman, 2013). Scheres and

TABLE 55-1. Some Risk Factors Associated with an Increased Risk for VTE

Obstetrical	General
Cesarean delivery	Age 35 years or older
Cesarean hysterectomy	Anatomical anomaly[a]
Diabetes mellitus	Antiphospholipid antibodies
Hemorrhage and anemia	Connective tissue disease
Hyperemesis	Dehydration
Immobility—prolonged bed rest	Hormonal contraceptives
Multifetal gestation	Hospitalization
Multiparity	Immobility
Preeclampsia	Infection and inflammatory disease
Puerperal infection	Inflammatory bowel disease
Stillbirth	Malignancy
	Nephrotic syndrome
	Obesity
	Orthopedic procedures
	Paraplegia
	Prior VTE
	Sickle-cell disease
	Smoking
	Surgery
	Thrombophilia

[a]Includes May-Thurner syndrome (iliac vein compression syndrome).
VTE = venous thromboembolism.

coworkers (2020) had similar observations for women with preeclampsia. Risks were significantly higher among women who had a stillbirth or who underwent peripartum hysterectomy. Last, as discussed in Chapter 57 (p. 1021), inflammatory bowel disease increases the risk two- to threefold (Kim, 2019).

THROMBOPHILIAS

Several important regulatory proteins act as inhibitors in the coagulation cascade (Fig. 55-1). Normal values for many of these proteins during pregnancy are found in the Appendix (p. 1228). Inherited or acquired deficiencies of these inhibitory proteins are collectively referred to as *thrombophilias*. These can lead to hypercoagulability and recurrent VTE (Connors, 2017). Although these disorders are collectively present in approximately 15 percent of white European populations, they are responsible for approximately 50 percent of all thromboembolic events during pregnancy (Pierangeli, 2011). Some aspects of the more common inherited thrombophilias related to VTE are summarized in Table 55-2.

Inherited Thrombophilias

Patients with inherited thrombophilic disorders often have a family history of thrombosis. These mutations are also found in up to half of all patients who present with VTE before the age of 45 years, particularly in those whose event occurred in the absence of well-recognized risk factors. Of greatest significance is a family history of sudden death due to pulmonary embolism or a history of multiple family members requiring long-term anticoagulation therapy because of recurrent thrombosis (Connors, 2017).

Antithrombin Deficiency

Synthesized in the liver, antithrombin is one of the most important inhibitors of thrombin and inactivates thrombin and factor Xa (Rhéaume, 2016). Notably, the rate of antithrombin interaction with its target is accelerated over 1000–fo1d by heparin. Antithrombin deficiency may result from hundreds of different mutations that are almost always autosomal dominant. Type I deficiency results from reduced synthesis of biologically normal antithrombin, and type II deficiency is characterized by normal levels of antithrombin with reduced functional activity.

Homozygous antithrombin deficiency is lethal. Heterozygous deficiency affects approximately 1 in 2500 individuals. It is the most thrombogenic of the heritable coagulopathies. The risk for thrombosis correlates with the degree of deficiency. Antithrombin deficiency is associated with a 25- to 50-fold higher relative risk of VTE in the general population and a sixfold increased risk of thromboembolic complications during pregnancy (Ilonczai, 2015). As shown in Table 55-2, those affected have an inordinately high risk of VTE during pregnancy.

Sabadell and associates (2010) studied the outcomes of 18 pregnancies complicated by antithrombin deficiency. Twelve of these women were treated with therapeutic doses of low-molecular-weight heparin (LMWH). Three of the untreated patients suffered a thromboembolic episode compared with none in the treated group. Untreated women also had a 50-percent risk of stillbirth and fetal-growth restriction. By comparison, none of the treated women had a stillbirth, but a fourth developed fetal-growth restriction. Abbattista and coworkers (2020) reported a 7-percent risk of VTE for women treated with LMWH during pregnancy and a 12-percent risk for those not treated. Similar results were reported by Ilonczai and colleagues (2015). Last, Garcia-Botella and associates (2016) described a mesenteric vein thrombosis in a pregnant woman with antithrombin deficiency.

Given such risk, affected women are managed during pregnancy with anticoagulation regardless of whether they have had a prior thrombosis (Abbattista, 2020; Bates, 2018). When anticoagulation is necessarily withheld, such as during surgery or delivery, or if VTE develops in an anticoagulated woman, treatment with recombinant human antithrombin may be protective (Paidas, 2016).

Protein C Deficiency

When thrombin is bound to thrombomodulin on endothelial cells of small vessels, its procoagulant activities are neutralized. This binding also activates protein C, a natural anticoagulant. It, in the presence of protein S, controls thrombin generation, in part, by inactivating factors Va and VIIIa (see Fig. 55-1). Protein C activity increases modestly but significantly throughout the first half of pregnancy, and some have speculated that this augmentation may play a role in maintaining early pregnancy through both anticoagulant and inflammatory regulatory pathways (Said, 2010).

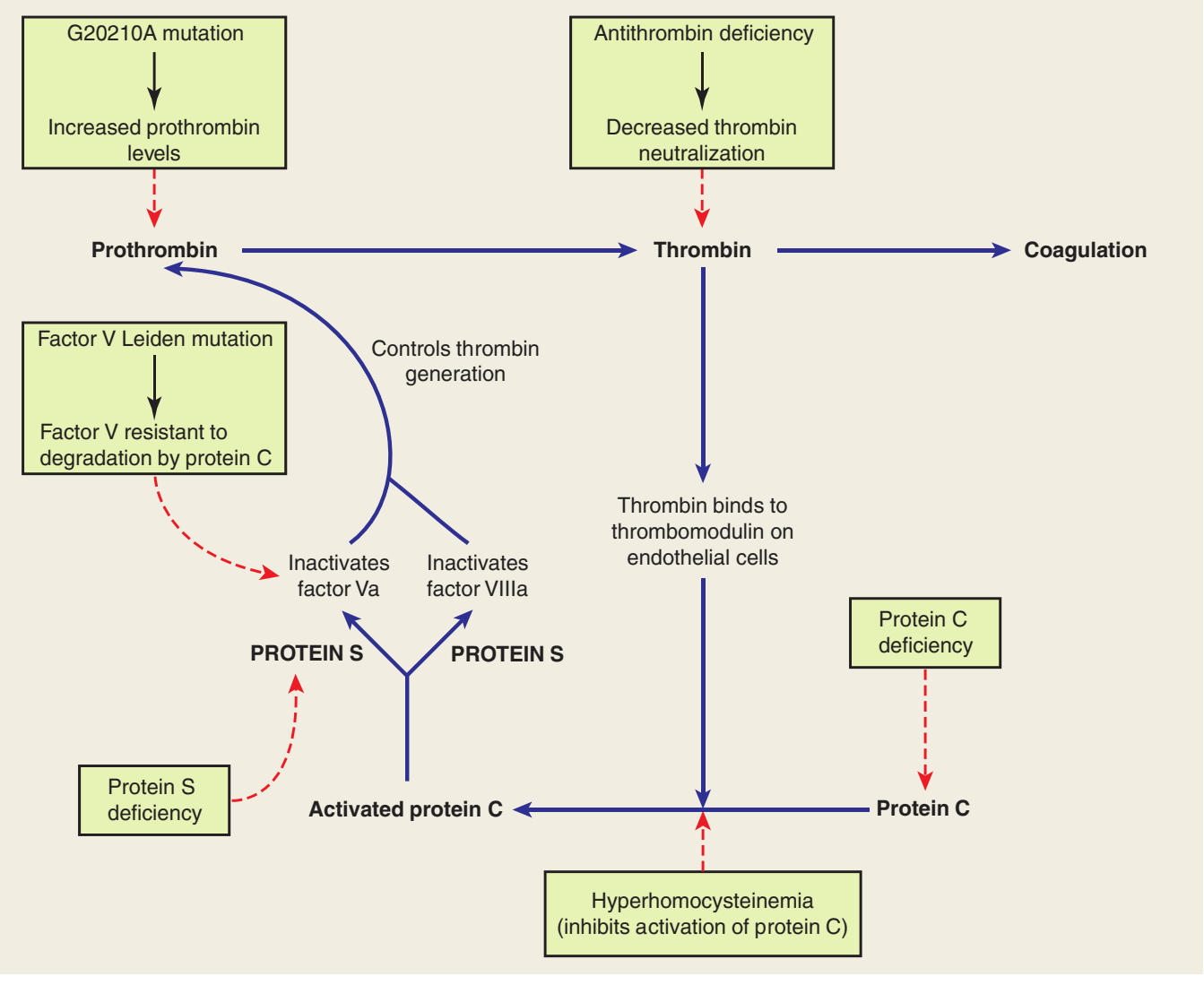

FIGURE 55-1 Inherited thrombophilias and their effect(s) on the coagulation cascade.

TABLE 55-2. Inherited Thrombophilias and Their Association with Venous Thromboembolism (VTE) in Pregnancy

	VTE Risk per Pregnancy (%)		
	No History	Prior VTE	Family History
Factor V Leiden heterozygote	0.5–3.1	10	0.06–1.2
Factor V Leiden homozygote	2.2–1.4	17	1–16
Prothrombin gene heterozygote	0.4–2.6	>10	0–0.73
Prothrombin gene homozygote	2–4	>17	1.6
Factor V Leiden/prothrombin double heterozygote	8.2	>20	0–2.4
Antithrombin deficiency	0.2–1.16	40	0–8
Protein C deficiency	0.1–5.4	4–17	0–5
Protein S deficiency	0.1–6.6	0–22	0–1.5
Hyperhomocysteinemia	0	0	<1

Data from Abbattista, 2020; American College of Obstetricians and Gynecologists, 2020a; Bates, 2018; Croles, 2017.

More than 160 different autosomal dominant mutations for the protein C gene have been described (Louis-Jacques, 2016). The prevalence of heterozygous protein C deficiency is 2 to 3 per 1000, but many of these individuals do not have a thrombosis history because the phenotypic expression is highly variable. These prevalence estimates correspond with functional activity threshold values of 50 to 60 percent, which are used by most laboratories. As shown in Table 55-2, these are associated with a six- to twelvefold higher risk for VTE (Lockwood, 2012). The rare cases of homozygous protein C deficiency may cause fatal neonatal purpura fulminans. Last, sepsis can result in purpura fulminans in the adult with heterozygous protein C deficiency (Bendapudi, 2021).

Protein S Deficiency

This circulating anticoagulant is activated by protein C, which enhances the capacity of protein S to inactivate factors Va and VIIIa (see Fig. 55-1). Protein S deficiency may be caused by more than 130 different mutations, with an aggregate heterozygous prevalence of approximately 0.3 to 1.3 per 1000 individuals (Louis-Jacques, 2016). Protein S deficiency may be measured by antigenically determined free, functional, and total S levels. All three decline substantively during normal gestation (Appendix, p. 1228). Thus, the diagnosis in pregnant women—as well as in those taking certain oral contraceptives—is difficult. If screening during pregnancy is necessary, threshold values for free protein S antigen levels in the second and third trimesters have been identified at <30 percent and <24 percent, respectively. The risk of VTE in pregnancy is increased severalfold (see Table 55-2). Among those with a positive family history, the VTE risk in pregnancy is 6 to 7 percent (American College of Obstetricians and Gynecologists, 2020a).

Conard and coworkers (1990) described thrombosis in five of 29 pregnant women with protein S deficiency. They, as well as Burneo and colleagues (2002), reported maternal cerebral vein thrombosis. Neonatal homozygous protein S deficiency is usually associated with purpura fulminans, the fatal clinical phenotype.

Factor V Leiden Mutation

This is the most prevalent of the known thrombophilia syndromes and is characterized by resistance of plasma to the anticoagulant effects of activated protein C. There are several mutations that create this resistance, but the most common is the factor V Leiden mutation. This missense mutation results from a substitution of glutamine for arginine at position 506 in the factor V polypeptide. As a result of this mutation, activated factor V is neutralized approximately tenfold more slowly by activated protein C (see Fig. 55-1). This leads to enhanced thrombin generation.

Heterozygous inheritance of factor V Leiden is the most common heritable thrombophilia. It is found in 3 to 15 percent of select European populations, 1.2 percent of African Americans, and 2.2 of Hispanic Americans, but is virtually absent in African blacks and Asians (American College of Obstetricians and Gynecologists, 2020a). Women who are heterozygous for factor V Leiden account for approximately 40 percent of VTE cases during pregnancy. However, the actual risk among pregnant women who are heterozygous and who do not have a personal history or a first-degree relative with a thrombotic episode before age 50 years is 5 to 12 events per 1000 births (see Table 55-2). In contrast, this risk is at least 10 percent among pregnant women with a personal or family history. Pregnant women who are homozygous without a personal or family history have a 1- to 4-percent risk for VTE, whereas those with such a history have an approximately 17-percent risk (American College of Obstetricians and Gynecologists, 2020a).

Diagnosis during pregnancy is performed by DNA analysis for the mutant factor V gene. Bioassay is not used because of the normal resistance that develops after early pregnancy from alterations in other coagulation protein concentrations. Of note, activated protein C resistance can also be caused by antiphospholipid syndrome, which is described on page 979 and also detailed in Chapter 62 (p. 1114).

To assess the prognostic significance of maternal factor V Leiden mutation during pregnancy, Kjellberg and associates (2010) compared the outcomes of 491 carriers with those of 1055 controls. All three of the thromboembolic events occurred among the carriers. But, preterm birth rates, birthweights, or hypertensive complication rates did not differ between the two groups. In a prospective observational study of almost 5000 women conducted by the Maternal-Fetal Medicine Units Network, the heterozygous mutant gene incidence was 2.7 percent (Dizon-Townson, 2005). Of three pulmonary emboli and one deep-vein thrombosis cases—a rate of 0.8 per 1000 pregnancies—none was among these carriers. Moreover, in the heterozygous women, the risks of preeclampsia, placental abruption, fetal-growth restriction, or pregnancy loss were not elevated. The investigators concluded that universal prenatal screening for the Leiden mutation and prophylaxis for carriers without a prior VTE is not indicated.

Prothrombin G20210A Mutation

This missense mutation in the prothrombin gene leads to excessive accumulation of prothrombin, which may be converted to thrombin. Prothrombin levels are increased approximately 30 percent in heterozygotes and 70 percent in homozygotes (MacCallum, 2014). As with factor V Leiden, a personal or family history of VTE in a first-degree relative before age 50 years raises the risk of VTE during pregnancy (see Table 55-2). For a heterozygous carrier with such a history, the risk exceeds 10 percent. Without such a history, heterozygous carriers of the mutation have less than a 1-percent risk of VTE during pregnancy (American College of Obstetricians and Gynecologists, 2020a).

Silver and coworkers (2010) tested nearly 4200 women for the prothrombin G20210A mutation. A total of 157—or 3.8 percent—of the women carried the mutation, and only one of these was homozygous. Carriers had similar rates of pregnancy loss, preeclampsia, fetal-growth restriction, and placental abruption compared with noncarriers. Three thromboembolic events occurred in women who tested negative for the mutation.

Homozygous patients, or those who are doubly heterozygous for a G20210A mutation with a factor V Leiden mutation, have a greater thromboembolism risk than heterozygous

carriers (Connors, 2017). Others have provided detailed information on pregnancy outcomes in women with such rare compound thrombophilias (Carroll, 2018; Lim, 2016).

Hyperhomocysteinemia

The most common cause of elevated homocysteine is the C667T thermolabile mutation of the 5, 10– methylene–tetrahydrofolate reductase (MTHFR) enzyme. Inheritance is autosomal recessive. Elevated homocysteine levels may also result from deficiency of one of several enzymes involved in methionine metabolism and from correctible nutritional deficiencies of folic acid, vitamin B_6, or vitamin B_{12}. During normal pregnancy, mean homocysteine plasma concentrations decline and make a diagnosis difficult (Lockwood, 2002).

A metaanalysis by den Heijer and associates (2005) reported an association between MTHFR polymorphisms and a slightly greater risk for thrombosis in international studies, but no such association was found in North American studies (den Heijer, 2005). The authors speculated that folic acid supplementation could explain the difference. Recall that folic acid serves as a cofactor in the remethylation reaction of homocysteine to methionine. Similarly, the American College of Chest Physicians posited that the lack of an association with thromboembolism could reflect the physiological reductions in homocysteine levels associated with pregnancy as well as the effects of widespread prenatal folic acid supplementation (Bates, 2012). The American College of Obstetricians and Gynecologists (2020a) has concluded that there is insufficient evidence to support assessment of MTHFR polymorphisms or measurement of fasting homocysteine levels in the evaluation for VTE.

Other Thrombophilia Mutations

Protein Z is a vitamin K–dependent protein that serves as a cofactor in factor Xa inactivation. Studies have found that low protein Z levels are associated with an elevated thromboembolism risk in nonpregnant patients and may be implicated in the pathogenesis of poor pregnancy outcomes (Almawi, 2013). Similarly, *plasminogen activator inhibitor type 1 (PAI-I)* is an important regulator of fibrinolysis. Certain polymorphisms in the gene promoter have been associated with slightly higher VTE risks. Although these thrombophilias may exacerbate risk among patients when coinherited with other thrombophilias, the American College of Obstetricians and Gynecologists (2020a) has concluded that evidence to recommend screening is insufficient.

Acquired Thrombophilias

Some examples of acquired hypercoagulable states include antiphospholipid syndrome (APS), heparin-induced thrombocytopenia, and cancer.

Antiphospholipid Syndrome

This prothrombotic disorder can affect both the venous and arterial circulations. The deeper veins of the lower limbs and the cerebral arterial circulation are the most frequent sites of venous and arterial thrombosis, respectively (Garcia, 2018; Konkle, 2018). Besides thrombosis, the other major clinical manifestations of APS are adverse obstetrical outcomes (Table 11-4, p. 205). Criteria for APS include (1) at least one otherwise unexplained fetal death at or beyond 10 weeks; (2) at least one preterm birth before 34 weeks' gestation because of eclampsia, severe preeclampsia, or placental insufficiency; or (3) at least three unexplained consecutive spontaneous abortions before 10 weeks. The syndrome is discussed in detail in Chapter 62 (p. 1114).

Testing for antiphospholipid antibodies should be performed in women with an unexplained arterial or venous thromboembolism or a history of one fetal loss or three or more recurrent embryonic or fetal losses (American College of Obstetricians and Gynecologists, 2020a). At this time, preterm severe preeclampsia and early-onset placental insufficiency do not support such testing. That said, there is evidence that antiphospholipid positivity confers a worse prognosis for pregnancies complicated by HELLP syndrome (Pécourt, 2021). These patients should be tested for the presence of three factors: (1) lupus anticoagulant, (2) anticardiolipin immunoglobulin G and M (IgG and IgM) antibodies, and (3) anti-β2 glycoprotein-I IgG and IgM antibodies. If any of these laboratory test results are positive, a confirmatory test is performed 12 weeks later (Connors, 2017).

Based on their study of 750 singleton pregnancies complicated by APS, Saccone and colleagues (2017) found that anticardiolipin antibody is the most common sole antiphospholipid antibody present. Women with APS have a 5- to 12-percent risk of thrombosis during pregnancy or the puerperium. Indeed, up to 25 percent of these thrombotic events occur during pregnancy or in the puerperium.

Thrombophilias and Pregnancy Complications

Contrary to past teaching, no definite causal link between inherited thrombophilias and adverse pregnancy outcomes exists (Ormesher, 2017). The confusion was caused by a number of observational studies that were later followed by large prospective cohort studies. Currently, the American College of Obstetricians and Gynecologists (2020a) does not recommend inherited thrombophilia screening for women with a history of fetal loss or adverse pregnancy outcomes such as fetal-growth restriction, placental abruption, and preeclampsia.

There are no convincing data that link inherited thrombophilias and fetal loss. It follows that there is no benefit to aspirin or heparin therapy as might accrue for recurrent pregnancy loss due to antiphospholipid antibodies (Chap. 62, p. 1116). Stillbirths also are not more common with heterozygous mutations, but there is a weak association with homozygous factor V Leiden mutation (Silver, 2016). Last, there is insufficient evidence to screen for inherited thrombophilias in women with a fetal death (Arachchillage, 2019).

Fetal-growth restriction also is not more common with inherited thrombophilias (American College of Obstetricians and Gynecologists, 2020a; Infante-Rivard, 2002). Likewise, there have been a number of prospective cohort studies that showed no association of inherited thrombophilias with *placental abruption* (Dizon-Townson, 2005; Silver, 2010). Conversely,

Alfirevic and coworkers (2002) reported an association with these and both heterozygosity and homozygosity for factor V Leiden mutations as well as heterozygous prothrombin G20210A mutation.

Studies showing an association of inherited thrombophilias and preeclampsia also are conflicting (American College of Obstetricians and Gynecologists, 2020a). One large systematic review and metaanalysis of nearly 22,000 women did not show an association between factor V Leiden or prothrombin gene mutations with preeclampsia (Rodger, 2010). Similarly, a more recent prospective study failed to show an association between preeclampsia and 12 hereditary thrombophilias (Fernandez Arias, 2019).

Thus, because of uncertainties in the magnitude of risk and in the benefits of prophylaxis given to prevent pregnancy complications in women with heritable thrombophilias, it remains unproven that universal screening is indicated (Louis-Jacques, 2016). In contrast, the association between APS and adverse pregnancy outcomes—including fetal loss, recurrent pregnancy loss, and preeclampsia—is much stronger (Liu, 2019).

Thrombophilia Screening

Given the relatively high incidence of thrombophilia in the population and the low incidence of VTE, universal screening during pregnancy is not cost-effective. Thus, a selective screening strategy is required. The American College of Obstetricians and Gynecologists (2020a) recommends that thrombophilia screening be considered in the following clinical circumstances: (1) a personal history of VTE with or without a recurrent risk factor such as fractures, surgery, or prolonged immobilization; and (2) a first-degree relative (parent or sibling) with a history of a high-risk inherited thrombophilia. As discussed previously, testing for inherited thrombophilias in women who have experienced recurrent fetal loss or adverse pregnancy outcomes is not recommended.

Methods of screening for the more common inherited thrombophilias are shown in Table 55-3. Whenever possible, laboratory testing is performed at least 6 weeks after the thrombotic event, while the patient is not pregnant, and when she is not receiving anticoagulation or hormonal therapy. Last, screening for hyperhomocysteinemia is not recommended (American College of Obstetricians and Gynecologists, 2020a).

DEEP-VEIN THROMBOSIS

Clinical Presentation

During pregnancy, most venous thromboses are confined to the deep veins of the lower extremity. Most of these are located in the iliofemoral and iliac veins without involvement of the calf veins (Chan, 2010). In contrast, in the general population, more than 80 percent of deep-vein thromboses involve calf veins (Huisman, 2015). The vast majority are left sided (Blanco-Molina, 2007). Greer (2003) hypothesizes that this results from compression of the left iliac vein by the right iliac and ovarian arteries, both of which cross the vein only on the left side. Yet, as described in Chapter 56 (p. 994), the ureter is compressed more on the right side.

Signs and symptoms vary depending on the degree of occlusion and the intensity of the inflammatory response. Classically, thrombosis involving the lower extremity is abrupt in onset, and there is pain and edema of the leg and thigh. The thrombus typically involves much of the deep-venous system to the iliofemoral region. Occasionally, reflex arterial spasm causes a pale, cool extremity with diminished pulsations. Calf measurements may identify a discordance in size. Alternatively, there may be appreciable clot, yet little pain, heat, or swelling. Importantly, calf pain, either spontaneous or in response to squeezing or to Achilles tendon stretching—*Homans sign*—may be caused by a strained muscle or contusion. *Importantly, 30 to 60 percent of women with a confirmed lower-extremity acute deep-vein thrombosis (DVT) have an asymptomatic pulmonary embolism* (p. 986).

Diagnosis

Clinical diagnosis of DVT is difficult without testing and is confirmed in only 10 percent of cases (Hull, 1990). Another

TABLE 55-3. How to Test for Thrombophilias

Thrombophilia	Testing Method	Is Testing Reliable During Pregnancy?	Is Testing Reliable During Acute Thrombosis?	Is Testing Reliable with Anticoagulation?
Factor V Leiden mutation	Activated protein C resistance assay (second generation)	Yes	Yes	No
	If abnormal: DNA analysis	Yes	Yes	Yes
Prothrombin gene mutation G20210A	DNA analysis	Yes	Yes	Yes
Protein C deficiency	Protein C activity (<65%)	Yes	No	No
Protein S deficiency	Functional assay (<55%)	No[a]	No	No
Antithrombin deficiency	Antithrombin activity (<60%)	Yes	No	No

[a]If screening in pregnancy is necessary, cutoff values for free protein S antigen levels in the second and third trimesters have been identified at less than 30% and less than 24%, respectively.

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challenge is that many of the common diagnostic tests that have been investigated extensively in nonpregnant patients have not been validated appropriately in pregnancy (Huisman, 2015). Shown in Figure 55-2 is one diagnostic algorithm that can be used for evaluation of pregnant women. With a few modifications, we follow a similar evaluation at Parkland Hospital.

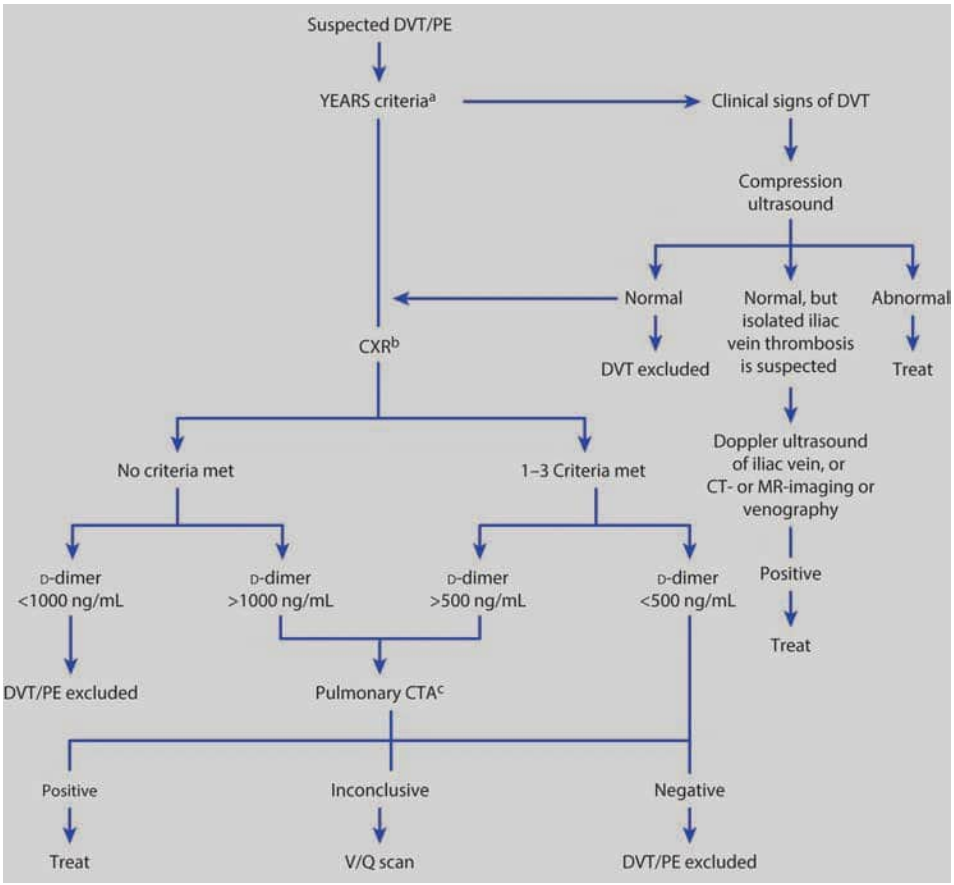

FIGURE 55-2 Algorithm to evalate suspected venous thromboembolism in pregnancy depending upon number of YEARS criteria met. Evidence of DVT should prompt compression ultrasound. [a]The three YEARS criteria are clinical signs of DVT, hemoptysis, and PE as the most likely diagnosis. [b]The American Thoracic Society and Society of Thoracic Radiology recommend CXR; [c]The American Society of Hematology recommends pulmonary V/Q scanning. CT = computed tomography; CTA = computed tomography angiography; CXR = chest x-ray; DVT = deep-vein thrombosis; MR = magnetic resonance; PE = pulmonary embolism; V/Q scan = ventilation perfusion scan. (From Bates, 2018; Guyatt, 2012; Leung, 2011; van der Hulle, 2019; van der Pol, 2019.)

Compression Ultrasonography

With suspected DVT, the initial diagnostic test recommended is compression ultrasonography of the proximal leg veins (American College of Obstetricians and Gynecologists, 2020b). The diagnosis is based on the noncompressibility and typical echoarchitecture of a thrombosed vein. For *nonpregnant* patients with suspected thrombosis, the safety of withholding anticoagulation for 1 week has been established in the setting of a normal compression ultrasound examination (Birdwell, 1998). Serial compression examinations are then performed because isolated undetected calf thromboses that ultimately extend into the proximal veins will do so within 1 to 2 weeks of presentation in approximately a fourth of patients. In *pregnant* women, however, normal findings with ultrasonography do not always exclude a pulmonary embolism. This is because the thrombosis may have already embolized or because it arose from iliac or other deep-pelvic veins, which are less accessible to ultrasound evaluation.

Two studies are helpful for evaluating whether serial examinations are necessary for pregnant women suspected of having a DVT. Chan and associates (2013) studied 221 pregnant and postpartum women presenting with a suspected DVT. The 205 women with a negative initial study result underwent serial testing, which was negative in all cases. Of these, one woman had a pulmonary embolism 7 weeks later. Le Gal and colleagues (2012) studied 210 pregnant and postpartum women with a suspected DVT. Of these, 177 women without a DVT were not anticoagulated and did not undergo serial testing. Two had an objectively confirmed thrombosis diagnosed within 3 months. In sum, these data suggest that a negative single complete compression ultrasonography study may safely exclude the diagnosis of DVT in most pregnant women.

Magnetic Resonance Imaging

This imaging technique allows excellent delineation of anatomical detail above the inguinal ligament. Thus, in many cases, magnetic resonance (MR) imaging is immensely useful for diagnosis of iliofemoral and pelvic vein thrombosis. The venous system can also be reconstructed using MR venography (Chap. 49, p. 875). MR imaging is 100-percent sensitive and 90-percent specific for detection of venographically proven DVT in nonpregnant patients (Erdman, 1990). Importantly, almost half of those without DVT were found to have nonthrombotic conditions that included cellulitis, myositis, edema, hematomas, and superficial phlebitis.

D-dimer Screening Tests

These specific fibrin degradation products are generated when fibrinolysin (plasminogen) degrades fibrin, as occurs in thromboembolism. Their measurement is usually incorporated into diagnostic algorithms for VTE in nonpregnant patients (Righini, 2018). This method was shown to be accurate in the YEARS study (van der Hulle, 2017). Screening with the D-dimer test in pregnancy, however, is problematic for several reasons. Depending

on assay sensitivity, D-dimer serum levels rise with gestational age along with substantively elevated plasma fibrinogen concentrations (Appendix, p. 1228) (Johnson, 2019). Levels are also affected by multifetal gestation and cesarean delivery (Hu, 2020; Miyamoto, 2020). Last, D-dimer concentrations can also be elevated in pregnancy complications such as placental abruption, preeclampsia, and sepsis (Cunningham, 2015).

Three large prospective studies have evaluated D-dimer testing in pregnant women to diagnose VTE. Righini and colleagues (2018) found that D-dimer measurement, bilateral leg ultrasound, and computed tomography-angiogram safely ruled out VTE. Subsequently, van der Pol and coworkers (2019) used a pregnancy-adapted YEARS algorithm to diagnose suspected pulmonary embolism. The algorithm used D-dimer measurements and clinical suspicion to confirm VTE. With none of the clinical criteria present, and with the D-dimer level <1000 ng/mL, or with one or more clinical criteria present and with the D-dimer level <500 ng/mL, pulmonary embolism was safely excluded (see Fig. 55-2). Last, the DiPEP study showed that neither clinical risk factors nor D-dimer levels were accurate in identifying pulmonary embolism in pregnant women (Goodacre, 2019). They concluded that pregnant women with suspected pulmonary embolism should all undergo imaging studies.

The findings of the YEARS study and subsequent others will no doubt guide care. However, currently the American College of Obstetricians and Gynecologists (2020b) recommends against the use of D-dimer assays to diagnose VTE in pregnant women. We agree, and in our view, these positive results need to be duplicated before adaptation of their widespread use in pregnant women. Still, a negative D-dimer assay should be reassuring, unless VTE is the most likely diagnosis (Viau-Lapointe, 2020).

Management of Venous Thromboembolism

Optimal management of VTE during pregnancy has not undergone major clinical study to provide evidence-based practices. There is, however, consensus for treatment with anticoagulation and limited activity. Thrombophilia testing does not change treatment (Connors, 2017). Anticoagulation is initiated with either unfractionated heparin (UFH) or LMWH (Table 55-4). Although either type is acceptable, most recommend one of the LMWHs (American College of Obstetricians and Gynecologists, 2020b; Kearon, 2016). The American Society of Hematology recommends preferential use of LMWH during pregnancy because of better bioavailability, longer plasma half-life, more predictable dose response, reduced risks of osteoporosis and thrombocytopenia, and less frequent dosing (Bates, 2018).

TABLE 55-4. Anticoagulation Regimen Definitions

Anticoagulation Regimen	Definition
Prophylactic LMWH[a]	Enoxaparin, 40 mg SC once daily Dalteparin, 5000 units SC once daily Nadroparin, 2850 units SC once daily Tinzaparin, 4500 units SC once daily
Therapeutic LMWH[b]	Enoxaparin, 1 mg/kg every 12 hours Dalteparin, 200 units/kg once daily Tinzaparin, 175 units/kg once daily Dalteparin, 100 units/kg every 12 hours Target an anti-Xa level in the therapeutic range of 0.6–1.0 units/mL 4 hours after last injection for twice daily regimen; slightly higher doses may be needed for a once-daily regimen.
Prophylactic UFH	UFH, 5000–7000 units SC every 12 hours in first trimester UFH 7500–10,000 units SC every 12 hours in the second trimester UFH, 10,000 units SC every 12 hours in the third trimester, unless the aPTT is elevated
Adjusted dose (therapeutic) UFH[b]	UFH, 10,000 units or more SC every 12 hours in doses adjusted to target aPTT in the therapeutic range (1.5–2.5 × control) 6 hours after injection
Postpartum anticoagulation	Prophylactic, intermediate, or adjusted-dose LMWH for 6–8 weeks as indicated. Oral anticoagulants may be considered postpartum based upon planned duration of therapy, lactation, and patient preference.
Surveillance	Clinical vigilance and appropriate objective investigation of women with symptoms suspicious of deep vein thrombosis or pulmonary embolism. VTE risk assessment should be performed prepregnancy or early in pregnancy and repeated if complications develop, particularly those necessitating hospitalization or prolonged immobility.

[a]Although at extremes of body weight, modification of dose may be required.
[b]Also referred to as weight adjusted, full treatment dose.
aPTT = activated partial thromboplastin time; INR = international normalized ratio; LMWH = low-molecular-weight heparin; SC = subcutaneously; UFH = unfractionated heparin.
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The duration of full anticoagulation varies, and no studies have defined the optimal duration for pregnancy-related thromboembolism. In nonpregnant patients, evidence supports a minimum treatment duration of 3 months (Kearon, 2012). For pregnant patients, the American College of Obstetricians and Gynecologists (2020b) recommends therapeutic anticoagulation for 3 to 6 months followed by intermediate or prophylactic therapy for the duration of pregnancy and the postpartum period. If the woman is not breastfeeding, direct acting oral agents can be considered (p. 985).

Recall that pulmonary embolism develops in as many as 60 percent of patients with untreated venous thrombosis, and anticoagulation decreases this risk to less than 5 percent. In nonpregnant patients, the mortality rate with a pulmonary embolism approximates 1 percent (Douketis, 1998; Pollack, 2011).

With DVT, over several days, leg pain dissipates. After symptoms have abated, graded ambulation is begun. Elastic stockings are fitted, and anticoagulation is continued. Recovery to this stage usually takes 7 to 10 days. Graduated compression stockings can be continued for 2 years after the diagnosis to reduce the incidence of postthrombotic syndrome (Brandjes, 1997). Symptoms include chronic leg paresthesias or pain, intractable edema, skin changes, and leg ulcers. According to the American Society of Hematology, catheter-directed thrombolytic therapy does not mitigate against this complication (Bates, 2018).

Unfractionated Heparin

This agent should be considered for the initial treatment of thromboembolism and in situations in which delivery, surgery, or thrombolysis may be necessary (American College of Obstetricians and Gynecologists, 2020b). UFH can be administered by one of two alternatives: (1) initial intravenous therapy followed by adjusted-dose subcutaneous UFH given every 12 hours; or (2) twice-daily, adjusted-dose subcutaneous UFH with doses adjusted to prolong the activated partial thromboplastin time (aPTT) into the therapeutic range 6 hours post injection (Table 55-5).

For intravenous therapy, several protocols are acceptable. In general, if UFH is used, it is initiated with a bolus intravenous dose of 70 to 100 U/kg, which is 5000 to 10,000 U. This is followed by continuous intravenous infusions beginning at 1000 U/hr or 15 to 20 U/kg/hr. This infusion rate is titrated to achieve an aPTT 1.5 to 2.5 times control values (Linnemann, 2016). Intravenous anticoagulation is maintained for about 5 to 7 days, after which treatment is converted to subcutaneous heparin to maintain the aPTT to at least 1.5 to 2.5 times control throughout the dosing interval. For women with lupus anticoagulant, aPTT does not accurately assess heparin anticoagulation, and thus anti–factor Xa levels are preferred.

Low-molecular-weight Heparin

This is a family of derivatives of unfractionated heparin, and their molecular weights average 4000 to 5000 daltons compared with 12,000 to 16,000 daltons for conventional heparin. None of these heparins cross the placenta, and all exert their anticoagulant activity by activating antithrombin. UFH has equivalent activity against factor Xa and thrombin compared with LMWHs, which have greater activity against factor Xa than against thrombin. They also have a more predictable anticoagulant response and fewer bleeding complications than UFH because of their better bioavailability, longer half-life, dose-independent clearance, and decreased interference with platelets (American College of Obstetricians and Gynecologists, 2020b; Bates, 2018). Their longer half-life prohibits neuraxial analgesia in laboring women. LMWH compounds are cleared by the kidneys and must be used cautiously when there is renal dysfunction.

Several studies have shown that VTE is treated effectively with LMWH (Quinlan, 2004; Tapson, 2008). Using serial venograms, Breddin and associates (2001) observed that these compounds were more effective than UFH in reducing thrombus size without increasing mortality rates or major bleeding complications. Several different treatment regimens using LMWH for treatment of acute VTE are listed in Table 55-4 (American College of Obstetricians and Gynecologists, 2020b).

Whether LMWH requires adjustments during the course of pregnancy is controversial (Berresheim, 2014). The American College of Obstetricians and Gynecologists (2020b) recommends monitoring with an anti-Xa level 4 hours after an injection with dose adjustment to maintain a therapeutic level. Large studies using clinical end points that demonstrate an optimal therapeutic range or show that dose adjustments increase therapy, safety, or efficacy are lacking. Accordingly, the American Society of Hematology and others have concluded that routine monitoring with anti-Xa levels is difficult to justify (Bates, 2018; McDonnell, 2017).

In general, heparin pharmacokinetics includes more rapid clearance of heparins as pregnancy progresses. The peaks of anti-Xa activity of enoxaparin (Lovenox) across pregnancy are shown in Figure 55-3. Similarly, tinzaparin (Innohep) with a dosage of 75 to 175 U/kg/d was necessary to achieve peak anti–factor Xa levels of 0.1 to 1.0 U/mL (Smith, 2004). In studies

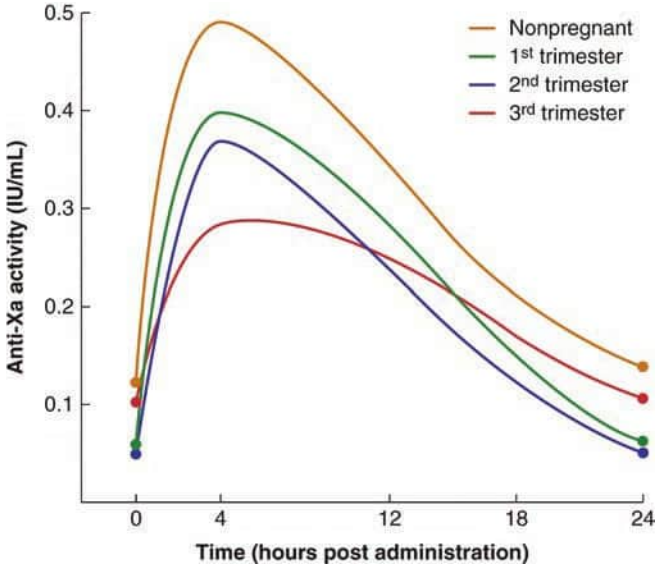

FIGURE 55-3 Anti–factor Xa activity with repeated daily administration of 40 mg enoxaparin subcutaneously in nonpregnant women and those from each trimester (Data from Lebaudy, 2008).

TABLE 55-5. Some Recommendations for Thromboprophylaxis During Pregnancy

Clinical Scenario	Pregnancy		Postpartum	
	ACOG[a]	ASH[b]	ACOG[a]	ASH[b]
Prior single VTE				
Risk factor no longer present	Surveillance only	Surveillance only	Surveillance *or* prophylactic heparin with additional risk factors[f]	Prophylactic *or* intermediate-dose heparin
Pregnancy- or estrogen-related or no known association	Prophylactic *or* intermediate-dose heparin	Prophylactic *or* intermediate-dose heparin	Prophylactic, intermediate, *or* therapeutic-dose heparin	Prophylactic *or* intermediate-dose heparin
Associated with a high-risk thrombophilia[d] or affected first-degree relative	Prophylactic, intermediate, *or* therapeutic-dose heparin	NSS	Prophylactic, intermediate, *or* therapeutic-dose heparin	Prophylactic *or* intermediate-dose heparin
Associated with a low-risk thrombophilia[e]	Prophylactic *or* intermediate-dose heparin	NSS	Prophylactic *or* intermediate-dose heparin	Prophylactic *or* intermediate-dose heparin
Two or more prior VTEs with or without thrombophilia				
Not receiving long-term anticoagulation	Intermediate *or* therapeutic-dose heparin	NSS	Intermediate *or* therapeutic-dose heparin	Prophylactic *or* intermediate-dose heparin
Receiving long-term anticoagulation	Therapeutic-dose heparin	Therapeutic-dose heparin	Resume long-term anticoagulation	Resume long-term anticoagulation
No prior VTE				
No thrombophilia	Surveillance	NSS	Surveillance *or* prophylactic heparin with additional risk factors[f]	NSS
High-risk thrombophilia	Surveillance only *or* prophylactic-dose heparin	Surveillance	Prophylactic *or* intermediate-dose heparin	Prophylactic heparin
Positive family history VTE *and* low-risk thrombophilia[c]	Surveillance *or* prophylactic-dose heparin	Surveillance	Prophylactic *or* intermediate-dose heparin	Surveillance
Low-risk thrombophilia	Surveillance	Surveillance	Surveillance; prophylactic-dose heparin with additional risk factors[f]	Surveillance
Compound heterozygous thrombophilia	Prophylactic *or* intermediate-dose heparin	Prophylactic heparin	Prophylactic *or* intermediate-dose heparin	Prophylactic heparin
Antiphospholipid antibodies				
History of VTE	Prophylactic heparin (?plus low-dose aspirin)	NSS	Prophylactic heparin; referral to specialist[g]	NSS
No prior VTE	Surveillance *or* prophylactic heparin plus low-dose aspirin with recurrent pregnancy loss or stillbirth[f]	NSS	Prophylactic heparin plus low-dose aspirin × 6 weeks with recurrent pregnancy loss or stillbirth[g]	NSS

[a]American College of Obstetricians and Gynecologists 2020a,b.
[b]American Society of Hematology (Bates, 2018).
[c]Postpartum treatment levels should be ≥ antepartum treatment.
[d]Antithrombin deficiency; doubly heterozygous or homozygous for prothrombin 20210A and factor V Leiden.
[e]Heterozygous factor V Leiden or prothrombin 20210A; protein S or C deficiency.
[f]First-degree relative with VTE at <50 years; other major thrombotic risk factors, e.g., obesity, prolonged immobility.
[g]Women with antiphospholipid syndrome should not use estrogen-containing contraceptives.
[h]Treatment is recommended if the diagnosis of antiphospholipid syndrome is based on three or more prior pregnancy losses.
NSS = not specifically stated; VTE = venous thromboembolism.
Prophylactic, intermediate-, and adjusted-dose regimens are listed in Table 55-4.

of dalteparin (Fragmin) pharmacokinetics, conventional starting doses of dalteparin—100 U/kg every 12 hours—were likely insufficient to maintain full anticoagulation in pregnant women (Barbour, 2004; Jacobsen, 2003). Thus, slightly higher doses than that shown in Table 55-4 may be required.

Any concerns regarding teratogenicity of enoxaparin have been obviated (American College of Obstetricians and Gynecologists, 2020b; Bates, 2021). A comprehensive study of 1267 pregnant women treated with tinzaparin found no cases of heparin-induced thrombocytopenia, maternal deaths, or complications from regional analgesia (Nelson-Piercy, 2011). A total of 43 women (3.4 percent) required medical intervention for bleeding. Of 15 stillbirths, four were judged as possibly being related to tinzaparin use. LMWHs have been judged to be safe during breastfeeding (Bates, 2018).

Labor and Delivery

Women receiving either therapeutic or prophylactic anticoagulation should be converted from LMWH to the shorter-half-life UFH in the last month of pregnancy or sooner if delivery appears imminent. The purpose of conversion to UFH has less to do with any risk of maternal bleeding at the time of delivery, but rather with neuraxial blockade complicated by an epidural or spinal hematoma (Chap. 25, p. 478). The Society for Obstetric Anesthesia and Perinatology recommends that UFH low-dose thromboprophylaxis be withheld for 4 to 6 hours; UFH intermediate-dose thromboprophylaxis for 12 hours; and UFH therapeutic dose for 24 hours before neuraxial analgesia (Leffert, 2018). For LMWH, the Society recommends to withhold low doses for 12 hours; intermediate doses 12 to 24 hours; and therapeutic doses 24 hours.

If a woman begins labor while taking UFH, clearance can be verified by an aPTT. Reversal of heparin with protamine sulfate—1 mg per 100 units heparin with a maximum dose of 50 mg—is rarely required and is not indicated with a prophylactic dose of heparin. For women in whom anticoagulation therapy has temporarily been discontinued, pneumatic compression devices are recommended.

Warfarin Compounds

Vitamin K antagonists are generally contraindicated because they readily cross the placenta and cause fetal death and malformations from hemorrhages. This is discussed in detail in Chapter 8 (p. 156). Their sole antepartum use is in women with a mechanical heart valve (Daughety, 2020). These compounds do not accumulate in breast milk and are thus safe during breastfeeding.

Postpartum venous thrombosis is usually treated with intravenous heparin and oral warfarin initiated simultaneously. The initial dose of warfarin is 5 to 10 mg for the first 2 days. Subsequent doses are titrated to achieve an international normalized ratio (INR) of 2 to 3. To avoid paradoxical thrombosis and skin necrosis from the early antiprotein C effect of warfarin, these women are maintained on therapeutic doses of UFH or LMWH for 5 days and until the INR is in a therapeutic range for 2 consecutive days (American College of Obstetricians and Gynecologists, 2020b).

Treatment in the puerperium may require larger doses of anticoagulant. Brooks and colleagues (2002) compared anticoagulation in postpartum women with that of age-matched nonpregnant controls. The former required a significantly larger median total dose of warfarin—45 versus 24 mg—and a longer time—7 versus 4 days—to achieve the target INR.

Direct-acting Oral Anticoagulants

Of these newer oral anticoagulants, dabigatran (Pradaxa) inhibits thrombin and rivaroxaban (Xarelto) and apixaban (Eliquis) inhibit factor Xa. These agents are becoming the drugs of choice for nonpregnant subjects with thromboembolism (Kruger, 2019). Currently, very few reports address these newer agents during pregnancy and breastfeeding, and thus the human reproductive risks are essentially unknown (Lameijer, 2018; Rosenbloom, 2019). Despite this, the GARFIELD-VTE study reported that direct-acting oral anticoagulant use in pregnant women was gaining favor (Jerjes-Sanchez, 2021). Dabigatran crosses the placenta, however, it is unknown whether any of these agents are excreted in breast milk (Bapat, 2014). At this time, because of the potential for infant harm, a decision should be made to either avoid breastfeeding or use an alternative anticoagulant, such as warfarin, in breastfeeding women (Bates, 2021; Kruger, 2019).

■ Complications of Anticoagulation

Three significant complications associated with anticoagulation are hemorrhage, thrombocytopenia, and osteoporosis. The latter two are unique to heparin, and their risk may be reduced with LMWHs. The most serious complication is hemorrhage, which is more likely if there has been recent surgery or lacerations. Troublesome bleeding is also more likely if the heparin dosage is excessive. Unfortunately, management schemes using laboratory testing to identify when a heparin dosage is sufficient to inhibit further thrombosis, yet not cause serious hemorrhage, have been discouraging.

Heparin-induced Thrombocytopenia

There are two types—the most common is a nonimmune, benign, reversible thrombocytopenia that develops within the first few days of therapy and resolves in approximately 5 days without therapy cessation. The second is the severe form of heparin-induced thrombocytopenia, which results from an immune reaction involving IgG antibodies directed against complexes of platelet factor 4 and heparin. The diagnosis of heparin-induced thrombocytopenia (HIT) is based on a drop in the platelet count of more than 50 percent or thrombosis beginning 5 to 10 days after the start of heparin in association with the appearance of platelet-activating HIT antibodies. The fall in platelet count in HIT occurs rapidly—over a period of 1 to 3 days—and is assessed relative to the highest platelet count after the start of heparin. The typical nadir is 40,000 to 80,000 platelets per microliter (Greinacher, 2015).

Although the incidence of HIT is approximately 3 to 5 percent in nonpregnant individuals, it is <0.1 percent in obstetrical patients (American College of Obstetricians and Gynecologists, 2020b). Fausett and coworkers (2001) reported no cases among 244 heparin-treated gravidas compared with 10 among 244 nonpregnant patients. Accordingly, the American

College of Chest Physicians recommends against platelet count monitoring when the risk of HIT is considered to be <1 percent (Linkins, 2012). In others, they suggest monitoring every 2 or 3 days from day 4 until 14.

Women with a presumptive diagnosis of HIT should have laboratory testing for antiplatelet antibodies or by functional assays. However, these tests often require several days to return results, so initial management should be directed by clinical findings. Heparin therapy is stopped, and alternative anticoagulation initiated. LMWH may not be entirely safe because it has some cross reactivity with UFH. The American Society of Hematology recommends use of fondaparinux (Arixtra), which is a pentasaccharide factor Xa inhibitor (Bates, 2018). Successful use in pregnancy has been reported (De Carolis, 2015; Elsaigh, 2015). Last, platelet transfusions are avoided (Greinacher, 2015).

Heparin-induced Osteoporosis

Bone loss may develop with long-term heparin administration—usually 6 months or longer—and is more prevalent in cigarette smokers. UFH can cause osteopenia, and this is less likely with LMWHs. Women treated with any heparin should be encouraged to take an oral daily 1500-mg calcium supplement (Cunningham, 2005; Lockwood, 2012).

■ Anticoagulation and Abortion

The treatment of DVT with heparin does not preclude pregnancy termination by careful curettage. After the products are removed without trauma to the reproductive tract, full-dose heparin can be restarted in several hours.

■ Anticoagulation and Delivery

The effects of heparin on blood loss at delivery depend on several variables: (1) dose, route, and timing of administration; (2) number and depth of incisions and lacerations; (3) intensity of postpartum myometrial contractions; and (4) presence of other coagulation defects. Blood loss should not be greatly increased with vaginal delivery if there are no lacerations, and the uterus promptly contracts. Unfortunately, such ideal circumstances do not always prevail. Thus, heparin therapy generally is stopped during labor and delivery.

The American College of Obstetricians and Gynecologists (2020b) recommends restarting UFH or LMWH no sooner than 4 to 6 hours after vaginal delivery or 6 to 12 hours after cesarean delivery. From their review, Moriuchi and associates (2019) found that *thromboprophylaxis* started within 24 hours after cesarean delivery was safe. At Parkland Hospital, we wait at least 24 hours to restart therapeutic-dose heparin after cesarean delivery or after vaginal delivery with significant lacerations.

SUPERFICIAL VENOUS THROMBOPHLEBITIS

Thrombosis limited strictly to the superficial veins of the saphenous system is typically associated with varicosities or as a sequela of an indwelling intravenous catheter. It is treated with analgesia, elastic support, heat, and rest. Superficial vein thrombosis raises the risk of DVT four- to six-fold. In a metaanalysis of nonpregnant patients with thrombophlebitis, 18 percent had a concomitant DVT and 7 percent had a pulmonary embolism (Di Minno, 2016). Although controversial, the American Society of Hematology suggests LMWH therapy (Bates, 2018).

PULMONARY EMBOLISM

Although it causes approximately 10 percent of maternal deaths, pulmonary embolism is relatively uncommon during pregnancy and the puerperium. According to Marik and Plante (2008), 70 percent of gravidas presenting with a pulmonary embolism have associated clinical evidence of DVT. And recall that between 30 and 60 percent of women with a DVT will have a coexisting silent pulmonary embolism.

■ Clinical Presentation

In almost 2500 nonpregnant patients with a proven pulmonary embolism, symptoms included dyspnea in 82 percent, chest pain in 49 percent, cough in 20 percent, syncope in 14 percent, and hemoptysis in 7 percent (Goldhaber, 1999). Other predominant clinical findings typically include tachypnea, apprehension, and tachycardia. In some cases, an accentuated pulmonic closure sound, rales, and/or friction rub is heard.

Right axis deviation and T-wave inversion in the anterior chest leads may be evident on the electrocardiogram. In most cases, chest radiography results are normal. In others, nonspecific findings may include atelectasis, an infiltrate, cardiomegaly, or an effusion. Vascular markings in the lung region supplied by the obstructed artery can be lost. Although most women are hypoxemic, a normal arterial blood gas analysis does not exclude pulmonary embolism. Approximately a third of young patients have P_{O2} values >80 mm Hg. Thus, the alveolar- arterial oxygen tension difference is a more useful indicator of disease. More than 86 percent of patients with acute pulmonary embolism will have an alveolar-arterial difference >20 mm Hg (Lockwood, 2012). Even with massive pulmonary embolism, signs, symptoms, and laboratory data to support the diagnosis may be deceptively nonspecific.

■ Massive and Submassive Pulmonary Embolism

Defined as embolism causing hemodynamic instability, these account for 5 to 10 percent of cases (Handal-Örefice, 2019). Acute mechanical obstruction of the pulmonary vasculature causes increased vascular resistance and pulmonary hypertension followed by acute right ventricular dilation. In otherwise healthy patients, significant pulmonary hypertension does not develop until 60 to 75 percent of the pulmonary vascular tree is occluded (Guyton, 1954). Moreover, circulatory collapse requires 75- to 80-percent obstruction. This is depicted in Figure 55-4 and emphasizes that most acutely symptomatic emboli are large and likely a saddle embolism (Singhal, 1973). These are suspected when the pulmonary artery pressure is substantively increased as estimated by echocardiography.

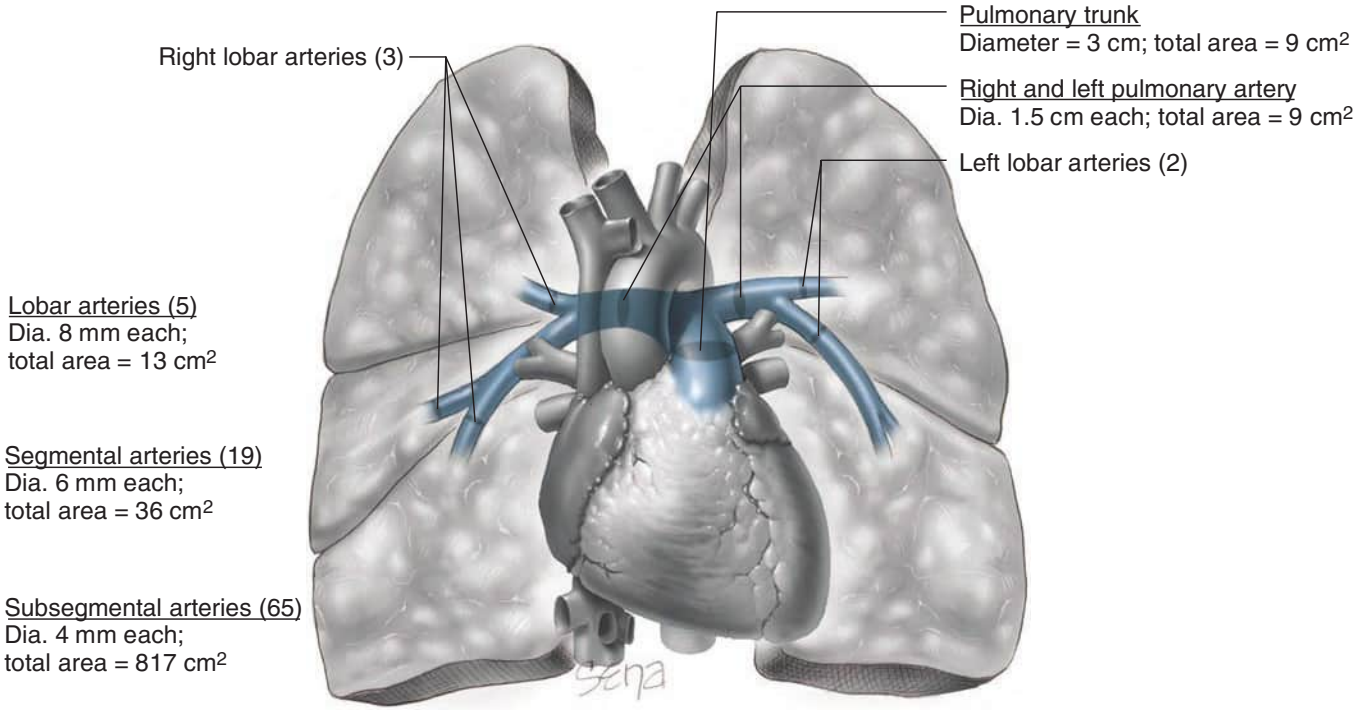

FIGURE 55-4 Schematic of pulmonary arterial circulation. Note that the cross-sectional area of the pulmonary trunk and the combined pulmonary arteries is 9 cm. A large saddle embolism could occlude 50 to 90 percent of the pulmonary tree, causing hemodynamic instability. As the arteries give off distal branches, the total surface area rapidly increases, that is, 13 cm for the combined five lobar arteries, 36 cm for the combined 19 segmental arteries, and more than 800 cm for the total 65 subsegmental arterial branches. Thus, hemodynamic instability is less likely with emboli past the lobar arteries.

Submassive embolism is diagnosed when there is evidence of right ventricular dysfunction (Handal-Örefice, 2019). The mortality rate approaches 25 percent, which compares with a 1-percent rate without such dysfunction (Kinane, 2008). It is important in these cases to infuse crystalloids carefully and to support blood pressure with vasopressors. Aggressive intravenous fluid infusion has been associated with worsening right-sided ventricular dysfunction (Konstantides, 2014). As discussed on page 988, oxygen treatment, tracheal intubation, and mechanical ventilation are completed preparatory to thrombolysis, filter placement, or embolectomy.

■ Diagnosis

In most cases, recognition of a pulmonary embolism requires a high index of suspicion that prompts objective evaluation. Exposure of the mother and fetus to ionizing radiation is a concern when investigating a suspected pulmonary embolism during pregnancy. However, this concern is largely overruled by the hazards of missing a potentially fatal diagnosis. Moreover, erroneously assigning a diagnosis of pulmonary embolism to a pregnant woman is also fraught with problems. It unnecessarily exposes the mother and fetus to the risks of anticoagulation treatment and will impact delivery plans, future contraception, and thromboprophylaxis during subsequent pregnancies. Therefore, investigations should aim for diagnostic certainty (Cohen, 2020).

Diagnosis of a pulmonary embolism follows the same algorithm as for DVT shown in Figure 55-2. In addition to compression ultrasound of the extremities, if a pulmonary embolism is suspected, chest x-ray and electrocardiogram may be revealing. Echocardiography is useful to detect other conditions that mimic pulmonary embolism—acute myocardial infarction, pericardial tamponade, and aortic dissection. Further imaging with computed tomography (CT) scanning, MR imaging, or ventilation-perfusion lung scanning confirms the diagnosis (American College of Obstetricians and Gynecologists, 2020b). As discussed later (p. 988), the American Society of Hematology recommends lung scanning as the first-line diagnostic tool (Bates, 2018). At Parkland Hospital we preferentially use CT-pulmonary angiography for suspected pulmonary embolism.

Computed Tomographic Pulmonary Angiography

Multidetector CT-pulmonary angiography (CTPA) is the most commonly employed technique to diagnose pulmonary embolism in nonpregnant patients. The technique is described further in Chapter 49 (p. 874), and an imaging example is shown in Figure 55-5. The estimated fetal radiation exposure averages 0.45 to 0.6 mGy. The estimated maternal breast dose is 10 to 70 mGy (Waksmonski, 2014).

CTPA has many advantages, but we find that the higher resolution allows detection of previously inaccessible smaller distal emboli that have uncertain clinical significance. Similar observations have been reported by others (Anderson, 2007; Hall, 2009). Bourjeily and colleagues (2012) performed a follow-up study of 318 pregnant women who had a negative CTPA performed for a suspected pulmonary embolism. All

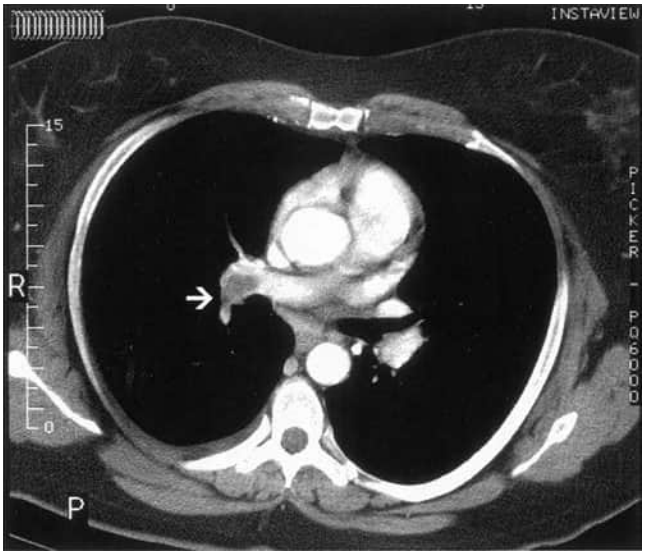

FIGURE 55-5 Axial image of the chest from a four-channel multidetector spiral computed tomographic scan performed after administration of intravenous contrast. There is enhancement of the pulmonary artery with a large thrombus on the right (*arrow*) consistent with pulmonary embolism. (Reproduced with permission from Dr. Michael Landay.)

were seen 3 months following their initial presentation or at 6 weeks postpartum. None of these women were subsequently diagnosed with a thromboembolism.

Ventilation-Perfusion Scintigraphy Lung Scan

This technique involves a small dose of radiotracer such as intravenously administered technetium-99m macroaggregated albumin. There is negligible fetal and maternal breast radiation exposure—0.1 to 0.4 mGy. The scan may not provide a definite diagnosis because many other conditions can cause perfusion defects. Examples are pneumonia or local bronchospasm. Chan and coworkers (2002) found that a fourth of ventilation-perfusion scans in pregnant women were nondiagnostic. In these instances, CTPA is preferred (Tromeur, 2017).

To compare the performance of lung scintigraphy and CTPA, Revel and associates (2011) evaluated 137 pregnant women with suspected pulmonary embolism. The two modalities performed comparably and had no significant differences between the proportions of positive, negative, or indeterminate results. Specifically, the proportion of indeterminate results for both approximated 20 percent, Similarly, one systematic review concluded that both CTPA and lung scintigraphy seem appropriate for exclusion of pulmonary embolism during pregnancy (van Mens, 2017).

Intravascular Pulmonary Angiography

This requires catheterization of the right side of the heart and is considered the reference test for pulmonary embolism. With newer-generation multidetector CT scanners, however, the role of invasive pulmonary angiography has been questioned. This is especially true given the higher radiation exposure for the fetus (Konstantinides, 2014). Other detractions are that it can be time consuming, uncomfortable, and associated with dye-induced allergy and renal failure. It is reserved for confirmation when less invasive tests are equivocal.

Management

Immediate treatment for pulmonary embolism is full anticoagulation similar to that for DVT as discussed on page 982 and shown in Table 55-4. There are several complementary procedures that may be indicated.

Vena Caval Filters

The woman who has very recently suffered a pulmonary embolism and who must undergo cesarean delivery presents a particularly serious problem. Reversal of anticoagulation may be followed by another embolus, and surgery while fully anticoagulated frequently results in life-threatening hemorrhage or troublesome hematomas. In these cases, placement of a vena caval filter should be considered before surgery (Marik, 2008). Moreover, in the very infrequent circumstances in which heparin therapy fails to prevent recurrent pulmonary embolism from the pelvis or legs or in which embolism develops from these sites despite heparin treatment, a vena caval filter may also be indicated. Such filters can also be used following massive emboli in patients who are not candidates for thrombolysis.

The device is inserted through either the jugular or femoral vein and can be inserted during labor (Jamjute, 2006). Routine filter placement has no added advantage to heparin given alone (Decousus, 1998). Retrievable filters may be used as short-term protection and then removed 1 to 2 weeks later (Liu, 2012). From their systematic review, Harris and colleagues (2016) found that complication rates in pregnant women with vena caval filters are comparable to those in nonpregnant patients. In another series of 24 filters placed in obstetrical patients, 29 percent had complications including removal failure (Rottenstreich, 2019).

Thrombolysis

Compared with heparin, thrombolytic agents provide more rapid lysis of pulmonary clots and improvement of pulmonary hypertension in life-threatening cases (Bates, 2021; Goldhaber, 2018). In one study of nonpregnant patients receiving heparin for an acute submassive pulmonary embolism, those receiving the recombinant tissue plasminogen activator *alteplase* had a lower risk of death or treatment escalation (Konstantinides, 2002). One metaanalysis of trials involving nonpregnant patients reported that the risk of recurrence or death was significantly lower in patients given thrombolytic agents and heparin compared with those given heparin alone—10 versus 17 percent (Agnelli, 2002). Importantly, however, there were five—2 percent—fatal bleeding episodes in the thrombolysis group and none in the heparin-only group.

There have been several case reports and reviews of thrombolysis in pregnant women. Leonhardt and coworkers (2006) identified 28 reports of tissue plasminogen activator use during pregnancy. Ten cases were for thromboembolism. Complication rates were similar to those in nonpregnant patients, and the authors concluded that such therapy should not be withheld during pregnancy if indicated. Akazawa and Nishida

(2017) reviewed 13 cases of systemic thrombolytic therapy administered during the first 48 hours after delivery. Blood transfusion was required in five of the eight cesarean deliveries, including three cases of hysterectomy and two cases of hematoma drainage. Sousa-Gomes and associates (2019) reviewed outcomes in 141 pregnant women undergoing thrombolysis for VTE or stroke. Maternal death complicated 3 percent of cases, and major bleeding occurred in 9 percent.

Embolectomy

Given the efficacy of thrombolysis and filters, surgical embolectomy is uncommonly indicated. Published experience with emergency embolectomy during pregnancy is limited to case reports (Colombier, 2015; Saeed, 2014). From their review, Ahearn and colleagues (2002) found that although the operative risk to the mother is reasonable, the stillbirth rate is 20 to 40 percent.

THROMBOPROPHYLAXIS

A Cochrane review of guidelines for thromboprophylaxis in pregnancy concluded that there is a lack of overall agreement about which women should be offered thromboprophylaxis (Middleton, 2021). The American Society of Hematology summarized that evidence-based recommendations rely largely on observational studies and on data extrapolated from nonpregnant patients. In many cases, this led them to *suggest*—rather than *recommend*—various schemes for thromboprophylaxis (Bates, 2018). In an earlier study, Cleary-Goldman and coworkers (2007) surveyed 151 fellows of the American College of Obstetricians and Gynecologists and reported that intervention without a clear indication is common. Table 55-5 lists several consensus recommendations for thromboprophylaxis. In some cases, more than one option is listed, thus illustrating the confusion that currently reigns. It is important to emphasize that the decision to treat with anticoagulation in pregnancy is influenced by personal VTE history, family history of VTE, severity of thrombophilias, and additional risk factors such as obesity, cesarean delivery, or prolonged immobility (American College of Obstetricians and Gynecologists, 2020a).

■ Prior Venous Thromboembolism

In general, either antepartum surveillance or heparin prophylaxis is recommended for women with prior VTE but without a recurrent risk factor. Tengborn and associates (1989), however, suggested that such management may not be effective. They reported outcomes in 87 pregnant Swedish women who had prior thromboembolic disease and were not tested for thrombophilias. Despite unfractionated heparin prophylaxis, which was usually 5000 U twice daily, 15 percent developed antepartum VTE recurrence. This compared with 12 percent not given heparin.

Brill-Edwards and colleagues (2000) prospectively studied 125 pregnant women with a single prior VTE. Antepartum heparin was not given, but anticoagulant therapy was given for 4 to 6 weeks postpartum. Six women had a recurrent venous thrombosis, but there were no recurrences in women without a known thrombophilia or whose prior thrombosis was associated with a temporary risk factor. A study of 88 women without antiphospholipid antibodies and who were not given antithrombotic prophylaxis reported a subsequent pregnancy- or puerperium-related VTE in 22 percent (De Stefano, 2006). Of 20 women whose original thrombosis was associated with a transient risk factor—not including pregnancy or oral contraceptive use—there were no recurrences during pregnancy, but two during the puerperium. These findings imply that women with a prior thrombosis in association with a thrombophilia or in the absence of a temporary risk factor generally should be given both antepartum and postpartum prophylaxis (Connors, 2017). These data also suggest that for women with a prior VTE, antithrombotic prophylaxis during pregnancy could be tailored according to the circumstances of the original event.

It is important to emphasize that VTE may recur despite antithrombotic prophylaxis. A study of 270 women who had at least one previous VTE found that 10 percent suffered a recurrent VTE (Galambosi, 2014). Twelve of these recurrences occurred early in pregnancy before the initiation of antithrombotic prophylaxis, and 16 occurred despite prophylactic use of LMWH.

Our practice at Parkland Hospital for many years for women with a history of prior VTE was to administer subcutaneous UFH, 5000 to 7500 units two to three times daily. More recently, we have used 40 mg of enoxaparin given subcutaneously daily with transition to UFH near delivery. With either regimen, the recurrence of documented DVT embolization has been uncommon.

■ Cesarean Delivery

The risk for DVT and especially for fatal thromboembolism rises many fold following cesarean delivery compared with that after vaginal delivery. When considering that a third of women giving birth in the United States yearly undergo cesarean delivery, pulmonary embolism is understandably a major cause of maternal mortality (Creanga, 2017; Petersen, 2019). That said, the lack of consensus described earlier by Middleton and coworkers (2021) creates considerable variation in the current recommendations promulgated by the American College of Obstetricians and Gynecologists, the Royal College of Obstetricians and Gynaecologists, and the American College of Chest Physicians (Palmerola, 2016).

Adherence to individual society guidelines following cesarean delivery confers a greater risk in some instances. According to the Society for Maternal-Fetal Medicine (2020), if American College guidelines were followed, only 1 percent of these women would be candidates for thromboprophylaxis. Almost 85 percent of the same cohort would be given thromboprophylaxis following Royal College guidelines and about 35 percent if American College of Chest Physician guidelines were followed. Some comparisons of these thromboprophylaxis guidelines are shown in Table 55-6.

Since 2011, the American College of Obstetricians and Gynecologists (2020b) recommends placement of pneumatic compression devices before cesarean delivery for all women not already receiving thromboprophylaxis. This recommendation was based primarily on consensus and expert opinion. For patients

TABLE 55-6. Thromboprophylaxis Guidelines for Women Undergoing Cesarean Delivery

Organization	Recommendations	Risk Factors
ACOG[a]	Pneumatic compression devices for all Pharmacological prophylaxis for risk factors	Risk factors not defined; individualize therapy
SMFM[b]	Pneumatic compression devices for all Prophylactic LMWH Intermediate-dose LMWH Individualized therapy	History of VTE Thrombophilia without history of a VTE Class III obesity with a thrombophilia or history of a VTE Combination of the above factors
RCOG[c]	Prophylactic LMWH for 10 days	Cesarean during labor BMI >40 kg/m^2 Medical comorbidities *or* 2 or more of the following: age >35, parity >3, obesity, smoker, varicose veins, systemic infection, preeclampsia, preterm delivery, stillbirth, operative vaginal delivery, PPH, prolonged admission
	Prophylactic LMWH for 6 weeks	Prior VTE High-risk thrombophilia Low-risk thrombophilia and family history of VTE Antenatal LMWH therapy

[a]ACOG = American College of Obstetricians and Gynecologists, 2020b.
[b]SMFM = Society for Maternal-Fetal Medicine, 2020.
[c]RCOG = Royal College of Obstetricians and Gynaecologists, 2015.
BMI = body mass index; CHF = congestive heart failure; DM = diabetes mellitus; IBD = inflammatory bowel disease; LMWH = low-molecular-weight heparin; PPH = postpartum hemorrhage; VTE = venous thromboembolism

undergoing cesarean delivery with additional risk factors for thromboembolism, both pneumatic compression devices and UFH or LMWH may be recommended. The College stipulated that cesarean delivery in an emergency setting should not be delayed because of the time necessary to begin thromboprophylaxis.

Implementation of this strategy by the Hospital Corporation of America, the largest for-profit obstetrical health care delivery system in the United States, was associated with a reduction in deaths from pulmonary embolism from 7 of 458,097 cesarean births to 1 of 465,880 cesarean births (Clark, 2011, 2014).

In 2016, the National Partnership for Maternal Safety published several consensus recommendations for the prevention of maternal VTE (D'Alton, 2016). These recommendations included expanded use of antenatal thromboprophylaxis for women hospitalized 3 days or longer, expanded use of prophylaxis during and after vaginal delivery, and expanded use of pharmacological prophylaxis to most women after cesarean delivery. In response, Sibai and Rouse (2016) expressed concern that these new recommendations derive from sparse data of questionable applicability to obstetrical patients. They called for better quality evidence to measure the benefits, harms, and costs of increased pharmacological thromboprophylaxis. As aptly expressed by Macones (2017), "an intervention, such as increased postcesarean pharmacologic thromboprophylaxis, where there are legitimate concerns about efficacy and safety, requires a much higher degree of evidence before a national guideline is implemented." We agree with these sentiments.

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CHAPTER 56

Renal and Urinary Tract Disorders

Disorders of the kidneys and urinary tract are commonly encountered in pregnancy. Some precede pregnancy—one example is nephrolithiasis. Pregnancy-induced changes may predispose to the development or worsening of urinary tract disorders—an example is the markedly increased risk for pyelonephritis. Last, renal pathology unique to pregnancy, such as preeclampsia, can develop. In one Australian study, kidney disorders had an incidence of 0.3 percent in 407,580 births (Fitzpatrick, 2019).

PREGNANCY-INDUCED URINARY TRACT CHANGES

During normal pregnancy, significant changes in both structure and function take place in the urinary tract (Chap. 4, p. 67). The kidneys become larger, and dilation of the renal calyces and ureters can be striking. Some dilation develops before 14 weeks and likely is due to progesterone-induced relaxation of the muscularis. More marked dilation is apparent beginning in midpregnancy and stems from ureteral compression, especially on the right side. *Vesicoureteral reflux* also occurs during pregnancy. Important consequences of these physiological changes are an increased risk of upper urinary infection and erroneous interpretation of studies.

Evidence of functional renal hypertrophy becomes apparent very soon after conception. Glomeruli are larger, although cell numbers are not greater (Strevens, 2003). Intrarenal vasodilation lowers resistance of both afferent and efferent arterioles, and leads to higher effective renal plasma flow and glomerular filtration (Helal, 2012; Hussein, 2014). By 12 weeks' gestation, the glomerular filtration rate (GFR) is already 20 percent above nonpregnant values (Hladunewich, 2004). Ultimately, renal plasma flow rises by 40 percent and GFR by 65 percent. Consequently, serum concentrations of creatinine and urea decline substantively across pregnancy. Thus, values within a nonpregnant normal range may be abnormal for pregnancy (Appendix, p. 1232). Other alterations include those related to acid–base homeostasis and osmoregulation.

Assessment of Renal Function During Pregnancy

Urinalysis results are essentially unchanged during normal pregnancy, except for occasional glucosuria. In nondiabetic gravidas, glucosuria is thought to stem from a pregnancy-related reduced rate of renal tubular glucose reabsorption (Welsh, 1960). This normal physiological change may add confusion and concerns for a gestational diabetes mellitus (GDM) diagnosis. Indeed, 1+ or greater urine dipstick readings have been associated with subsequent GDM diagnosis later in pregnancy. Despite this association, urine dipstick testing alone shows poor sensitivity

to diagnose GDM (Buhlin, 2004; Olagbuji, 2015). For women with glucosuria, no guidelines in the United States direct practice, but in the United Kingdom, early oral glucose testing is considered for those with an isolated 2+ or repetitive 1+ urine dipstick readings (National Institute for Health And Clinical Excellence, 2015). This seems to be a reasonable approach.

Protein excretion is slightly elevated, but it seldom reaches levels that are detected by usual screening methods. Higby and colleagues (1994) reported 24-hour protein excretion in normal pregnancy to be 115 mg, with a 95-percent confidence level of 260 mg/d (Chap. 4, p. 68). This value did not significantly differ by trimester. Albumin constitutes only a small part of total protein excretion, and amounts range from 5 to 30 mg/d. From their review, Airoldi and Weinstein (2007) concluded that proteinuria must exceed 300 mg/d to be considered abnormal. Many consider 500 mg/d to be important with gestational hypertension. As an initial surrogate for 24-hour collections, quantification of the urinary protein-to-creatinine ratio in a spot urine sample is helpful in estimating a 24-hour protein excretion rate. The ratio is nearly the same numerically as the number of grams of protein excreted in urine per day. This measurement is best obtained from a first morning void. Surprisingly, women with lower urinary tract infections do not have more proteinuria (Stephens, 2019).

Blood is another urinalysis marker. In one study, 3 percent of 4307 nulliparas who were screened before 20 weeks' gestation had *idiopathic hematuria*, defined as 1+ or greater blood on urine dipstick (Stehman-Breen, 2002). These women had a twofold higher risk of developing preeclampsia. However, the link between preeclampsia and hematuria has not been found by all (Brown, 2005; Shahriaki, 2016). In another study of 1000 women screened during pregnancy, Brown and coworkers (2005) reported a 15-percent incidence of dipstick microscopic hematuria. Most women had trace levels of hematuria, and the false-positive rate with this tool was 40 percent. Notably, other elements such as vitamin C, povidone-iodine, myoglobin, free hemoglobin can produce false-positive results. Thus, positive dipstick results should prompt formal urinalysis. Microscopic hematuria is defined as >3 red blood cells (RBCs) per high-powered field (HPF).

For verified asymptomatic microscopic hematuria, few guidelines direct the best evaluation. History and physical often point to benign causes. If not, initial exclusion of infection by urinalysis or culture is reasonable. For early glomerular disease, serum creatinine and blood urea nitrogen levels, a spot protein-to-creatinine ratio or 24-hour urine collection, and urinalysis with examination of urine sediment can aid diagnosis. With this last step, proteinuria, dysmorphic RBCs, and cellular casts are characteristics. To help exclude neoplastic or stone disease, magnetic resonance urography (MRU) of the upper and lower urinary tract and cystoscopy is suitable in pregnancy (Davis, 2012). However, the American College of Obstetricians and Gynecologists (2017) recommends against the last steps to exclude cancer for asymptomatic, low-risk, never-smoking women younger than 50 years who have ≤25 RBCs seen per HPF.

If the serum creatinine level in pregnancy persistently exceeds 0.9 mg/dL (75 µmol/L), intrinsic renal disease should be suspected (Wiles, 2019a). In these cases, some determine the creatinine clearance as an estimate of the GFR.

Of imaging tools, *sonography* informs on renal size, relative consistency, and elements of obstruction. Full-sequence *intravenous pyelography* is not done routinely. However, the clinical situation may warrant *one-shot pyelography*, in which contrast medium injection is followed after 30 minutes by one or two abdominal radiographs (Chap. 49, p. 873). Magnetic resonance (MR) imaging of renal masses provides excellent results due to its excellent resolution at soft-tissue interfaces (Putra, 2009). *Cystoscopy* is performed for the same indications as in the nonpregnant population. *Ureteroscopy* similarly may be indicated and carries an approximate 5-percent complication rate during stone removal during pregnancy (Johnson, 2012).

Although relatively safe during pregnancy, *renal biopsy* usually is postponed unless results may change therapy. From a review of 243 biopsies in pregnant women, the incidence of complications was 7 percent compared with 1 percent in postpartum women (Piccoli, 2013). Lindheimer and colleagues (2013) recommend its consideration for those with rapid deterioration of renal function of unclear etiology or with symptomatic nephrotic syndrome. We have found biopsy helpful in selected cases to direct management. Renal biopsy performed in *normal* pregnant volunteers showed that approximately 50 percent had slight to moderate glomerular endotheliosis (Strevens, 2003). In contrast, all 27 women with proteinuric hypertension had moderate to severe endotheliosis.

Pregnancy After Unilateral Nephrectomy

After removal of one kidney, a remaining normal kidney provides augmented compensatory renal function. With pregnancy, this is further amplified. Functional evaluation of the remaining kidney is essential, even though most women have no difficulty in pregnancy. At minimum, the serum creatinine level is measured and a urine spot protein:creatinine ratio is determined. No long-term permanent consequences accompany kidney donation done before pregnancy. However, the incidence of subsequent preeclampsia is greater (Davis, 2019; Steele, 2019; Vannevel, 2018).

URINARY TRACT INFECTIONS

Asymptomatic or *covert bacteriuria* is frequent in pregnancy and is an infection precursor. True infections of the urinary tract are the most prevalent bacterial infections during pregnancy. Symptomatic infection includes *cystitis*, or it may involve the renal calyces, pelvis, and parenchyma to cause *pyelonephritis*.

Organisms from the normal perineal flora cause urinary infections. *Escherichia coli* strains most commonly cause nonobstructive pyelonephritis. In approximately 90 percent of these organisms, *adhesins* such as P- and S-fimbriae are present. These are cell-surface protein structures that enhance bacterial adherence to vaginal and uroepithelial cells and virulence (Hooton, 2012; Spurbeck, 2011). Maternal deaths have been attributed to *E coli* bearing Dr^+ and P adhesins (Sledzińska, 2011).

Urinary stasis, vesicoureteral reflux, and diabetes mellitus predispose to symptomatic upper urinary infections. Moreover, data suggest that pregnant women have more severe sequelae from urosepsis. As one influence, the T helper cell (Th1:Th2)

ratio of normal pregnancy is reversed (Chap. 4, p. 61). Additionally, various perturbations of cytokine expression have been reported (Chaemsaithong, 2013).

In the puerperium, several risk factors also predispose a woman to urinary infections. Bladder sensitivity to intravesical fluid tension is often diminished as a consequence of labor trauma or conduction analgesia (Chap. 36, p. 638). Also, the sensation of bladder distention can be masked by discomfort from an episiotomy, periurethral laceration, or vaginal wall hematoma. Normal postpartum diuresis, while usually protective, may worsen bladder overdistention, and catheterization performed to relieve retention may lead to urinary infection.

Asymptomatic Bacteriuria

This refers to persistent, actively multiplying bacteria within the urinary tract in asymptomatic women. It is defined as one or more bacterial species that has a count $\geq 10^5$ colony-forming units/mL determined by urine culture of a voided specimen (Infectious Disease Society of America, 2019). Its prevalence in sexually active nonpregnant women is 2 to 6 percent (Hooten, 2000; Nicolle, 2003). The highest incidence is in African-American multiparas with sickle-cell trait, and the lowest incidence is in affluent white women of low parity. Asymptomatic infection is also more common in women with diabetes (Schneeberger, 2014). In most women, bacteriuria is recurrent or persistent, and thus it frequently is discovered during prenatal care. The incidence during pregnancy is similar to that in nonpregnant women and varies from 2 to 7 percent (Nicolle, 2003).

Bacteriuria is typically already present at the time of the first prenatal visit. An initial positive urine culture result should prompt treatment, after which, fewer than 1 percent of women develop a symptomatic UTI (Whalley, 1967). It may be prudent to treat lower concentrations, because pyelonephritis develops in some women with colony counts of only 20,000 to 50,000 organisms/mL (Lucas, 1993).

Significance

If asymptomatic bacteriuria (ASB) is not treated, approximately 25 percent of affected women will develop symptomatic infection during pregnancy. Eradication of bacteriuria with antimicrobial agents prevents most of these. The American Academy of Pediatrics and the American College of Obstetricians and Gynecologists (2017), as well as the U.S. Preventive Services Task Force (2019), recommend screening for bacteriuria at the first prenatal visit (Chap. 10, p. 181). Standard urine cultures may not be cost effective when the prevalence is low. Instead, less expensive screening tests such as the leukocyte esterase and nitrite dipstick are cost-effective (Chu, 2018). At Parkland Hospital, culture screening is done because of a 5- to 8-percent prevalence of bacteriuria. Susceptibility determination is not necessary because initial treatment is empirical (Hooton, 2012). Last, a special agar-coated dipstick culture technique has excellent positive and negative predictive values (Rogozińska, 2016).

Other than pyelonephritis prevention, it is unclear whether ASB treatment provides other benefits. In many studies, there was no distinction from symptomatic infection. For example, in a cohort of 25,746 mother-newborn pairs, Schieve and coworkers (1994) reported UTI to be associated with increased risks for low-birthweight neonates, preterm delivery, pregnancy-associated hypertension, and anemia. These findings vary from those of Gilstrap and colleagues (1981b) and Whalley (1967), who studied asymptomatic infection. A California database study reported 160,000 women with UTIs were treated in the emergency department or hospital (Baer, 2021). These presumed symptomatic infections were associated with a 1.4-fold higher preterm delivery rate in those <37 weeks.

Treatment

Bacteriuria responds to empirical treatment with any of several antimicrobial regimens listed in Table 56-1. *E coli* is the most common species isolated in pregnant women (Le Blanc, 1964; Nicolle, 2003). Selection can be based on in vitro susceptibilities. However, in our extensive experience, empirical oral treatment for 10 days with nitrofurantoin macrocrystals, 100 mg at bedtime, is usually effective. Lumbiganon and associates (2009) reported satisfactory results with a 7-day oral course of nitrofurantoin, 100 mg given twice daily. Single-dose antimicrobial therapy also has been used with success for bacteriuria. The important caveat is that, regardless of regimen given, the recurrence rate approximates 30 percent. This may indicate covert upper tract infection and the need for longer therapy.

TABLE 56-1. Oral Antimicrobial Agents Used for Treatment of Pregnant Women with Asymptomatic Bacteriuria

Single-dose treatment
Amoxicillin, 3 g
Ampicillin, 2 g
Cephalosporin, 2 g
Nitrofurantoin, 200 mg
Trimethoprim-sulfamethoxazole, 320/1600 mg
3-day course
Amoxicillin, 500 mg three times daily
Ampicillin, 250 mg four times daily
Cephalosporin, 250 mg four times daily
Nitrofurantoin, 50 to 100 mg four times daily or 100 mg twice daily
Trimethoprim-sulfamethoxazole, 160/800 mg two times daily
Other
Nitrofurantoin, 100 mg four times daily for 10 days
Nitrofurantoin, 100 mg twice daily for 5 to 7 days
Nitrofurantoin, 100 mg at bedtime for 10 days
For treatment failures
Nitrofurantoin, 100 mg four times daily for 21 days
Suppression for bacterial persistence or recurrence
Nitrofurantoin, 100 mg at bedtime for remainder of pregnancy

Periodic surveillance is necessary to prevent recurrent UTIs (Schneeberger, 2015). The first recurrence is considered a treatment failure and extended therapy for 21 days is considered. For women with persistent or frequent ASB, suppressive therapy for the remainder of pregnancy can be given. We routinely use nitrofurantoin, 100 mg orally at bedtime. Its rare but serious side effects are pulmonary and hepatic toxicity.

Cystitis and Urethritis

According to the Centers for Disease Control and Prevention, 7.2 percent of pregnant women were treated as an outpatient for a UTI in 2014 (Ailes, 2018). Cystitis is characterized by dysuria, urgency, and frequency but causes few associated systemic findings. Pyuria and bacteriuria are usually found. Microscopic hematuria is common, and occasionally gross hematuria stems from hemorrhagic cystitis. Although cystitis is usually uncomplicated, the upper urinary tract may become involved by ascending infection. Almost 40 percent of pregnant women with acute pyelonephritis have preceding symptoms of lower tract infection (Gilstrap, 1981a).

Women with cystitis respond readily to any of several regimens. Most of the three-day regimens listed in Table 56-1 are usually 90-percent effective. Single-dose therapy is less effective, and if it is used, concomitant pyelonephritis must be confidently excluded.

Lower urinary tract symptoms with pyuria accompanied by a sterile urine culture may be from urethritis caused by *Chlamydia trachomatis*. Mucopurulent cervicitis usually coexists, and azithromycin therapy is effective (Chap. 68, p. 1212).

Acute Pyelonephritis

Infection of the renal parenchyma is the most common serious nonobstetrical medical complication of pregnancy. One study of the Nationwide Inpatient Sample found that nearly 29,000 hospitalizations in 2006 were for acute pyelonephritis in pregnancy (Jolley, 2012). The highest rates were noted for adolescents at 17.5 per 1000 and for Hispanic women at 10.1 per 1000. In another study of more than 70,000 pregnancies in a managed care organization, 3.5 percent of antepartum admissions were for urinary infections (Gazmararian, 2002). The seriousness is underscored by the observations of Snyder and coworkers (2013) that pyelonephritis was the leading cause of septic shock during pregnancy. Moreover, in a 2-year audit of admissions to the Parkland Hospital Obstetrical Intermediate Care Unit, 12 percent of antepartum admissions were for sepsis caused by pyelonephritis (Zeeman, 2003). Of concern, maternal urosepsis may be related to an increased incidence of cerebral palsy in preterm newborns (Jacobsson, 2002). Fortunately, data do not suggest serious long-term maternal sequelae (Raz, 2003).

Clinical Findings

Renal infection develops more frequently in the second half of pregnancy, and nulliparity and young age are risk factors (Hill, 2005). Pyelonephritis is unilateral and right-sided in more than half of cases, and it is bilateral in a fourth. Its abrupt onset is marked by fever, shaking chills, and aching pain in one or both lumbar regions. Anorexia, nausea, and vomiting may worsen dehydration. Tenderness usually can be elicited by percussion in one or both costovertebral angles. The urinary sediment contains many leukocytes, frequently in clumps, and numerous bacteria. The differential diagnosis includes, among others, labor, chorioamnionitis, appendicitis, placental abruption, or infarcted leiomyoma.

Bacteremia is demonstrated in 15 to 20 percent of these women. *E coli* is isolated from urine or blood in 70 to 80 percent of infections, *Klebsiella pneumoniae* in 3 to 5 percent, *Enterobacter* or *Proteus* species in 3 to 5 percent, and gram-positive organisms, including group B *Streptococcus* and *Staphylococcus aureus*, in up to 10 percent of cases (Hill, 2005; Wing, 2000). Evidence of sepsis is common, and this is discussed in detail in Chapter 50 (p. 888).

During care, plasma creatinine is monitored, because 5 percent of pregnant women develop renal dysfunction despite aggressive fluid resuscitation (Hill, 2005). Follow-up studies have demonstrated that this endotoxin-induced damage is reversible in the long term (Whalley, 1975). In up to 10 percent of women, varying degrees of respiratory insufficiency, including frank pulmonary edema, may result from endotoxin-induced alveolar injury (Cunningham, 1987; Sheffield, 2005; Snyder, 2013). In some cases, pulmonary injury may be so severe that it causes *acute respiratory distress syndrome (ARDS)*.

Uterine activity from endotoxins is common and is related to fever severity. In a study by Millar and associates (2003), women with pyelonephritis averaged 5 contractions per hour at admission, and this declined to 2 per hour within 6 hours of intravenous fluid and antimicrobial administration. β-agonist therapy for tocolysis raises the likelihood of respiratory insufficiency from permeability edema because of the sodium- and fluid-retaining properties of those agents (Chap. 50, p. 883). In one study, the incidence of pulmonary edema in women with pyelonephritis who were given β-agonists was 8 percent—a fourfold increase compared with that expected (Towers, 1991).

Endotoxin-induced *hemolysis* is common, and approximately a third of patients with pyelonephritis develop anemia (Cox, 1991). With recovery, hemoglobin regeneration is normal because acute infection does not affect erythropoietin production (Cavenee, 1994).

Management

One scheme for management of acute pyelonephritis is shown in Table 56-2. Although we obtain blood cultures when the patient temperature exceeds 39°C, prospective trials show them to be of limited clinical utility (Wing, 2000). *Intravenous hydration to ensure adequate urinary output is the cornerstone of treatment.* Antimicrobials also are begun promptly with the caution that they may initially worsen endotoxemia from bacterial lysis. Ongoing surveillance for worsening of sepsis is monitored by serial determinations of urinary output, blood pressure, pulse, temperature, and oxygen saturation. High fever should be lowered with a cooling blanket and acetaminophen. This is especially important in early pregnancy because of possible teratogenic effects of hyperthermia.

TABLE 56-2. Management of the Pregnant Woman with Acute Pyelonephritis

Hospitalize patient
Obtain urine and blood cultures
Evaluate hemogram, serum creatinine, and electrolytes
Monitor vital signs frequently, including urinary output—consider indwelling catheter
Establish urinary output ≥50 mL/h with IV crystalloid solution
Administer IV antimicrobial therapy (see text)
Obtain chest radiograph if there is dyspnea or tachypnea
Repeat hematology and chemistry studies in 48 h
Change to oral antimicrobials when afebrile
Discharge when afebrile 24 h, consider antimicrobial therapy for 7-10 d
Repeat urine culture 1–2 wks after antimicrobial therapy completed

IV = intravenous.
From Lucas, 1994; Sheffield, 2005.

Antimicrobial therapy usually is empirical, and ampicillin plus gentamicin; cefazolin or ceftriaxone; or an extended-spectrum antibiotic were all 95-percent effective in randomized trials (Sanchez-Ramos, 1995; Wing, 1998, 2000). Fewer than half of *E coli* strains are sensitive to ampicillin in vitro, but gentamicin plus ampicillin or plus a cephalosporin generally have a synergistic effect and excellent activity (Johnson, 2018). Serum creatinine levels are monitored if nephrotoxic drugs are given. Initial treatment at Parkland Hospital is ampicillin plus gentamicin. Some recommend suitable substitutes if bacterial studies show in vitro resistance. With any of the regimens discussed, response is usually prompt, and 95 percent of women are afebrile by 72 hours (Hill, 2005; Wing, 2000). After discharge, most recommend oral therapy to complete 10 to 14 days (Hooton, 2012; Johnson, 2018).

Recurrent infection—either covert or symptomatic—is common and develops in 30 to 40 percent of women following completion of pyelonephritis treatment. Unless other measures are taken to ensure urine sterility, nitrofurantoin, 100 mg orally at bedtime given for the remainder of the pregnancy, reduces bacteriuria recurrence.

Persistent Infection

Generally, stepwise defervescence of approximately 1°F per day follows intravenous hydration and antimicrobial therapy. Upwards of 20 percent of women are febrile for more than 4 days (Valent, 2017). With persistent spiking fever or lack of clinical improvement by 48 to 72 hours, urinary tract obstruction, calculi, or abscess is considered (Johnson, 2018). In these women, renal sonography is recommended to search for these.

Obstruction manifests by abnormal ureteral or pyelocaliceal dilation. Nephrolithiasis, however, is not always seen in a renal sonogram (Butler, 2000; Maikranz, 1987). If stones are strongly suspected despite a nondiagnostic sonographic examination, a plain abdominal radiograph will identify nearly 90 percent. Another option is the modified *one-shot intravenous pyelography* (p. 995) (Butler, 2000). Last, persistent infection can be due to an intrarenal or perinephric abscess or phlegmon (Cox, 1988; Rafi, 2012). MR imaging is preferred for abscess detection if renal sonography is nonconclusive (Rubilotta, 2014).

Obstruction relief is important, and we have found that percutaneous nephrostomy is preferable because the stents are more easily replaced. Another method is cystoscopic placement of a double-J ureteral stent. These stents are usually left in place until after delivery and often become encrusted and need replacing (Lindquester, 2021). Last, in some women, surgical removal of stones may be needed (p. 1000). Renal abscesses larger than 3 cm may necessitate percutaneous drainage or surgical treatment (Coelho, 2007; Mandal, 2017; Siegel, 1996).

Outpatient Management of Pyelonephritis

This is an option for nonpregnant women with uncomplicated pyelonephritis (Fox, 2017; Johnson, 2018). Wing and colleagues (1999) described such management in 92 pregnant women who were first given in-hospital intramuscular ceftriaxone, two 1-g doses 24 hours apart. At this point, one third of the group was considered suitable for outpatient therapy, and these women were randomly assigned either to discharge and oral antimicrobials or to continued hospitalization with intravenous therapy. A third of the outpatient management group was unable to adhere to the treatment regimen and was admitted. These findings suggest that outpatient management of pyelonephritis is applicable only to very few pregnant women.

■ Reflux Nephropathy

This refers to loss of nephron mass from patchy interstitial scarring and tubular atrophy due to high-pressure reflux of sterile urine from the bladder to the kidneys. In adults, long-term complications include hypertension, which may be severe if renal damage is demonstrable (Beck, 2018). Moreover, reports describing 879 pregnancies in 432 women with reflux nephropathy indicate that impaired renal function and bilateral renal scarring were associated with higher rates of pregnancy-associated hypertensive disorders (Attini, 2018). Many also had surgical correction of reflux as children, and these women commonly have bacteriuria when pregnant (Mor, 2003). In other women with reflux nephropathy, no clear history implicates recurrent cystitis, acute pyelonephritis, or obstructive disease (Gebäck, 2016). Chronic renal disease and pregnancy outcome is discussed further later (p. 1003).

NEPHROLITHIASIS

Kidney stones develop in 9 percent of women during their lifetime with an average age of onset in the third decade (Curhan, 2018). Calcium salts make up approximately 80 percent of stones, and hyperparathyroidism should be excluded. Calcium oxalate stones are most common in young nonpregnant women, but in pregnancy most stones—65 to 75 percent—are calcium phosphate or hydroxyapatite (Tan, 2013).

Nephrolithiasis is more common in women with prior pregnancies than in nulligravidas. Normal physiological changes of the urinary system may promote stone formation, and elevation of urinary pH reduces calcium phosphate solubility (Reinstatler, 2017). More than half of patients who have a stone typically form another stone within 10 years.

Contrary to past teachings, a low-calcium diet *promotes* stone formation. Current recommendations to prevent recurrences include hydration and a diet low in sodium and protein (Curhan, 2018). Thiazide diuretics also diminish stone formation. In general, obstruction, infection, intractable pain, and heavy bleeding are indications for stone removal. Extraction by a flexible basket via cystoscopy, although used less often than in the past, is still a reasonable consideration for pregnant women. In nonpregnant patients, stone destruction by *lithotripsy* is preferred to surgical therapy in most cases. Limited information guides the use of lithotripsy during pregnancy, and it is not generally recommended.

■ Stone Disease During Pregnancy

The reported incidence of stone disease complicating pregnancy varies widely. At the low end, Butler and coworkers (2000) found an incidence of 0.3 admissions per 1000 pregnancies in more than 186,000 deliveries at Parkland Hospital. In an Israeli study, the incidence in nearly 220,000 pregnancies was 0.8 per 1000 (Rosenberg, 2011). Most stone episodes are diagnosed in the second and third trimesters of pregnancy (Dai, 2021). Bladder stones are rare, but recurrent infection and labor obstructed by stones have been reported (Ait Benkaddour, 2006; Ruan, 2011).

Data are conflicting whether women with kidney stones have an increased risk for adverse pregnancy outcomes. Swartz and colleagues (2007) reported a preterm delivery rate of 10.6 percent in women with nephrolithiasis compared with 6.4 percent in normal controls. A nationwide case-control study from Taiwan also reported 20- to 40-percent increases in low-birthweight newborns and preterm births (Chung, 2013). To the contrary, a case-control study from Hungary reported that pregnancy outcomes, including preterm delivery, were similar in women with and without stone disease (Banhidy, 2007). Comparable conclusions were drawn from the Israeli study noted earlier (Rosenberg, 2011). Women who have formed stones prior to pregnancy have a higher incidence of gestational diabetes and preeclampsia (Tangren, 2018).

Diagnosis

More than 90 percent of pregnant women with nephrolithiasis present with pain. However, some evidence suggests that pregnant women may have fewer symptoms with stone passage because of normal urinary tract dilation (Tan, 2013). Gross hematuria is less common than in nonpregnant women and has an incidence of 2 to 23 percent (Butler, 2000; Lewis, 2003).

Sonography is the first-line study to visualize stones, but as discussed above, many are undetected (McAleer, 2004). Abnormal urinary tract dilation or absent ureteral "jets" of urine into the bladder are indirect indicators of urolithiasis (Fig. 56-1). If abnormal dilation is seen but no stone is visualized, one-shot pyelography may be useful.

Helical computed tomography (CT) scanning is preferred imaging for nonpregnant individuals. In pregnancy, MR imaging is the second-line test following a nondiagnostic sonographic evaluation (Masselli, 2013). However, if CT imaging is needed, White and colleagues (2007) recommend unenhanced helical CT and cite an average fetal radiation dose to be 7 mGy.

Management

Treatment depends on symptoms and gestational age (Semins, 2013). Intravenous hydration and analgesics are given. Patients strain collected urine to identify passed stones. In half of women with symptomatic stones, infection will be identified, and this is treated vigorously. Although calculi infrequently cause symptomatic obstruction during pregnancy, persistent pyelonephritis should prompt a search for obstruction due to nephrolithiasis.

Approximately 75 percent of symptomatic women will improve with conservative therapy, and the stone usually passes spontaneously (Tan, 2013). Others require an invasive procedure such as ureteral stenting, ureteroscopy, percutaneous nephrostomy, transureteral laser lithotripsy, or basket extraction (Butler, 2000; Hosseini, 2017). Watterson and coworkers

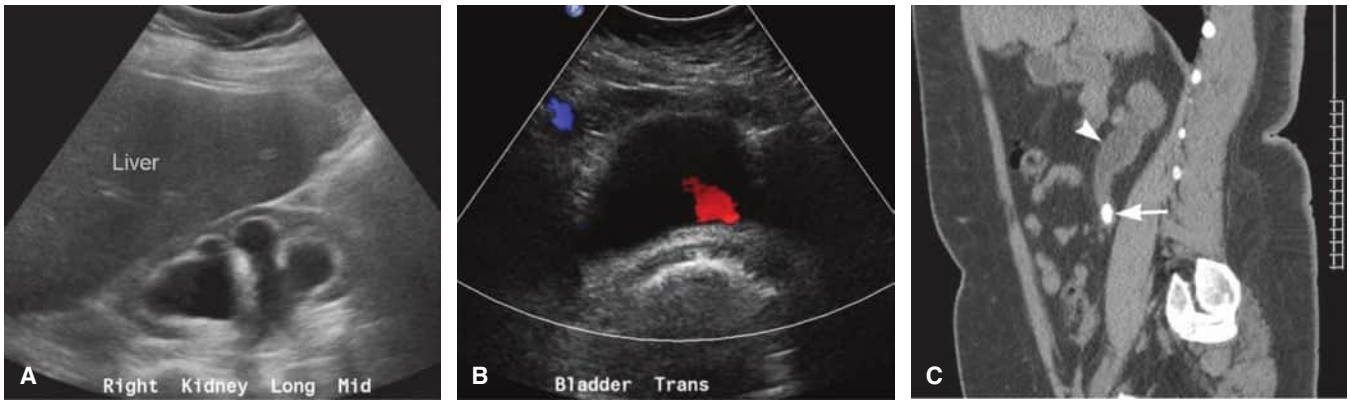

FIGURE 56-1 **A.** Sonographic image of the right upper quadrant demonstrates severe hydronephrosis and thinned echogenic renal parenchyma. **B.** Application of color Doppler during sonography of the bladder reveals a urine jet (*red streak*) from the left ureteral orifice. No flow was noted from the right orifice during observation. **C.** Sagittal CT image shows an obstructing stone in the mid right ureter (*arrow*) and hydroureteronephrosis (*arrow head*).

(2002) described successful transureteral holmium:YAG laser lithotripsy in nine of 10 women. Ultimately, less than 2 percent of symptomatic pregnant women require surgical exploration following one of the procedures listed above (Swartz, 2007). The need for fluoroscopy limits the utility of percutaneous nephrolithotomy. Extracorporeal shock-wave lithotripsy is contraindicated in pregnancy.

PREGNANCY AFTER RENAL TRANSPLANTATION

In 2020, more than 100,000 registrants were waiting for renal transplantations through the Organ Procurement and Transplantation Network—OPTN (2020). The 1-year graft survival rate is 95 percent for those from living donors and is 90 percent from deceased donors. Survival rates approximately doubled in the 1990s, due in large part to the introduction of cyclosporine and muromonab-CD3 (Orthoclone OKT3) to prevent and treat organ rejection. The latter is a monoclonal antibody against the CD3 receptor of T cells. Since then, mycophenolate mofetil and tacrolimus have further reduced acute rejection episodes. However, the former is teratogenic (Briggs, 2017). In the report from the National Transplant Pregnancy Registry, 23 percent of fetuses exposed to mycophenolate had birth defects (Coscia, 2010). Importantly, resumption of renal function after transplantation promptly restores fertility in reproductive-aged women (Yaprak, 2019). Thus, these women should be counseled to use contraception, especially those treated with mycophenolate. In one study, more than half of transplant recipients reported that they were not counseled regarding contraception (French, 2013).

Pregnancy Outcomes

Women with solid organ transplant have higher severe maternal morbidity rates (Sabr, 2019). Deshpande and associates (2011) reviewed the outcomes of more than 4700 pregnancies in renal transplant recipients. Approximately 70 percent of pregnancies resulted in a live birth. However, rates of preeclampsia, gestational diabetes, and preterm delivery were substantially greater. Similar outcomes were described for the Australian and New Zealand Transplant Registry (Wyld, 2013). In the United Kingdom, Bramham and colleagues (2013) identified a live-birth rate that exceeded 90 percent in renal transplant recipients. Half were delivered before 37 weeks' gestation, but only 9 percent before 32 weeks. Low birthweight complicated half of pregnancies, and growth restriction complicated 25 percent. Notably, the incidence of fetal malformations was not increased, except in those who took mycophenolate mofetil.

The incidence of preeclampsia is high in all transplant recipients. In the UK National Cohort Study reported by Bramham and associates (2013), the incidence of preeclampsia was 22 percent. From their review, Josephson and McKay (2011) cite an incidence of one third of pregnancies but question the validity of this frequency. Importantly, in some cases, rejection is difficult to distinguish from preeclampsia. That said, the incidence of rejection episodes approximates only 2 percent (Bramham, 2013). Viral infections—especially polyomavirus hominis 1, also called *BK virus*—are frequent. In addition, gestational diabetes is found in approximately 5 percent. Both are likely related to immunosuppression therapy. Similar outcomes have been reported by several other investigators (Al Duraihimh, 2008; Cruz Lemini, 2007; Ghafari, 2008).

The Italian Society of Nephrology recommends that women who have undergone transplantation satisfy several requisites before attempting pregnancy (Cabiddu, 2018). First, women should be in good general health for at least 1 to 2 years after transplantation. Second, renal function should be stable. Parameters include a GFR ≥60 mL/min, serum creatinine level <2 mg/dL, and proteinuria <500 mg/d. Third, there should be no recent evidence for graft rejection and no treatment with teratogenic drugs. Last, hypertension should be absent or well controlled.

Cyclosporine and tacrolimus are given routinely to renal transplantation recipients. Coincident with expected pregnancy-related intravascular volume expansion, cyclosporine blood levels decline during pregnancy. However, this was not reported to be associated with rejection episodes (Thomas, 1997). Unfortunately, these agents are nephrotoxic and may also cause renal hypertension. In fact, they likely contribute substantively to the chronic renal disease that develops in 10 to 20 percent of patients with nonrenal solid organ transplantation (Goes, 2007).

Concern persists regarding the possible late effects in offspring subjected to immunosuppressive therapy in utero. These include malignancy, germ cell dysfunction, and malformations in the children of the offspring. In addition, cyclosporine is secreted in breast milk (Moretti, 2003). In two small studies, these children had normal neurological and intellectual function (Morales-Buenrostro, 2019; Schreiber-Zamora, 2019).

Last, pregnancy-induced renal hyperfiltration theoretically may impair long-term graft survival. However, Sturgiss and Davison (1995) found no evidence for this in one study of 34 allograft recipients followed for a mean of 15 years.

Management

Close surveillance is necessary. Covert bacteriuria is treated, and if it is recurrent, suppressive treatment is given for the remainder of the pregnancy. Serial hepatic enzyme concentrations and blood counts are monitored for toxic effects of azathioprine and cyclosporine. Some recommend measurement of serum cyclosporine levels. Gestational diabetes is more common if corticosteroids are taken, and in these cases overt diabetes must be excluded with glucose tolerance testing done at the initiation of prenatal care. Surveillance for opportunistic infections from herpesvirus, cytomegalovirus, and toxoplasmosis is important because these infections are common. Some recommend surveillance for BK virus in women known to be infected, however, diagnosis and treatment are problematic.

Renal function is monitored, and the GFR usually increases 20 to 25 percent. If a significant rise in the serum creatinine level is detected, its cause must be determined. Possibilities include acute rejection, cyclosporine toxicity, preeclampsia, infection, and urinary tract obstruction. Evidence of pyelonephritis or graft rejection should prompt admission for aggressive management. Imaging studies and kidney biopsy may be indicated.

The woman is carefully monitored for development or worsening of underlying hypertension, and especially of superimposed preeclampsia. Management of hypertension during pregnancy is the same as for patients without an organ transplant (Chap. 53, p. 950).

Vigilant fetal surveillance is indicated because of the higher incidences of fetal-growth restriction and preterm delivery. Although cesarean delivery is reserved for obstetrical indications, occasionally the transplanted kidney obstructs labor, and the overall cesarean delivery rate approaches 80 percent (Bramham, 2013; Madej, 2018; Rocha, 2013).

POLYCYSTIC KIDNEY DISEASE

This usually autosomally dominant systemic disease primarily affects the kidneys. Its basic pathophysiology is a *ciliopathy* that affects renal tubules, although only approximately 5 percent develop cysts (Zhou, 2018). The incidence is about 1 in 1000 births and it causes approximately 5 to 10 percent of end-stage renal disease in the United States. Although genetically heterogeneous, almost 85 percent of cases are due to *PKD1* gene mutations on chromosome 16, and the other 15 percent to *PKD2* mutations on chromosome 4. Prenatal diagnosis is available if the mutation has been identified in a family member or if linkage has been established in the family. Preimplantation genetic screening reduces the risk of affected fetuses to 1 to 2 percent (Murphy, 2018).

Renal complications more commonly affect men than women, and symptoms usually appear in the third or fourth decade. Flank pain, hematuria, proteinuria, abdominal masses, and associated calculi and infection are frequent findings. Hypertension develops in 75 percent, and progression to renal failure is a major problem. Superimposed acute renal failure also may develop from infection or obstruction from ureteral angulation. Specifically, renal cyst may displace and create angles along the normal ureteral course.

Other organs are commonly involved. Asymptomatic *hepatic cysts* coexist in a third of patients with polycystic kidneys. Hepatic involvement is more common and more aggressive in women than in men. Approximately 10 percent of patients with polycystic kidney disease die from rupture of an associated *intracranial berry aneurysm*. Up to a fourth of patients have *cardiac valvular lesions*, which include mitral valve prolapse and mitral, aortic, and tricuspid valvular incompetence.

Pregnancy Outcomes

The prognosis for pregnancy in women with polycystic kidney disease depends on the degree of associated hypertension and renal insufficiency. Urinary infections are common. Chapman and coworkers (1994) compared pregnancy outcomes in 235 affected women who had 605 pregnancies with those of 108 unaffected family members who had 244 pregnancies. Composite perinatal complication rates were similar—33 versus 26 percent—but hypertension, including preeclampsia, was more common in women with polycystic kidneys. Pregnancy does not seem to accelerate the natural disease course (Lindheimer, 2007).

GLOMERULAR DISEASES

The glomerulus and its capillaries are subject to numerous conditions and agents that can lead to acute and chronic diseases. Glomerular damage can be caused by toxins or infections or from systemic disorders such as hypertension or diabetes. It may also be idiopathic. When there is capillary inflammation, the process is termed *glomerulonephritis*, and in many of these cases, an autoimmune process is involved. Glomerular disease or glomerulonephritis may result from a single stimulus such as that following group A streptococcal infections. It may also be a manifestation of a multisystem disease such as systemic lupus erythematosus or diabetes (Blom, 2017).

Persistent glomerulonephritis eventually leads to decline of renal function. Progression is variable and often does not become apparent until chronic renal insufficiency is diagnosed. Lewis and Neilsen (2018) group glomerular injuries into six syndromes based on clinical patterns (Table 56-3). Some underlying disorders—examples include infections, vasculitides, and diabetes—can result in one clinical pattern in different individuals. Last, disorders within each of these categories

TABLE 56-3. Patterns of Clinical Glomerulonephritis

Acute nephritic syndromes: poststreptococcal, infective endocarditis, SLE, antiglomerular basement membrane disease, IgA nephropathy, ANCA vasculitis, Henoch-Schönlein purpura, cryoglobulinemia, membranoproliferative and mesangioproliferative glomerulonephritis
Pulmonary-renal syndromes: Goodpasture, ANCA vasculitis, Henoch-Schönlein purpura, cryoglobulinemia
Nephrotic syndromes: minimal change disease, focal segmental glomerulosclerosis, membranous glomerulonephritis, diabetes, amyloidosis, others
Basement membrane syndromes: antiglomerular basement membrane disease, others
Glomerular vascular syndromes: atherosclerosis, chronic hypertension, sickle-cell disease, thrombotic microangiopathies, antiphospholipid antibody syndrome, ANCA vasculitis, others
Infectious disease–associated syndromes: poststreptococcal, infective endocarditis, HIV, HBV, HCV, syphilis, others

ANCA = antineutrophilic cytoplasmic antibodies; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; IgA = immunoglobulin A; SLE = systemic lupus erythematosus.

may be seen in young women, and thus, these may already be established before pregnancy or may first manifest then.

As with any renal disorder, goals to achieve optimal pregnancy outcomes aim to stabilize rapid disease progression, minimize proteinuria with use of appropriate immunosuppressive agents, control hypertension, and delay pregnancy until these are achieved.

Acute Nephritic Syndromes

Acute glomerulonephritis may result from any of several causes (see Table 56-3). The clinical presentation usually includes hypertension, hematuria, red-cell casts, pyuria, and proteinuria. Varying degrees of renal insufficiency and salt and water retention result in edema, hypertension, and circulatory congestion (Lewis, 2018). The prognosis and treatment of nephritic syndromes depends on their etiology. Some recede spontaneously or with treatment. However, in some patients, *rapidly progressive glomerulonephritis* leads to end-stage renal failure. In others, *chronic glomerulonephritis* develops and manifests as slowly progressive renal disease.

The prototype is *acute poststreptococcal glomerulonephritis*, which is historically interesting because it was confused with eclampsia until the mid-1800s. *Immunoglobulin A (IgA) nephropathy*, also known as *Berger disease*, is the most common form of acute glomerulonephritis worldwide (Blom, 2017). The isolated form of IgA nephropathy occurs sporadically, and it may be related to *Henoch-Schönlein purpura* as the systemic form. Another isolated nephritis type may be due to anti–glomerular basement membrane antibodies, which are typically IgG. These IgG antibodies may also involve the lungs to manifest as a pulmonary-renal syndrome with alveolar hemorrhage, which is termed *Goodpasture syndrome*.

Pregnancy

Acute nephritic syndromes during pregnancy can be difficult to differentiate from severe preeclampsia. One example is systemic lupus erythematosus with a flare during the second half of pregnancy (Zhao, 2013). In some cases, renal biopsy may be necessary to determine etiology and direct management (Lindheimer, 2013; Ramin, 2006). This is discussed further in Chapter 62 (p. 1112).

Whatever the underlying etiology, glomerular diseases have profound effects on pregnancy outcome. In an older study, Packham and coworkers (1989) described 395 pregnancies in 238 women with *primary* glomerulonephritis diagnosed before pregnancy. The most common lesions identified by biopsy were membranous glomerulonephritis, IgA glomerulonephritis, and diffuse mesangial glomerulonephritis. Although most of these women had normal renal function, half developed hypertension, a fourth was delivered preterm, and the perinatal mortality rate after 28 weeks' gestation was 80 per 1000. As expected, the worst perinatal outcomes were in women with impaired renal function, early or severe hypertension, and nephrotic-range proteinuria. O'Shaughnessy and colleagues (2017) confirmed these findings. In 48 pregnancies complicated by glomerulonephritis, a third developed preeclampsia, 39 percent had a doubling of protein excretion, and 27 percent had a ≥50-percent rise in serum creatinine levels. Half of the pregnancies ended in preterm birth and 13 percent in perinatal death.

Similar outcomes have been reported for pregnancies in women with IgA nephropathy. From one review of 376 pregnancies, investigators reported a perinatal mortality rate of 12-percent; preterm delivery, 9 percent; low birthweight, 10 percent; and preeclampsia, 7 percent (Liu, 2016). Progression of renal insufficiency during pregnancy is controversial. From their reports, Su and coworkers (2017), but not Wang and colleagues (2019), found that women with IgA nephropathy had renal insufficiency progression during pregnancy.

Nephrotic Syndromes

Heavy proteinuria is the hallmark of the nephrotic syndromes. Several primary and secondary kidney disorders cause immunological- or toxic-mediated injury and glomerular capillary-wall breakdown that allows excessive filtration of plasma proteins. In addition to heavy urine protein excretion, the syndrome is characterized by hypoalbuminemia, hypercholesterolemia, and edema. Hypertension is frequently comorbid. This, coupled with albumin nephrotoxicity, contributes to eventual renal insufficiency.

Some of the more common causes of the nephrotic syndrome are listed in Table 56-4. Treatment depends on etiology, and renal biopsy will disclose microscopic abnormalities that may help direct care. Edema is problematic, especially during pregnancy. Normal amounts of dietary protein of high biological value are encouraged, and this practice contrasts with high-protein diets, which increase proteinuria. The incidence of thromboembolism is greater and varies with the severity of hypertension, proteinuria, and renal insufficiency (Spotti, 2019). Renal vein thrombosis is particularly worrisome, although both arterial and venous thromboses may develop. Explanations for this risk are platelet hyperactivity, urinary loss of antithrombotic factors, and increased production of prothrombotic factors by the liver (Mirrakhimov, 2014). Some recommend that

TABLE 56-4. Causes of the Nephrotic Syndrome in Adults

Focal segmental glomerulosclerosis (FSGS) (35%): viruses, hypertension, reflux nephropathy, sickle-cell disease
Membranous glomerulonephritis (~20%): idiopathic (most cases), malignancy, infection, connective tissue diseases
Minimal change disease (MCD) (10–15%): primary idiopathic (most cases), drug-induced (NSAIDs), allergies, viral infections
Diabetic nephropathy: most common cause of ESRD
Glomerular deposition diseases: light-chain, amyloidosis

ESRD = end-stage renal disease; NSAIDs = nonsteroidal antiinflammatory drugs.

women with a serum albumin <2 g/dL or 24-hour urinary protein excretion >3.5 g should be given thromboprophylaxis throughout pregnancy (Blom, 2017). Some cases of nephrosis from primary glomerular disease respond to glucocorticosteroids and other immunosuppressants or cytotoxic drug therapy. In most cases caused by infection or drugs, proteinuria recedes once the underlying cause is corrected.

Pregnancy

Maternal and perinatal outcomes in women with a nephrotic syndrome depend on its underlying cause and severity. Whenever possible, these should be ascertained, and renal biopsy may be indicated to determine if there is a treatable etiology. Half of women with nephrotic-range proteinuria will have higher daily protein excretion as pregnancy progresses (Packham, 1989). In women with nephrosis cared for at Parkland Hospital, we reported that two thirds had protein excretion that exceeded 3 g/d (Stettler, 1992). At the same time, however, if these women had only mild degrees of renal dysfunction, they displayed a normally augmented GFR across pregnancy (Cunningham, 1990).

Management of edema during pregnancy can be particularly challenging, as it is intensified by normally rising hydrostatic pressure in the lower extremities. In some women, massive vulvar edema may develop in those with comorbid conditions such as diabetes, syphilis, preeclampsia, and others (Fig. 56-2) (Jakobi, 1995). Another major problem is that up to half of these women with nephrosis have chronic hypertension that may require treatment (Chap. 53, p. 950). In these, as well as in previously normotensive women, preeclampsia is common and often develops early in pregnancy (Morgan, 2016).

Most women with a nephrotic syndrome who do not have severe hypertension or renal insufficiency will have successful pregnancy outcomes. Conversely, if there is renal insufficiency, moderate to severe hypertension, or both, the prognosis is much worse. Our experiences caring for such women with 65 pregnancies at Parkland Hospital showed that complications are frequent (Stettler, 1992). Protein excretion during pregnancy averaged 4 g/d, and a third of the women had classic nephrotic syndrome.

FIGURE 56-2 Massive vulvar edema in a pregnant woman with marked proteinuria due to preeclampsia.

Some degree of renal insufficiency was seen in 75 percent, chronic hypertension in 40 percent, and persistent anemia in 25 percent. Importantly, preeclampsia developed in 60 percent, and 45 percent had preterm deliveries. Even so, after excluding abortions, 53 of 57 neonates were born alive. De Castro and associates (2017) reported similar results from 26 pregnancies complicated by a mean protein excretion of 8 g/d.

Long-Term Outcomes

Women identified to have nephrotic syndromes either before or during pregnancy are at risk for serious long-term adverse outcomes. Of the women cared for at Parkland Hospital, at least 20 percent of women followed for 10 years progressed to end-stage renal failure (Stettler, 1992). Similarly, Chen and associates (2001) reported short-term outcomes in 15 women with nephrotic syndromes. By 2 years, three of these women had died, three had developed chronic renal failure, and two had progressed to end-stage renal disease. Women with serum creatinine levels >1.4 mg/dL and 24-hour protein excretion >1 g/d have the shortest renal survival times following pregnancy (Imbasciati, 2007).

CHRONIC KIDNEY DISEASE

This describes a pathophysiological process that can progress to end-stage renal disease. The National Kidney Foundation (2019) describes six stages of chronic kidney disease (CKD) defined by decreasing GFR. It progresses from stage 0, in which GFR is ≥90 mL/min/1.73 m^2, to stage 5, in which GFR is <15 mL/min/1.73 m^2.

Several diseases result in progressively declining renal function, including the glomerular diseases discussed earlier. Those that most commonly lead to end-stage disease requiring dialysis and kidney transplantation include diabetes mellitus, chronic hypertension, glomerulonephritis, and polycystic kidney disease (Bargman, 2018).

Most reproductive-aged women with these just-mentioned diseases have varying degrees of renal insufficiency, proteinuria, or both. To counsel regarding fertility and pregnancy outcome, the degree of renal functional impairment and of associated hypertension are assessed. In general, successful pregnancy outcome may be more related to these two factors than to the specific underlying renal disorder. An overall prognosis can be estimated by considering women with CKD in arbitrary categories of renal function (Davison, 2011). These include normal or *mild impairment*—defined as a serum creatinine <1.5 mg/dL; *moderate impairment*—defined as a serum creatinine 1.5 to 3.0 mg/dL; and *severe renal insufficiency*—defined as a serum creatinine >3.0 mg/dL. Some recommend using these older categories, although others suggest adopting the classification of the National Kidney Foundation described above (Davison, 2011; Piccoli, 2010, 2011). Thus, obstetricians must be familiar with both.

■ Pregnancy and Chronic Kidney Disease

The severity of renal insufficiency, along with any underlying hypertension, strongly influences pregnancy outcome. Additionally, comorbidities secondary to a systemic disorder—for

example, diabetes or systemic lupus erythematosus—portend a worse prognosis (Blom, 2017). For all women with CKD, the incidences of hypertension and preeclampsia, preterm and growth-restricted neonates, and other problems are high. Low-dose aspirin starting at 12 to 28 weeks is recommended to help lower preeclampsia rates (Chap. 41, p. 705).

Loss of renal tissue is associated with compensatory intrarenal vasodilation and hypertrophy of the surviving nephrons. The resultant hyperperfusion and hyperfiltration eventually damage surviving nephrons to cause *nephrosclerosis* and worsening renal function. With mild renal insufficiency, pregnancy causes greater augmentation of renal plasma flow and GFR (Helal, 2012). With progressively worsening renal function, renal plasma flow is augmented little, if any. In one study, only half of women with moderate renal insufficiency demonstrated pregnancy-augmented glomerular filtration, and women with severe disease had no increase (Cunningham, 1990).

Importantly, chronic renal insufficiency also curtails normal pregnancy-induced hypervolemia. Blood volume expansion during pregnancy is related to disease severity and correlates inversely with serum creatinine concentration. As shown in Figure 56-3, women with mild to moderate renal dysfunction have blood volume expansion that averages 55 percent above nonpregnant volumes. However, with severe renal insufficiency, volume expansion averages only 25 percent, which is similar to that seen with hemoconcentration from eclampsia. In addition, these women have variable degrees of chronic anemia due to intrinsic renal disease. Thus, they are at risk for hypovolemia and acute blood loss anemia with even normal blood loss at delivery.

Renal Disease with Preserved Function

In some women, although glomerular disease has not yet caused renal insufficiency, incidences of pregnancy complications are still increased. As shown in Table 56-5, these problems are less frequent than in cohorts of women with moderate and severe renal insufficiency. Two older studies illustrate this. In one, Surian and colleagues (1984) described outcomes of 123 pregnancies in women with biopsy-proven glomerular disease. Although only a few of these women had renal dysfunction, 40 percent developed obstetrical or renal complications. In another study of 395 pregnancies in women with preexisting glomerulonephritis and minimal renal insufficiency, impaired renal function developed in 15 percent of these women during pregnancy, and 60 percent had worsening proteinuria (Packham, 1989). Only 12 percent had antecedent chronic hypertension, however, more than half of the pregnancies were complicated by hypertension. The perinatal mortality rate was 140 per 1000, and even without early-onset or severe hypertension or nephrotic-range proteinuria, the rate was 50 per 1000. Importantly, in 5 percent of these women, worsening renal function was permanent.

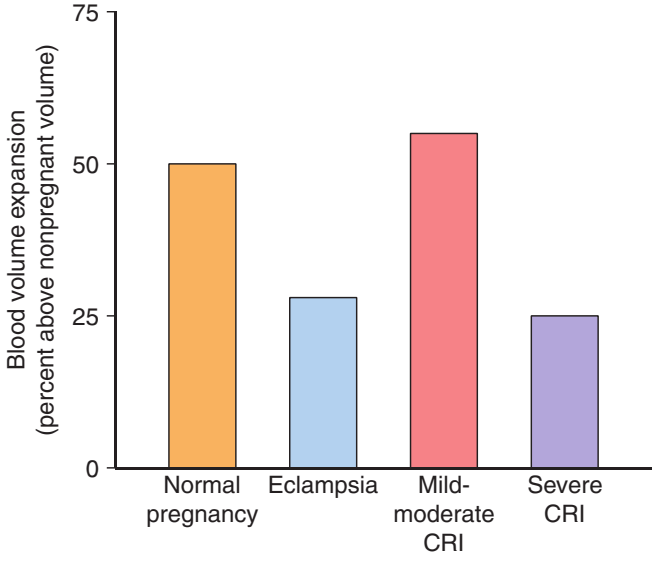

FIGURE 56-3 Blood volume expansion in 44 normally pregnant women at term compared with 29 who had eclampsia; 10 with moderate chronic renal insufficiency (CRI)—serum creatinine 1.5 to 2.9 mg/dL; and four with severe CRI—serum creatinine ≥3.0 mg/dL. (Data from Cunningham, 1990; Zeeman, 2009.)

TABLE 56-5. Complications (%) Associated with Chronic Kidney Disease During Pregnancy

Complication	Preserved Function	Renal Insufficiency: Moderate and Severe	Renal Insufficiency: Severe
Chronic hypertension	25	30–70	50
Gestational hypertension	20–50	30–50	75
Worsening renal function	8–15	20–43	35
Permanent dysfunction	4–5	10–20	35
Preterm delivery	7	30–60	73
Fetal-growth restriction	8–14	30–38	57
Perinatal mortality	5–14	4–7	0

Data from Alsuwaida, 2011; Cunningham, 1990; Farwell, 2013; He, 2018; Imbasciati, 2007; Maruotti, 2012; Nevis, 2011; Piccoli, 2010, 2011; Stettler, 1992; Trevisan, 2004; Zhang, 2015.

Chronic Renal Insufficiency

As noted, pregnancy complication rates are higher in women with CKD and renal insufficiency compared with women who have preserved renal function. Furthermore, adverse outcomes are generally directly related to the degree of renal impairment. Of the more recent reports shown in Table 56-5, outcomes of women with moderate or severe renal insufficiency are usually not separated. A systematic review of 1514 pregnancies in women with CKD described increased odds ratios of preeclampsia, 10.4; preterm delivery, 6.3; fetal-growth restriction, 4.9; and cesarean delivery, 2.7 (Zhang, 2015).

Other investigators have described pregnancies complicated by moderate or severe renal insufficiency (Cunningham, 1990;

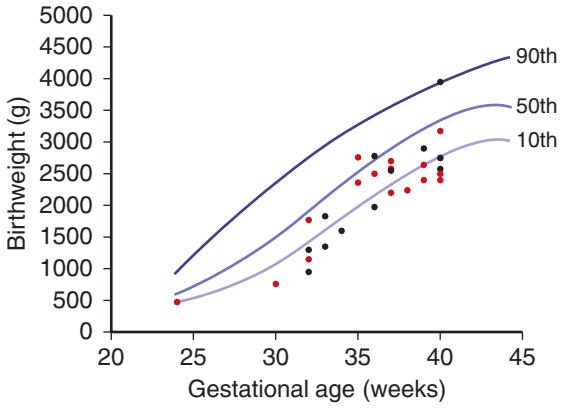

FIGURE 56-4 Birthweight percentiles of infants born to 29 women at Parkland Hospital with mild to moderate renal insufficiency—serum creatinine 1.4–2.4 mg/dL (*black points*) and severe renal insufficiency—serum creatinine ≥2.5 mg/dL (*red points*). (Data from Cunningham, 1990; Stettler, 1992. Growth curves are those reported by Alexander, 1996.)

Imbasciati, 2007; Jones, 1996). Despite a high incidence of chronic hypertension, anemia, preeclampsia, preterm delivery, and fetal-growth restriction, perinatal outcomes were generally acceptable. As shown in Figure 56-4, fetal growth is frequently impaired and related to renal dysfunction severity.

Management

Prenatal care for women with CKD incorporates several important aspects. Frequent monitoring of blood pressure is paramount, and serum creatinine levels and 24-hour protein excretion are quantified as indicated. Bacteriuria is treated to lower the risk of pyelonephritis and further nephron loss. Protein-restricted diets are not recommended. In some women with anemia from chronic renal insufficiency, a response is seen with recombinant erythropoietin. However, hypertension is a common side effect. Serial sonography is performed to follow fetal growth. The differentiation between worsening hypertension and superimposed preeclampsia is problematic. Preliminary data indicate that the angiogenic biomarkers *placental growth factor (PlGF)* and its soluble receptor, *soluble fms-like tyrosine kinase 1 (sFlt-1)*, may be useful to separate chronic from gestational hypertension (Fishel Bartal, 2020). This is described in Chapter 40 (p. 694).

Long-Term Effects

Pregnancy may accelerate CKD progression by augmenting hyperfiltration and glomerular pressure to worsen nephrosclerosis (Bargman, 2018). Women with severe renal insufficiency have greater susceptibility. Jungers and associates (1995) reported few long-term pregnancy-related adverse effects in 360 women with chronic glomerulonephritis and antecedent normal renal function. In a study from Parkland Hospital, 20 percent of pregnant women with moderate to severe renal insufficiency developed end-stage renal failure by a mean of 4 years (Cunningham, 1990). He and coworkers (2018) confirmed these findings in women who had stage 3 or 4 CKD.

As noted, progression is common for many women with chronic renal disorders. At 1 year after pregnancy, Jones and Hayslett (1996) reported that 10 percent of the women had developed end-stage renal failure—stage 5 CKD. Similar findings in women with a median follow-up of 3 years were described by Imbasciati and colleagues (2007). By this time, end-stage disease was apparent in 30 percent of women whose prepregnancy serum creatinine was ≥1.4 mg/dL and who had proteinuria >1 g/d.

Chronic proteinuria is also a marker for subsequent development of renal failure. In one study, 20 percent of women with chronic proteinuria discovered during pregnancy progressed to end-stage renal failure within several years (Stettler, 1992). Another study reported that an equal number of nonpregnant women had identical loss of function when similar durations were compared (Zhang, 2015). It may be that pregnancy does not hasten an already predetermined declining renal function.

Dialysis During Pregnancy

Significantly impaired renal function is accompanied by subfertility that may be corrected with chronic renal replacement therapy—either hemodialysis or peritoneal dialysis (Wiles, 2019b). Not unexpectedly, maternal complications are common and include severe hypertension, placental abruption, heart failure, and sepsis. To illustrate this, the outcomes of 233 pregnancies in women undergoing dialysis are shown in Table 56-6. The high incidences of hypertension, low birthweight, and preterm delivery result in a perinatal mortality rate of 250 per 1000. Piccoli and associates (2016) performed a systematic review and described 681 pregnancies in 647 women undergoing dialysis. Of these, 616 had hemodialysis and 65 had peritoneal dialysis. They chronicled a high incidence of hypertension, preterm delivery, and fetal-growth restriction, and the perinatal mortality was 180 per 1000. They found an inverse relationship between hours of dialysis per week and adverse outcomes. Last, they reported that hemodialysis was superior to peritoneal dialysis.

For the woman already undergoing either method of dialysis, it seems reasonable to continue that method with consideration for its increasing frequency. In the woman who has never been dialyzed, the threshold for initiation during pregnancy is unclear. Hladunewich and colleagues (2016) recommend consideration for dialysis when the creatinine clearance is 20 mL/min or less. Extension of dialysis frequency to five to six times weekly may be necessary to avoid abrupt volume changes that cause hypotension.

Hladunewich and coworkers (2011) recommend attention to certain protocols that include replacement of substances lost through dialysis. Multivitamin doses are doubled, and oral calcium and iron salts are provided along with sufficient dietary protein and calories. Chronic anemia is treated with erythropoietin. To meet pregnancy changes, extra calcium is added to the dialysate along with less bicarbonate.

ACUTE KIDNEY INJURY

Previously termed *acute renal failure*, acute kidney injury (AKI) is now used to describe impairment of kidney function over days

TABLE 56-6. Pregnancy Outcomes in Women Undergoing Dialysis During Pregnancy

	Pregnancies			Pregnancy Outcomes (%)			
Study (Year)	N	Delivery (weeks)	Birthweight (g)	Hypertension	Hydramnios	Perinatal Mortality	Surviving Infants
Toma (1999)	54	31.9	1545	35	44	33	67
Chao (2002)	13	32	1540	72	46	31	69
Tan (2006)	11	31	1390	36	18	18	82
Chou (2008)	13	30.8	1510	57	71	50	50
Luders (2010)	52	32.7	1555	67	40	13	87
Shahir (2013)	13	NS	2130	19[a]	14	22	78
Jesudason (2014)	77	33.8	1750	NS	NS	20	80
Approximate averages	233	~32	~1600	~50	~44	~25	~75

[a]Preeclampsia only.
NS = not stated.

to weeks that leads to retention of nitrogenous and other waste products normally excreted by the kidneys. Current definitions include a rise in a serum creatinine level of at least 0.3 mg/dL within 48 hours, or ≥50 percent increase from baseline within a week, or urine output reduced to <0.5 mL/kg per hour for >6 hours (Waikar, 2018).

Criteria for diagnosis in pregnancy have not been standardized (Gonzalez Suarez, 2019). Most studies use a definition in which serum creatinine levels rise ≥0.3 mg/dL from baseline. Animal studies have shown that pregnancy protects the kidney from acute ischemic injury (Popkov, 2018). Although the incidence of AKI in pregnancy has dropped substantially, it still occasionally causes significant obstetrical morbidity and mortality. In a Canadian study, the incidence was reported to be 2.68 per 10,000 births between 2009 and 2010 (Mehrabadi, 2014). Outcomes are available from four older studies comprising a total of 266 women with AKI (Drakeley, 2002; Nzerue, 1998; Sibai, 1990; Turney, 1989). Approximately 70 percent had preeclampsia, 50 percent had obstetrical hemorrhage, and 30 percent had a placental abruption. Almost 20 percent required dialysis, and the maternal mortality rate approximated 15 percent.

Although obstetrical cases of AKI requiring dialysis are less frequent today, acute renal ischemia is still commonly associated with severe preeclampsia and hemorrhage (Conti-Ramsden, 2019; Jim, 2017; Prakash, 2018). Notable contributors are placental abruption and hemolysis, elevated liver enzymes, and low platelet count (HELLP) syndrome. Sepsis is another, especially in resource-poor countries (Acharya, 2013). AKI also often complicates acute fatty liver of pregnancy. Nelson and colleagues (2013) reported some degree of renal insufficiency in virtually all of 52 such women cared for at Parkland Hospital (Chap. 58, p. 1034). Dehydration caused by severe hyperemesis gravidarum also can lead to AKI (Hill, 2002). Other causes include thrombotic microangiopathies (Chap. 59, p. 1060).

Diagnosis and Management

In most women, renal failure develops postpartum, thus management is usually not complicated by fetal considerations. Diagnostically, an acute rise in serum creatinine levels is most often due to renal ischemia. But oliguria also is an important sign of acutely impaired renal function. In obstetrical cases, both prerenal and intrarenal factors commonly coincide. For example, with total placental abruption, severe hypovolemia results from massive hemorrhage, and frequently associated preeclampsia causes preexistent renal ischemia (Chap. 40, p. 689).

When azotemia is severe and oliguria persists, some form of renal replacement treatment may be indicated. Hemofiltration or dialysis is initiated before patients markedly deteriorate, and hemodynamic measurements are normalized. Medication dose adjustments are imperative, and magnesium sulfate is a prominent example (Waikar, 2018). Early dialysis appears to reduce the mortality rate appreciably and may enhance the extent of renal function recovery. With time, renal function usually returns to normal or near normal. Even so, women in subsequent pregnancies have higher incidences of hypertension and adverse fetal outcomes (Tangren, 2017).

Prevention

AKI in obstetrics is most often due to acute blood loss and especially that associated with preeclampsia. Thus, it may often be prevented by the following means:

1. Prompt and vigorous volume replacement with crystalloid solutions and blood in instances of massive hemorrhage, such as in placental abruption, placenta previa, uterine rupture, and postpartum uterine atony (Chap. 44, p. 771).
2. Delivery or termination of pregnancies complicated by severe preeclampsia or eclampsia, and careful blood transfusion if blood loss is more than average (Chap. 41, p. 712).
3. Close observation for early signs of sepsis and shock in women with pyelonephritis, septic abortion, chorioamnionitis, or other pelvic infections (Chap. 50, p. 887).
4. Avoidance of loop diuretics to treat oliguria before ensuring that blood volume and cardiac output are adequate for renal perfusion.
5. Judicious use of vasoconstrictor drugs to treat hypotension, and only after it has been determined that pathological vasodilation is the cause.

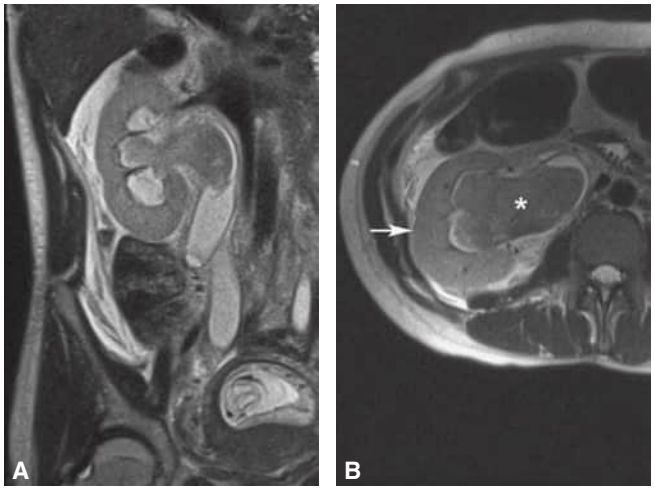

FIGURE 56-5 A. Magnetic resonance image in a coronal plane of a pregnant woman with unilateral hydronephrosis caused by ureteral obstruction. The serum creatinine was 8 mg/dL and decreased to 0.8 mg/dL after a percutaneous nephrostomy tube was placed. **B.** Left kidney (*arrow*) and associated hydronephrosis (*asterisk*) are again noted in this axial plane image.

Irreversible ischemic renal failure caused by *acute cortical necrosis* has become exceedingly uncommon in obstetrics. Before widespread availability of dialysis, it complicated a fourth of obstetrical renal failure cases (Grünfeld, 1987; Turney, 1989). Most cases followed placental abruption, preeclampsia-eclampsia, and endotoxin-induced shock. Once common with septic abortion, this is a rare cause in the United States today (Jim, 2017). Histologically, the lesion appears to result from thrombosis of segments of the renal vascular system. The lesions may be focal, patchy, confluent, or gross. Clinically, renal cortical necrosis follows the course of acute renal failure, and its differentiation from acute tubular necrosis is not possible during the early phase. The prognosis depends on the extent of the necrosis. Recovery of function is variable, and stable renal insufficiency may result.

■ Obstructive Renal Failure

Rarely, bilateral ureteral compression by a very large pregnant uterus obstructs ureters to cause severe oliguria and azotemia. An example is shown in Figure 56-5. Brandes and Fritsche (1991) reviewed 13 cases that were the consequence of a markedly overdistended uterus. They described a woman with twins who developed anuria and a serum creatinine level of 12.2 mg/dL at 34 weeks' gestation. After amniotomy, urine flow resumed at 500 mL/h, and a rapid decline in serum creatinine levels to normal range followed. Eckford and Gingell (1991) described 10 women in whom ureteral obstruction was relieved by stenting. The stents were left in place for a mean of 15.5 weeks and removed 4 to 6 weeks postpartum.

We have observed this phenomenon on several occasions. In our experience, women with previous urinary tract surgery for reflux are more likely to have such obstructions (Satin, 1993). Partial ureteral obstruction may be accompanied by fluid retention and significant hypertension. When the obstructive uropathy is relieved, diuresis ensues and hypertension dissipates. In one woman with massive hydramnios (9.4 L) and an anencephalic fetus, amniocentesis and removal of some of the amnionic fluid was followed promptly by diuresis, a decline in the plasma creatinine concentration, and an improvement of hypertension.

LOWER URINARY TRACT LESIONS

■ Urethral Diverticulum

Infrequently complicating pregnancy, this type of diverticulum is thought to originate from an enlarging paraurethral gland abscess that ruptures into the urethral lumen (Fig. 56-6). As infection clears, the remaining dilated diverticular sac and its ostium into the urethra persist. Associated findings may be urine collecting within and then dribbling from the sac, pain, palpable mass, and recurrent urinary infections. In general, a diverticulum is managed expectantly during pregnancy. Rarely, drainage may be necessary, or surgery required (Iyer, 2013). If additional antepartum evaluation is needed, MR imaging is preferred for its superior soft-tissue resolution and ability to define complex diverticula (Dwarkasing, 2011; Pathi, 2013).

■ Urinary Tract Fistulas

Fistulas found during pregnancy likely existed previously, but in rare cases, they form during pregnancy. In developed countries, *vesicovaginal fistula* following a McDonald cerclage has been reported (Massengill, 2012). These fistulas may also form with the prolonged obstructed labor that is more commonly seen in resource-poor countries. In these cases, the genital tract is compressed between the fetal head and bony pelvis. Brief pressure is not significant, but prolonged pressure leads to tissue necrosis and subsequent fistula formation (Wall, 2012). *Vesicouterine fistulas* that developed after prior cesarean delivery have been described (DiMarco, 2006; Manjunatha, 2012). Rarely, *vesicocervical fistula* may follow cesarean delivery or may form if the anterior cervical lip is compressed against the symphysis pubis (Dudderidge, 2005).

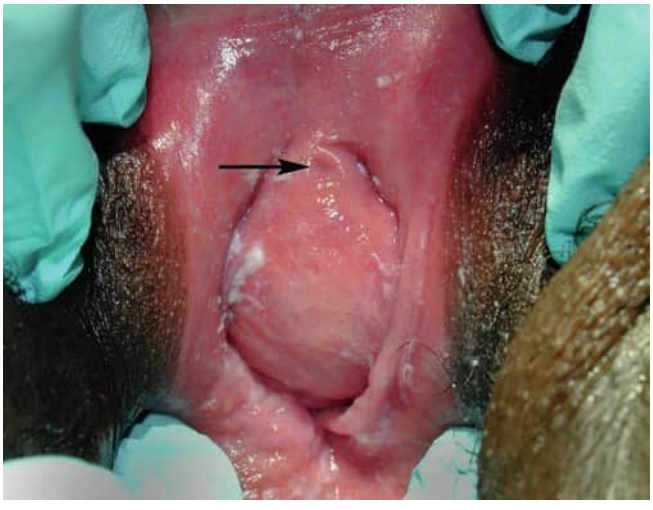

FIGURE 56-6 Asymptomatic urethral diverticulum, seen as a midline bulge beneath the urethral meatus (*arrow*), identified during initial prenatal care examination.

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CHAPTER 57

Gastrointestinal Disorders

During normal pregnancy, the gastrointestinal (GI) tract and its appendages undergo remarkable anatomical, physiological, and functional alterations. These changes, which are discussed in detail in Chapter 4 (p. 70), can appreciably alter clinical findings normally relied on for diagnosis and treatment. Moreover, as pregnancy progresses, GI findings become more difficult to assess. The clinical examination is often obscured by a large uterus that displaces abdominal organs and can alter the location and intensity of pain and tenderness.

GENERAL CONSIDERATIONS

Diagnostic Techniques

Endoscopy

Several endoscopic methods can be used to evaluate the gastrointestinal (GI) tract during pregnancy without reliance on radiographic techniques. With fiberoptic endoscopic instruments, the esophagus, stomach, duodenum, and colon can be inspected (Savas, 2014; Song, 2018). The proximal jejunum also can be studied, and the ampulla of Vater cannulated to perform *endoscopic retrograde cholangiopancreatography—ERCP* (Fogel, 2014; Hedström, 2017). Experience in pregnancy with *video capsule endoscopy* for small-bowel evaluation remains limited (Bandorski, 2016). Normal pregnancy-related slowing of GI motility and thus increased transit time as well as the recorder capsule's electromagnetic field are theoretical concerns.

Upper gastrointestinal endoscopy is used for diagnosis and management of several problems. Common bile duct exploration and drainage are used for choledocholithiasis (Chap. 58, p. 1043). Sclerotherapy and placement of *percutaneous endoscopic gastrostomy (PEG)* tubes also are performed endoscopically.

Colonoscopy is indispensible for viewing the entire colon and distal ileum. Except for the midtrimester, reports of colonoscopy during pregnancy are limited, but most results suggest that it should be performed if necessary (De Lima, 2015; Ludvigsson, 2017). Pregnancy indications include chronic abdominal pain, hematochezia, and diarrhea (Cappell, 2011). Bowel preparation is completed using polyethylene glycol electrolyte (GoLYTELY) or sodium sulfate (Suprep) solutions (American Society for Gastrointestinal Endoscopy, 2015). With these, most women avoid serious dehydration that may cause diminished uteroplacental perfusion. In select cases, tap water enemas

TABLE 57-1. Preprocedural Considerations for Gastrointestinal Endoscopy During Pregnancy

Plan consultation with an obstetrician, gastroenterologist, and anesthesiologist
Place patient in left lateral decubitus position
Use lowest effective dose of sedation necessary
Give prophylactic antibiotics as indicated. Penicillin, cephalosporin, erythromycin, and clindamycin are safe options
Minimize procedure time
Obtain fetal heart tones at the discretion of the obstetrician. In general, pre- and post-procedure heart tones are adequate
For colonoscopy, favor preparation with PEG-ES or with tap water enemas depending on GI level to be evaluated

GI = gastrointestinal; PEG-ES = polyethylene glycol electrolyte solution.
From American Society for Gastrointestinal Endoscopy, 2012, 2015.

may be an alternative for rectosigmoidoscopy to avoid some of these risks.

Endoscopic procedures should be performed when indicated and ideally in the second trimester (American Society for Gastrointestinal Endoscopy, 2012; Ludvigsson, 2017). A multidisciplinary approach with obstetricians, gastroenterologists, and anesthesiologists is prudent. Table 57-1 outlines preprocedural considerations in pregnancy.

Noninvasive Imaging Techniques

The ideal technique for GI tract imaging during pregnancy is abdominal sonography. However, the gravid uterus may obscure abdominal organs making evaluation difficult. Magnetic resonance (MR) imaging allows inspection of the abdomen and retroperitoneal space yet avoids radiation exposure from computed tomography (CT) (Khandelwal, 2013). Examples are MR cholangiopancreatography (MRCP) and MR enterography (MRE) (Oto, 2009; Stern, 2014). These and other imaging modalities, and their safe use in pregnancy, are discussed in Chapter 49.

Laparotomy and Laparoscopy

Surgery is lifesaving for certain GI conditions—perforative appendicitis being the most common example. Intraabdominal surgery is the most frequently performed nonobstetrical procedure during pregnancy (Devroe, 2019). Laparoscopic procedures have replaced traditional surgical techniques for many abdominal disorders during pregnancy (Ye, 2019). These are discussed in detail with descriptions of surgical technique in Chapter 49 (p. 867) and in *Cunningham and Gilstrap's Operative Obstetrics*, 3rd edition (Kho, 2017). Guidelines for laparoscopy during pregnancy have been provided by the American College of Obstetricians and Gynecologists (2019) and the Society of American Gastrointestinal and Endoscopic Surgeons (Pearl, 2017).

■ Nutritional Support

Specialized nutritional support can be delivered *enterally*, usually via nasogastric tube feedings, or *parenterally* by venous catheter access, either peripherally or centrally.

When possible, enteral alimentation is preferable because it has fewer serious complications (Hoffer, 2018; Stokke, 2015). In obstetrical patients, very few conditions prohibit enteral nutrition as a first effort to prevent catabolism. For extreme cases, such as recalcitrant hyperemesis gravidarum, percutaneous endoscopic gastrostomy with a jejunal port (PEG-J tube) has been described.

Parenteral nutrition provides nutrients when the intestinal tract must be quiescent. *Peripheral parenteral nutrition (PPN)* administers dilute nutrient admixtures and is appropriate for short-term use. Central venous access is necessary for *central parenteral nutrition (CPN)* because its hyperosmolarity requires rapid dilution in a high-flow vascular system (Robinson, 2018; Worthington, 2017). These solutions provide 24 to 40 kcal/kg/d, principally as a hypertonic glucose solution. Various conditions may prompt CPN during pregnancy (Table 57-2). The most common indications are short bowel syndrome and dysmotility disorders, and feeding duration averages 33 days (Billiauws, 2017).

TABLE 57-2. Some Conditions Treated with Enteral or Parenteral Nutrition During Pregnancy[a]

Achalasia
Anorexia nervosa
Appendiceal rupture
Bowel obstruction
Burns
Cholecystitis
Crohn disease
Diabetic gastropathy
Esophageal injury
Hyperemesis gravidarum
Jejunoileal bypass
Malignancies
Ostomy obstruction
Pancreatitis
Preeclampsia syndrome
Short bowel syndrome
Stroke
Ulcerative colitis

[a]Complications arranged alphabetically.
From Billiauws, 2017; Folk, 2004; Guglielmi, 2006; Mahadevan, 2019; Porter, 2014; Russo-Stieglitz, 1999; Saha, 2009; Spiliopoulos, 2013.

Parenteral nutrition complications are frequent and may be severe (Hoffer, 2018). The most common is catheter sepsis, and Folk (2004) reported a 25-percent incidence in 27 women with hyperemesis gravidarum. The Centers for Disease Control and Prevention provides detailed guidelines to prevent catheter-related sepsis (O'Grady, 2011). Other maternal complications include upper-extremity venous thrombosis, volume overload, and reversible liver dysfunction. Perinatal complications are rare, however, fetal subdural hematoma caused by maternal vitamin K deficiency has been described (Sakai, 2003).

Appreciable morbidity is also associated with long-term use of a *peripherally inserted central catheter (PICC)*. Again, infection is the most common serious long-term complication (Hoffer, 2018; Holmgren, 2008). In a series of 84 such catheters inserted in 66 pregnant women, Cape and coworkers (2014) reported a 56-percent complication rate, and bacteremia was the most frequent. For short-term nutrition lasting a few weeks, PICC placement and its greater benefit-versus-risk ratio seems reasonable (Worthington, 2017).

UPPER GASTROINTESTINAL TRACT DISORDERS

Hyperemesis Gravidarum

Mild to moderate nausea and vomiting are especially common in pregnant women until approximately 16 weeks' gestation (Chap. 10, p. 191). In a small but significant proportion of these, however, it is severe and unresponsive to simple dietary modification and antiemetics. *Hyperemesis gravidarum* is defined variably as severe unrelenting nausea and vomiting that produces weight loss, dehydration, ketosis, alkalosis from loss of hydrochloric acid, and hypokalemia. Acidosis develops from partial starvation. In some women, transient hepatic dysfunction develops, and biliary sludge accumulates (Table 58-1, p. 1031). Other causes should first be considered because hyperemesis gravidarum is a diagnosis of exclusion.

Study criteria are not standardized, and thus population incidences vary (Koot, 2018). However, an ethnic or familial predilection has been described (London, 2017). In several population-based studies, the hospitalization rate for hyperemesis gravidarum was 0.5 to 2.1 percent (Fiaschi, 2019; Vikanes, 2013). Up to 25 percent of those hospitalized in a previous pregnancy for hyperemesis will again require admission (Nurmi, 2018).

The etiopathogenesis of hyperemesis gravidarum is unknown and is likely multifactorial. High or rapidly rising serum levels of pregnancy-related hormones such as human chorionic gonadotropin (hCG), estrogen, progesterone, placental growth hormone, prolactin, thyroxine, and adrenocortical hormones are implicated (London, 2017; Verberg, 2005). Other associated hormones include ghrelins, leptin, nesfatin-1, and peptide YY 3–36 (Albayrak, 2013; Gungor, 2013).

Superimposed on this hormonal cornucopia are many biological and environmental factors. Moreover, in some but not all severe cases, interrelated psychological components play a major role (Mitchell-Jones, 2017; Senturk, 2017). Factors that increase the risk for admission include hyperthyroidism, previous pregnancy complicated by hyperemesis, diabetes, GI illnesses, some restrictive diets, and asthma (Fell, 2006; Fiaschi, 2016; Mullin, 2012). An association of *Helicobacter pylori* infection has been proposed, but evidence is inconclusive (Goldberg, 2007; London, 2017). Chronic marijuana use may cause the similar *cannabinoid hyperemesis syndrome* (Alaniz, 2015; Andrews, 2015). And for unknown reasons—perhaps estrogen-related—a female fetus raises the risk but smoking and obesity decrease it by 1.5-fold (Cedergren, 2008; Fiaschi, 2016). Some have reported a relationship between severe hyperemesis gravidarum and anemia, venous thromboembolism (VTE), gestational hypertension, and preeclampsia (Fiaschi, 2018). An association between hyperemesis and preterm birth is unclear (Kleine, 2017). Koren and colleagues (2018) suggested that prolonged vomiting may cause metabolic abnormalities that interfere with fetal brain development. No long-term maternal consequences follow hyperemesis. Specifically, two population-based studies found no unfavorable cardiovascular risks in Norwegian women (Fossum, 2017, 2018).

Complications

Vomiting may be prolonged, frequent, and severe, and a list of potentially fatal complications is given in Table 57-3. Various degrees of acute kidney injury from dehydration are encountered, and rhabdomyolysis may be contributory (Lassey, 2016). Rarely, we and others have encountered women with renal failure requiring dialysis (Dayangan Sayan, 2018; Hill, 2002). *Mallory-Weiss* tears result from continuous retching. Other complications include pneumothorax, pneumomediastinum, diaphragmatic rupture, and gastroesophageal rupture—*Boerhaave syndrome* (American College of Obstetricians and Gynecologists, 2018; Chen, 2012).

At least two serious vitamin deficiencies have been reported with hyperemesis in pregnancy. One is *Wernicke encephalopathy* from thiamine deficiency (Di Gangi, 2012; Palacios-Marqués, 2012). A systematic review reported that ocular signs, confusion, and ataxia were common, and approximately 60 percent had this triad (Oudman, 2019). In some women, an abnormal electroencephalogram (EEG) may be seen, and usually MR imaging shows findings (Oudman, 2019; Vaknin, 2006; Zara,

TABLE 57-3. Some Serious and Life-Threatening Complications Reported with Hyperemesis Gravidarum[a]

Acute kidney injury—may require dialysis
Depression—cause versus effect?
Diaphragmatic rupture
Esophageal rupture—Boerhaave syndrome
Hyperalimentation complications
Hypokalemia—arrhythmias, cardiac arrest
Hypoprothrombinemia—vitamin K deficiency
Mallory–Weiss tears—bleeding, pneumothorax, pneumomediastinum, pneumopericardium
Rhabdomyolysis
Wernicke encephalopathy—thiamine deficiency

[a]Complications arranged alphabetically.

2012). One woman had recurrent encephalopathy in a subsequent pregnancy (Stephens, 2019). Maternal deaths have been described, and long-term sequelae include blindness, convulsions, and coma (Oudman, 2019; Selitsky, 2006). *Vitamin K* is a second potential deficiency. Maternal coagulopathy, fetal intracranial hemorrhage, and vitamin K embryopathy have been reported (Kawamura, 2008; Lane, 2015; Nijsten, 2021).

Management

One management algorithm for nausea and vomiting of pregnancy is shown in Figure 57-1. Most women with mild to moderate symptoms respond to outpatient therapy with any of several first-line antiemetic agents (Boelig, 2018, McParlin, 2016). One mainstay is *Diclegis*—a combination of doxylamine (10 mg) plus pyridoxine (10 mg). The usual dose is two tablets orally at bedtime, and it appears safe and effective (Briggs, 2017; Koren, 2014). If relief is insufficient, one additional first-morning tablet is added to the bedtime dose. This can be further escalated to include one first-morning, one midafternoon, and two bedtime tablets (Duchesnay Inc., 2018). At our institution, for cost savings, we prescribe these two agents individually. The formula is one half of a 25-mg Unisom (doxylamine) tablet plus a 25-mg vitamin B_6 (pyridoxine) tablet. The same graduated dosing is used but does not exceed three total daily doses.

Ondansetron (Zofran) is slightly more effective than the combination of doxylamine and pyridoxine (Oliveira, 2014; Pasternak, 2013). In some studies, the former has been associated with birth defects (Briggs, 2017). However, after a recent systematic review of Cochrane and Reprotox databases, authors concluded that ondansetron is not teratogenic (Kaplan, 2019). Other drawbacks include potential maternal effects from prolonged QT-interval and serotonin syndrome. For these reasons it is preferably reserved for severe cases after 8 weeks' gestation (Lavecchia, 2018).

When simple measures fail, intravenous (IV) crystalloid solutions are given to correct dehydration, ketonemia, electrolyte deficits, and acid-base imbalances. Hypokalemia is common, and cardiac arrest has been reported (Walch, 2018). No benefits are gained by infusing 5-percent dextrose along with crystalloids (Tan, 2013). Thiamine, 100 mg, is usually diluted in 1 L of the selected crystalloid to prevent Wernicke encephalopathy for women who require IV hydration and have vomited for more than 3 weeks (Giugale, 2015). It is infused at the maintenance rate desired for patient hydration. This thiamine dose is provided daily for the next 2 to 3 days and is followed by IV multivitamins if IV hydration continues (Levichek, 2002).

If vomiting persists after rehydration and failed outpatient management, hospitalization is recommended (American College of Obstetricians and Gynecologists, 2018). IV hydration is continued and antiemetics such as promethazine, prochlorperazine, chlorpromazine, or metoclopramide are given parenterally (Table 57-4). Several antiemetics are associated with the long-QT syndrome, discussed in Chapter 52 (p. 936). Outpatient treatment regimens at the hospital also are effective (McCarthy, 2014).

Some, but not all, studies indicate that treatment with *glucocorticosteroids* is not effective (Sridharan, 2020; Yost, 2003). They are recommended only for refractory cases because of their putative teratogenicity (American College of Obstetricians and Gynecologists, 2018).

With persistent vomiting after hospitalization, appropriate steps should be taken to exclude possible underlying diseases as a cause of hyperemesis.

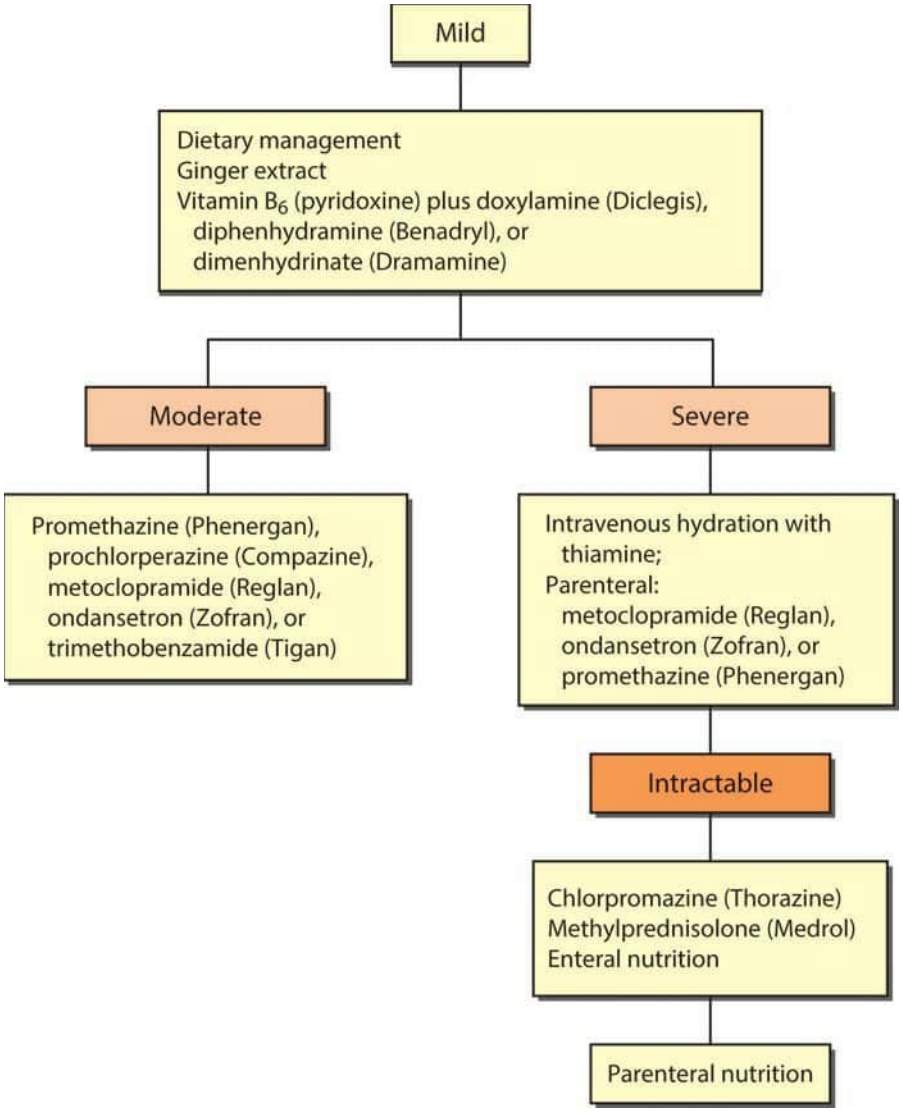

FIGURE 57-1 Algorithm for outpatient and inpatient management of pregnancy nausea and vomiting, and hyperemesis gravidarum.

TABLE 57-4. Medications for Gastrointestinal Disorders in Pregnancy

Medication (Brand Name)	Usual Dosing	Route(s)
Options for nausea and vomiting		
Antihistamine		
Doxylamine + pyridoxine (Diclegis)[a]	At bedtime; up to 4 times daily	PO
Phenothiazines	**Every 6 hr**	
Promethazine (Phenergan)[c]	12.5–25 mg	IM, IV, PO, PR
Prochlorperazine (Compazine)[c]	5–10 (25 PR) mg	IM, IV, PO, PR
Chlorpromazine (Thorazine)[c]	25–50 mg	IM, PO
Serotonin antagonist	**Every 8 hr**	
Ondansetron (Zofran)[b]	8 mg	IV, PO
Benzamides	**Every 6 hr**	
Metoclopramide (Reglan)[b]	5–15 mg	IM, IV, PO
Trimethobenzamide (Tigan)	300 mg	PO
Oral options for gastroesophageal reflux disease (GERD)		
Proton-pump inhibitors		
Pantoprazole (Protonix)[b]	40 mg daily for up to 8 wks	
Lansoprazole (Prevacid)[b]	15 mg daily for up to 8 wks	
Omeprazole (Prilosec, Zegerid)[c]	20 mg daily for 4–8 wks	
Dexlansoprazole (Dexilant)[c]	30 mg daily for up to 4 wks	
H2-receptor antagonists		
Cimetidine (Tagamet)[b]	400 mg 4 times daily for up to 12 wks 800 mg twice daily for up to 12 wks	
Nizatidine (Axid)[b]	150 mg twice daily	
Famotidine (Pepcid)[b]	20 mg twice daily up to 6 wks	

[a]Food and Drug Administration category A.
[b]Food and Drug Administration category B.
[c]Food and Drug Administration category C.
IM = intramuscularly; IV = intravenously; PO = orally; PR = rectally.

That said, in one study, endoscopy did not change management in 49 women (Debby, 2008). Other potential sources include gastroenteritis, cholecystitis, pancreatitis, hepatitis, peptic ulcer, and pyelonephritis. In addition, severe preeclampsia and fatty liver are more likely after midpregnancy. Although clinical thyrotoxicosis has been implicated as a cause of hyperemesis, it is more likely that abnormally elevated serum thyroxine levels are a surrogate for higher-than-average serum hCG levels (Sun, 2014). This is discussed further in Chapter 5 (p. 97). In our experiences, serum free thyroxine levels normalize quickly with hydration and emesis treatment.

With treatment, most women will have a positive response and may be sent home with oral antiemetic therapy. The readmission rate is 25 to 35 percent in most prospective studies. Risks for anxiety and depression are increased in these women (Mitchell-Jones, 2017; Senturk, 2017). At Parkland Hospital, more than one third of women with hyperemesis required readmission. Patient characteristics had limited utility in predicting the risk of readmission. For example, maternal demographics, substance use, psychiatric illness, and initial hospitalization length were not associated with readmission (White, 2018). If psychiatric and social factors contribute to the illness, the woman usually improves remarkably while hospitalized (Swallow, 2004). However, symptoms relapse in a fourth of these women, and some go on to develop *posttraumatic stress syndrome* (Chap. 64, p. 1150) (Christodoulou-Smith, 2011; McCarthy, 2011; Nurmi, 2018). For some women, hyperemesis may be an indication for elective termination (Poursharif, 2007).

Grooten and colleagues (2017) showed that early enteral tube feeding has no advantages. However, in the small percentage of women who have recalcitrant vomiting after intensive therapy, consideration is given for enteral nutrition (p. 1013). Stokke and associates (2015) described successful use of nasojejunal feeding for up to 41 days in 107 such women. Use of sonography to confirm correct tube placement has been described and avoids radiation exposure (Swartzlander, 2013). PEG-J tubes also have been reported (Saha, 2009; Schrag, 2007).

Only a very few women will require parenteral nutrition (American College of Obstetricians and Gynecologists, 2018; Yost, 2003). In a study of 599 women, however, Peled and coworkers (2014) reported that 20 percent required central parenteral nutrition.

Gastroesophageal Reflux Disease

Symptomatic reflux is seen in up to 15 percent of nonpregnant individuals (Kahrilas, 2018). The spectrum of sequelae includes esophagitis, stricture, Barrett esophagus, and adenocarcinoma.

The main symptom of reflux is *pyrosis* (heartburn), which is especially common in pregnancy. In one study, its prevalence rose from 26 percent in the first trimester to 36 percent in the second and 51 percent in the third trimester (Fill Malfertheiner, 2017). The retrosternal burning sensation stems from esophagitis caused by gastroesophageal reflux of stomach acid, which follows relaxation of the lower esophageal sphincter. The diagnosis is typically made from symptoms alone.

Symptoms usually respond to abstaining from tobacco and alcohol, eating small meals, elevating the head of the bed, limiting postprandial recumbency, and avoiding "trigger" foods. These may include fatty foods, tomato-based foods, and coffee. Oral antacids are first-line therapy. If severe symptoms persist, a proton-pump inhibitor is given and an H_2-receptor antagonist and sucralfate can be added (see Table 57-4). Both classes are generally safe for use in pregnancy (Briggs, 2017). From preliminary data, proton-pump inhibitors taken early in pregnancy may increase the risk for preeclampsia (Hastie, 2019). Sucralfate is the aluminum salt of sulfated sucrose and inhibits pepsin. Approximately 10 percent of the aluminum salt is absorbed, and this agent is considered safe for pregnant women (Briggs, 2017). A 1-g sucralfate tablet is taken orally 1 hour before each of the three meals and at bedtime for up to 8 weeks. Antacids are not used within a half hour before or after sucralfate doses. Despite attempts with these options, if relief is not attained, endoscopy should be considered. *Misoprostol* is contraindicated because it stimulates labor (Chap. 26, p. 490).

In nonpregnant patients, surgical fundoplication can be performed (Kahrilas, 2018). Although the procedure is not done during pregnancy, Biertho and colleagues (2006) described 25 women who had undergone laparoscopic Nissen fundoplication before pregnancy. Only 20 percent had reflux symptoms during pregnancy.

Hiatal Hernia

The older literature is informative regarding hiatal hernias in pregnancy. Upper gastrointestinal radiographs performed in 195 women in late pregnancy showed that 20 percent of 116 multiparas and 5 percent of 79 nulliparas had a hiatal hernia (Rigler, 1935). Of 10 women studied postpartum, hernia persisted in three at 1 to 18 months.

The relationship of hiatal hernia with reflux esophagitis is not clear. One study demonstrated no association and showed that the lower esophageal sphincter functioned effectively even when displaced intrathoracically (Cohen, 1971). Nevertheless, during pregnancy, hiatal hernias may cause vomiting, epigastric pain, and bleeding from ulceration. Schwentner (2011) reported severe herniation requiring surgical repair in a woman with a 12-week gestation. Curran and coworkers (1999) described a 30-week pregnancy complicated by gastric outlet obstruction from a paraesophageal hernia.

Diaphragmatic Hernia

These are caused by herniations of abdominal contents through either the foramen of Bochdalek or Morgagni. Fortunately, they rarely complicate pregnancy. In one review of 18 pregnant women who developed acute obstruction within a diaphragmatic hernia, the maternal mortality rate was 45 percent (Kurzel, 1988). Herniation has been reported in one woman who had antireflux surgery in early pregnancy (Brygger, 2013). Several case reports also describe spontaneous diaphragmatic rupture from elevated intraabdominal pressure during delivery (Chen, 2012; Sharifah, 2003). Surgical treatment is considered in symptomatic gravidas and is individualized according to gestational age and clinical setting (Ménassa, 2019; Whang, 2018).

Achalasia

In this rare motility disorder, the lower esophageal sphincter fails to relax properly with swallowing. The esophageal muscularis also displays nonperistaltic contraction activity (Kahrilas, 2018). The defect is caused by inflammatory destruction of the myenteric (Auerbach) plexus within smooth muscle of the lower esophagus and its sphincter. Postganglionic cholinergic neurons are unaffected, and thus sphincter stimulation is unopposed.

Symptoms are dysphagia, chest pain, and regurgitation. Barium swallow radiography demonstrates *bird beak* or *ace of spades* narrowing at the distal esophagus. Endoscopy is performed to exclude gastric carcinoma, and manometry is confirmatory.

During pregnancy, normal physiological relaxation of the lower esophageal sphincter in women with achalasia theoretically should not occur. In one series, half of these women had worsened symptoms, but reflux is uncommon (Vogel, 2018). In other pregnancy studies, most women did not have worsening symptoms (Khudyak, 2006). At least one maternal death was reported at 24 weeks' gestation and perforation of a 14-cm-diameter megaesophagus was implicated (Fassina, 1995).

Management of achalasia includes a soft diet and anticholinergic drugs. With persistent symptoms, other options include nitrates, calcium-channel antagonists, and botulinum toxin A injected locally (Hooft, 2015; Kahrilas, 2018). Balloon dilation of the sphincter may be necessary, and 85 percent of nonpregnant patients respond (Vogel, 2018). *One caveat is that esophageal perforation is a serious complication of dilation.* If dilation or medical therapy fail to provide relief, myotomy is considered. In one report, a 29-week pregnant woman with achalasia was treated for 10 weeks with peripheral parenteral nutrition, and surgical myotomy was done postpartum (Spiliopoulos, 2013).

Peptic Ulcer Disease

The lifetime prevalence of acid peptic disorders in women is 10 percent (Del Valle, 2018). Erosive ulcer disease involves the stomach and duodenum. Gastroduodenal ulcers commonly are caused by chronic gastritis from *Helicobacter pylori*, or they develop from nonsteroidal antiinflammatory drug (NSAID) use. Neither is common in pregnancy (McKenna, 2003; Weyermann, 2003). Rosen and coworkers (2021) reported 2535 pregnant women with peptic ulcer disease and found that complications were less frequent than in nonpregnant controls.

Acid secretion also is important, and this underlies the efficacy of antisecretory agents. Natural gastroprotection during

pregnancy probably originates from physiological changes that include reduced gastric acid secretion, decreased motility, and considerably increased mucus secretion (Hytten, 1991). Despite this, ulcer disease may be underdiagnosed because of frequent treatment for reflux esophagitis (Mehta, 2010). In the past 55 years at Parkland Hospital, during which time we have cared for more than 600,000 pregnant women, we have encountered very few who had proven ulcer disease. Perforation is rare (Goel, 2014). Before appropriate therapy was commonplace, Clark (1953) studied 313 pregnancies in 118 women with ulcer disease and noted a clear remission during pregnancy in almost 90 percent. However, benefits were short lived. Symptoms recurred in more than half by 3 months postpartum and in almost all by 2 years.

The mainstay of management is eradication of *H pylori* and prevention of NSAID-induced disease. Antacids are usually self-prescribed, but other first-line therapy is a proton-pump inhibitor or H_2-receptor blocker (see Table 57-4) (Del Valle, 2018; Laine, 2012). Sucralfate can be added and provides a protective coating at the ulcer base.

With active ulcers, a search for *H pylori* is undertaken. Diagnostic aids include the urea breath test, serological testing, fecal testing, or endoscopic biopsy. If any of these yield positive results, combination antimicrobial plus proton-pump inhibitor therapy is indicated (Chey, 2017). Several effective oral treatment regimens do not include tetracycline and can be used during pregnancy. One 14-day regimen includes clarithromycin, 500 mg twice daily, which is paired either with amoxicillin, 1000 mg twice daily or with metronidazole, 500 mg three times daily. These antibiotics are given with a proton-pump inhibitor (Del Valle, 2018).

Upper Gastrointestinal Bleeding

In some women, persistent vomiting is accompanied by worrisome upper gastrointestinal bleeding. Occasionally, a peptic ulcer is the source. However, most of these women have small linear mucosal tears near the gastroesophageal junction—*Mallory-Weiss tears* (p. 1014). Bleeding usually responds promptly to conservative measures that include IV proton-pump inhibitors and topical antacids (Laine, 2012). Transfusions may be needed, and if bleeding persists, endoscopy is usually indicated (O'Mahony, 2007). With sustained retching, the less common, but more serious, esophageal rupture—*Boerhaave syndrome*—may develop from high esophageal pressure.

SMALL BOWEL AND COLON DISORDERS

The small bowel has diminished motility during pregnancy. Lawson and colleagues (1985) showed that the small bowel mean transit times of 99, 125, and 137 minutes in each successive trimester, respectively, were slower than 75 minutes when nonpregnant. Muscular relaxation of the colon is accompanied by increased absorption of water and sodium that predisposes to constipation. This complaint is reported by almost 25 percent of women at some time during pregnancy and the puerperium (Everson, 1992). Symptoms are usually only mildly bothersome, and initial treatment includes increasing fluid intake (>8 glasses/d) and fiber consumption (20 to 35 g/d) (Body, 2016). If these lifestyle modifications fail, bulk-forming agents such as methylcellulose may be added, and in severe cases the stimulant laxative bisacodyl. We have encountered several pregnant women who developed megacolon from impacted stool. These women almost invariably had chronically abused stimulatory laxatives.

Acute Diarrhea

The estimated monthly prevalence of diarrhea among adults is 3 to 7 percent (DuPont, 2014). Diarrhea can be classified as acute (<2 weeks), persistent (2 to 4 weeks), and chronic (>4 weeks). Most cases of acute diarrhea are caused by infectious agents, and a third result from foodborne pathogens. The large variety of viruses, bacteria, helminths, and protozoa that cause diarrhea in adults also afflict pregnant women. These are usually accompanied by vomiting, fever, and abdominal pain. Some of these are discussed in Chapter 64 (p. 1197).

Evaluation of acute diarrhea depends on its severity and duration. Some indications for evaluation include profuse watery diarrhea with dehydration, grossly bloody stools, fever >38°C, duration >48 hr without improvement, recent antimicrobial use, and diarrhea in the immunocompromised patient (Camilleri, 2018; DuPont, 2014). Cases of moderately severe diarrhea with fecal leukocytes or gross blood may be treated with empirical antibiotics rather than evaluation. However, risks and benefits should be considered, and it is reasonable to withhold treatment until stool testing is completed to exclude infection. Some features of the more common acute diarrheal syndromes and their treatment are shown in Table 57-5.

The mainstay of treatment is IV hydration using normal saline or Ringer lactate and potassium supplementation in amounts to restore maternal blood volume and to ensure uteroplacental perfusion. Vital signs and urine output are monitored for signs of sepsis. For moderately severe nonfebrile illness without bloody diarrhea or recent travel, antimotility agents such as loperamide (Imodium) may be useful. An initial 4-mg (two capsules) dose can be followed with another 2-mg capsule after subsequently passed watery stools. Dosages should not exceed 8 mg/d, and loperamide is not used for more than 48 h. Bismuth subsalicylate (Pepto-Bismol) also may alleviate symptoms. The recommended dosage is 30 mL (525 mg) of its liquid form or two tablets (263 mg/tablet) chewed well each 30 to 60 min and not to exceed eight doses in 24 h. The drug will produce harmless black stools (Riddle, 2016).

Judicious use of antimicrobial agents is warranted. For moderately to severely ill women, some recommend empirical treatment with ciprofloxacin, 500 mg twice daily for 3 days. Specific pathogens are treated as needed when identified (see Table 57-5). Syndromes for which treatment is usually unnecessary include those caused by *Escherichia coli*, staphylococcal species, *Bacillus cereus*, and norovirus. Severe illness caused by *Salmonella* species is treated with ciprofloxacin or trimethoprim-sulfamethoxazole; by *Campylobacter* species with azithromycin; by *Clostridioides difficile* with oral vancomycin or fidaxomicin; and by *Giardia* species and *Entamoeba histolytica* with metronidazole (DuPont, 2014; McDonald, 2018; Rocha-Castro, 2016).

TABLE 57-5. Etiology, Clinical Features, and Treatment of Common Acute Diarrheal Syndromes

Agents	Incubation	Emesis	Pain	Fever	Diarrhea	Treatment
Toxin producers	1–72 hr	3–4+	1–2+	0–1+	3–4+, watery	
1. *Staphylococcus* spp.						1. None
2. *C perfringens*						2. None
3. *E coli* (enterotoxin)						3. Ciprofloxacin
4. *B cereus*						4. None
Enteroadherent	1–8 days	0–1+	1–3+	0–2+	1–2+, watery, mushy	
1. *E coli*						1. Ciprofloxacin
2. *Giardia* spp.						2. Tinidazole
3. Helminths						3. As detected
Cytotoxin producers	1–3 days	0–1+	3–4+	1–2+	1–3+, watery, then bloody	
1. *C difficile*						1. Vancomycin
2. *E coli* (hemorrhagic)						2. None
Inflammatory						
Minimal	1–3 days	1–3+	2–3+	3–4+	1–3+, watery	
1. *Rotavirus*						1. None
2. *Norovirus*						2. None
Variable	12 hr–11 days	0–3+	2–4+	3–4+	1–4+ watery or bloody	
3. *Salmonella* spp.						3. Ciprofloxacin
4. *Campylobacter* spp.						4. Azithromycin
5. *Vibrio* spp.						5. Doxycycline
Severe	12 hr–8 days	0–1+	3–4+	3–4+	1–2+, bloody	
6. *Shigella* spp.						6. Ciprofloxacin
7. *E coli*						7. Ciprofloxacin
8. *Entamoeba histolytica*						8. Metronidazole

B cereus = *Bacillus cereus*; *C difficile* = *Clostridioides difficile*; *C perfringens* = *Clostridium perfringens*; *E coli* = *Escherichia coli*; spp. = species.
Modified from Camilleri, 2018; DuPont, 2014; McDonald, 2018.

Clostridioides difficile Infection

Formally known as *Clostridium difficile*, this anaerobic gram-positive bacillus is transmitted by the fecal-oral route. In a study from China, 3.7 percent of normal gravidas were colonized (Ye, 2016). It is the most frequent nosocomial infection in the United States. In 2011, 453,000 cases of *C difficile* and 29,000 associated deaths were reported by the Centers for Disease Control and Prevention (Lessa, 2015). Its incidence in pregnant women has doubled during the past decade (Ruiter-Ligeti, 2018). The most important risk factor is antibiotic use, and the highest risk is with aminopenicillins, clindamycin, cephalosporins, and fluoroquinolones. Other risk factors include inflammatory bowel disease, immunosuppression, advanced age, and gastrointestinal surgery. Most cases are hospital-acquired, however, 10 percent are community-acquired cases (Gerding, 2018). With severe colitis, the infection-related mortality rate is 5 percent.

Laboratory diagnosis from a stool sample uses nucleic-acid amplification testing (NAAT) for *C difficile* itself or uses an enzyme-immunoassay-based algorithm for a unique *C difficile* enzyme or its toxins A and B (McDonald, 2018). Less often, infection may be diagnosed endoscopically (Fig. 57-2). Only patients with new-onset diarrhea and ≥3 unformed stool of unexplained etiology should be tested, and posttreatment testing is not recommended. Prevention is by soap-and-water hand

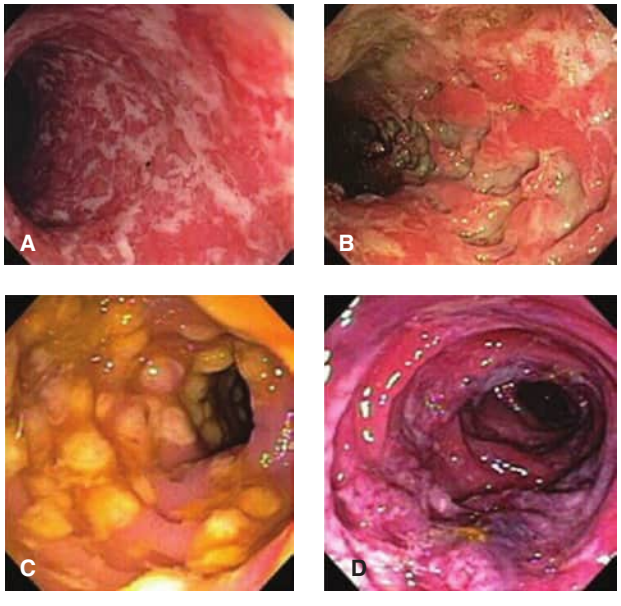

FIGURE 57-2 Causes of colitis. **A.** Ulcerative colitis with diffuse ulcerations and exudates. **B.** Crohn colitis with deep ulcers. **C.** Pseudomembranous colitis with yellow, adherent membranes. **D.** Ischemic colitis. (Reproduced with permission from Song LM, Topazian M: Gastrointestinal endoscopy. In Jameson JL, Fauci AS, Kasper DL, et al (eds): Harrison's Principles of Internal Medicine, 20th ed. New York, NY: McGraw Hill; 2018.)

TABLE 57-6. Some Shared and Differentiating Characteristics of Inflammatory Bowel Disease

	Ulcerative Colitis	Crohn Disease
Shared Characteristics		
Hereditary	More than 100 disease-associated genetic loci–a third shared; Jewish predominance; familial in 5–10% of cases; Turner syndrome; immune dysregulation	
Other	Chronic and intermittent with exacerbations and remissions; extraintestinal manifestations: arthritis, erythema nodosum, uveitis	
Differentiating Characteristics		
Major symptoms	Diarrhea, tenesmus, rectal bleeding, cramping pain; chronic, intermittent; anemia	Fibrostenotic–recurrent RLQ colicky pain; fever Fistulizing–cutaneous, bladder, interenteric
Bowel involvement	Mucosa and submucosa of large bowel; usually begins at rectum (40% proctitis only); continuous disease	Deep layers small and large bowel; commonly transmural; discontinuous involvement; strictures and fistulas
Endoscopy	Granular and friable erythematous mucosa; bleeding; rectal involvement	Patchy; segmental colitis; rectum spared; perianal involvement
Serum antibodies	Antineutrophil cytoplasmic (pANCA) ~70%	Anti–*S cerevisiae* ~50%
Complications	Toxic megacolon; strictures; arthritis; cancer (3–5%)	Fistulas; arthritis; toxic megacolon; small bowel obstruction
Management	Medical; proctocolectomy curative	Medical; segmental and fistula resection

RLQ = right lower quadrant; *S cerevisiae* = *Saccharomyces cerevisiae*.
From Friedman, 2018; Lichtenstein, 2009.

washing, and infected individuals are isolated. Treatment consists of stopping the offending antibiotics and giving 10 days of oral vancomycin, 125 mg four times daily, or fidaxomicin (Dificid), 200 mg twice daily (McDonald, 2018). The risk of recurrence after an initial episode is 20 percent. Fecal microbial transplantation may become standard for recurrent clostridial colitis (Saeedi, 2017).

Inflammatory Bowel Disease

Two presumably noninfectious forms of intestinal inflammation are ulcerative colitis and Crohn disease. Differentiation between these is important because treatment differs. That said, they both share common features, and sometimes are indistinguishable if Crohn disease involves the colon. The features shown in Table 57-6 permit a reasonably confident diagnostic differentiation in most cases. The etiopathogenesis is enigmatic in both, but a genetic predisposition is suspected, especially for Crohn disease. Inflammation is thought to result from dysregulated mucosal immune function in response to commensal microbiota, with or without an autoimmune component (Friedman, 2018).

Ulcerative Colitis

This is a mucosal disorder with inflammation confined to the superficial luminal layers of the colon. It typically begins at the rectum and extends proximally for a variable distance. In approximately 40 percent of cases, disease is confined to the rectum or the rectosigmoid, but 20 percent have pancolitis. For unknown reasons, prior appendectomy protects against ulcerative colitis (Friedman, 2018). Endoscopic findings include mucosal granularity and friability that is interspersed with mucosal ulcerations and a mucopurulent exudate (see Fig. 57-2).

Major symptoms of ulcerative colitis include diarrhea, rectal bleeding, tenesmus, and abdominal cramps. The disease is characterized by exacerbations and remissions. *Toxic megacolon* and catastrophic hemorrhage are particularly dangerous complications that may necessitate colectomy. *Extraintestinal manifestations* include arthritis, uveitis, and erythema nodosum. The risk of associated colon cancer approaches 1 percent per year. With either ulcerative colitis or Crohn disease, risks for VTE are higher in even asymptomatic women (Friedman, 2018; Mahadevan, 2019).

Crohn Disease

Also known as regional enteritis, Crohn ileitis, or granulomatous colitis, Crohn disease has more protean manifestations than ulcerative colitis. It involves not only the mucosa but also the deeper bowel layers (see Fig. 57-2). Lesions can be seen throughout the entire GI tract, from the mouth to the anus, but it typically is segmental (Friedman, 2018). Approximately 30 percent of patients have only small-bowel involvement, 25 percent have isolated colonic involvement, and 40 percent have both, usually with the terminal ileum and colon involved. Perianal fistulas and abscesses develop in a third of those with colonic involvement.

Symptoms depend on which bowel segment(s) is involved. Thus, complaints may include lower-right-sided cramping abdominal pain, diarrhea, weight loss, low-grade fever, and obstructive symptoms. The disease is chronic with exacerbations and remissions, and importantly, it cannot be cured medically or surgically. Approximately a third of patients require surgery within the first year after diagnosis, and thereafter, the rate is 5 percent per year. Reactive arthritis is common, and the GI cancer risk, although not as great as with ulcerative colitis, is increased substantially.

Inflammatory Bowel Disease and Fertility

Subfertility in women is linked to active disease, but normal fertility is likely with quiescent colitis (Mahadevan, 2019). Subfertility may also be partially attributed to sulfasalazine, which causes reversible sperm abnormalities (Feagins, 2009).

For women requiring surgical resection, a laparoscopic approach has a higher subsequent fertility rate (Beyer-Berjot, 2013). With colectomy, however, although fertility is improved, up to half of women will be persistently infertile (Bartels, 2012; Lee, 2019a). Sexual function and fertility are only modestly affected by ileal pouch–anal anastomosis (Hor, 2016).

Inflammatory Bowel Disease and Pregnancy

Because ulcerative colitis and Crohn disease are relatively common in young women, these disorders are encountered with some frequency in pregnancy. In many studies, the outcomes are grouped together for both entities. For example, in a study from Australia, Shand and colleagues (2016) reported a prevalence of 1 inflammatory bowel disease (IBD) case in 320 births. In this regard, some generalizations can be made. First, consensus supports that pregnancy does not increase the likelihood of an IBD flare (Mahadevan, 2019). Indeed, in a 10-year surveillance of women in the European Collaborative on Inflammatory Bowel Disease, the likelihood of a flare during pregnancy was lower than the preconceptional rate (Riis, 2006). Although most women with quiescent disease in early pregnancy do not have relapses, when a flare develops, it may be severe. Also, and as discussed subsequently, active disease in early pregnancy increases the likelihood of disease relapse during pregnancy (de Lima-Karagiannis, 2016).

In general, most usual treatment regimens may be continued during pregnancy. Diagnostic evaluations should be undertaken if needed to direct management, and surgery should be performed if indicated (Mahadevan, 2019). Fecal calprotectin, an inflammatory biomarker in stool samples, is a valid tool in pregnancy to identify IBD flares (Julsgaard, 2017; Lichtenstein, 2018; Rubin, 2019).

At first glance, it appears that adverse pregnancy outcomes are increased with IBD (Boyd, 2015; Getahun, 2014). Initially, this was attributed to the fact that most studies included women with either form of disease. Specifically, Crohn disease was noted to be linked to excessive morbidity. But, according to Reddy (2008) and others, these adverse outcomes were in women with severe disease and multiple recurrences. Indeed, in the prospective European case-control ECCO-EpiCom study of 332 pregnant women with IBD, outcomes were similar in women with ulcerative colitis or Crohn disease compared with unaffected pregnant women (Bortoli, 2011). Still, women with active disease during pregnancy have an increased frequency of preterm births (Kammerlander, 2017; Shand, 2016). Importantly, perinatal mortality rates are not appreciably increased.

Ulcerative Colitis and Pregnancy. In one review of 755 pregnancies, colitis that was quiescent at conception worsened in approximately a third of pregnancies (Fonager, 1998). In women with active disease at the time of conception, approximately 45 percent worsened, 25 percent remained unchanged, and only 25 percent improved. These observations are similar to those described in a review by Miller (1986) as well as in later reports (de Lima-Karagiannis, 2016; Oron, 2012).

Osteoporosis is a significant complication in up to a third of affected women. Thus, vitamin D—800 IU daily—and calcium—1200 mg daily—are given. Folic acid, 2 to 4 mg orally daily, is recommended preconceptionally and during the first trimester for neural-tube defect prevention (Mahadevan, 2019). This high dose counteracts the antifolate actions of sulfasalazine. Flares may be caused by psychogenic stress, and reassurance is important. Last, the venous thromboembolism risk is doubled, but thromboprophylaxis is not routinely provided (Hansen, 2017).

Management for colitis for the most part mirrors that outside of pregnancy. Treatment of active colitis and maintenance therapy incorporate drugs that deliver 5-aminosalicyclic acid (5-ASA), also known as mesalamine. *Sulfasalazine (Azulfidine)* is the prototype, and its 5-ASA moiety inhibits prostaglandin synthase in colonic mucosa. Others include *olsalazine (Dipentum), balsalazide (Colazal),* and delayed-release 5-ASA derivatives *(Apriso, Asacol, Pentasa, Lialda)*. Glucocorticoids are beneficial and are given orally, parenterally, or by enema for moderate or severe disease that does not respond to 5-ASA. Corticosteroids provide a high remission rate for active disease, but they are not given for maintenance therapy (Friedman, 2018). Recalcitrant disease is managed with immunomodulating drugs, including *azathioprine*, *6-mercaptopurine*, *cyclosporine*, or *tacrolimus*, which all appear relatively safe in pregnancy (Briggs, 2017; Mozaffari, 2015). Importantly, *methotrexate* is teratogenic and contraindicated in pregnancy (Chap. 8, p. 152).

In the past, biologics were reserved for recalcitrant, moderate to severe disease. Because of their considerable efficacy, however, these medications are now frequently given *initially* for this severity of disease to prevent future complications. These agents are antibodies against tumor necrosis factor alpha (TNF-α). Those recommended for IBD treatment are shown in Table 57-7 (Mahadevan, 2019). Women who begin pregnancy while taking biologics should continue these through pregnancy until several weeks before delivery to help avoid maternal infections from immunosuppression. These agents are administered

TABLE 57-7. Biologics Used to Treat Inflammatory Bowel Disease in Pregnancy

Drug (Brand Name)	Recommendations
Adalimumab (Humira)	Last dose 2–3 wks before EDC
Certolizumab pegol (Cimzia)	Continue throughout pregnancy
Infliximab (Remicade)	Last dose 6–10 wks before EDC
Natalizumab (Tysabri)	Last dose 4–6 wks before EDC
Ustekinumab (Stelara)	Last dose 6–10 wks before EDC
Vedolizumab (Entyvio)	Last dose 6–10 wks before EDC

EDC = estimated date of confinement.

IV or subcutaneously. Several studies support their safety in pregnancy, although there are concerns that their discontinuance may prompt a relapse (Chaparro, 2018; Friedman, 2018; Luu, 2018). Another worry is that they may cause immunosuppression in the newborn, and early neonatal vaccination with live-attenuated agents are delayed for at least 6 months (Esteve-Solé, 2017; Julsgaard, 2016).

Colorectal endoscopy is performed as indicated. Surgical management is tailored to disease severity (Killeen, 2017). During pregnancy, colectomy and ostomy creation for fulminant colitis may be needed as a lifesaving measure, and it has been described during each trimester. Dozois (2006) reviewed 42 such cases and found that, in general, outcomes have been good with partial or complete colectomy. Parenteral nutrition is occasionally needed for women with prolonged exacerbations.

For women with an ileal pouch and an anal anastomosis, frequency of bowel movements, fecal incontinence, and pouchitis may temporarily worsen with pregnancy. The last is an inflammatory condition of the ileoanal pouch probably due to bacterial proliferation and stasis. Pouchitis usually responds to ciprofloxacin or metronidazole. In one rare case, adhesions to the growing uterus led to ileal pouch perforation (Aouthmany, 2004).

In general, women with uncomplicated colitis can be delivered vaginally (Foulon, 2017). That said, the cesarean delivery rate in these women is increased (Burke, 2017). It is controversial whether women who have had a prior proctocolectomy and ileal pouch–anal anastomosis can be safely delivered vaginally. Hahnloser (2004) reviewed delivery routes in women with 235 pregnancies before and 232 pregnancies after ileoanal pouch surgery. Functional outcomes were similar, and it was concluded that cesarean delivery should be reserved for obstetrical indications. To the contrary, following their systematic review, Foulon and coworkers (2017) recommended cesarean delivery with the caveat that *uncomplicated* vaginal delivery was safe.

As discussed, quiescent ulcerative colitis likely has minimal adverse effects on pregnancy outcome. Modigliani (2000) reviewed perinatal outcomes in 2398 pregnancies and reported them to be not substantively different from those in the general obstetrical population. Specifically, the incidences of spontaneous abortion, preterm delivery, and stillbirth were remarkably low. These authors and others also describe a cesarean delivery rate that was substantially higher than that for normal controls (Burke, 2017; Mahadevan, 2015). The previously described ECCO-EpiCom study reported similar outcomes in 187 gravidas with ulcerative colitis compared with normal control women (Bortoli, 2011).

Crohn Disease and Pregnancy. In general, Crohn disease activity during pregnancy is related to its status around the time of conception. In a cohort study of 279 pregnancies conceived by 186 women whose disease was inactive at conception, a fourth relapsed during pregnancy (Fonager, 1998). In 93 with active disease at conception, however, two thirds either remained active or worsened. Other reviews describe similar findings (Miller, 1986; Oron, 2012).

Calcium, vitamin D, and folic acid supplementation mirror that for ulcerative colitis. For maintenance during asymptomatic periods, no regimen is universally effective. *Sulfasalazine* is effective for some, but the newer 5-ASA formulations are better tolerated. Glucocorticoids induce a 60- to 70-percent remission rate (Friedman, 2018). *Prednisone* therapy may control moderate to severe flares but is less effective for small-bowel involvement. Immunomodulators such as *azathioprine*, *6-mercaptopurine*, *cyclosporine,* and *tacrolimus* are used for active disease and for maintenance. These appear relatively safe during pregnancy (Chaparro, 2018; Luu, 2018). As discussed in Chapter 8 (p. 152), methotrexate is contraindicated in pregnancy. As with ulcerative colitis, treatment with TNF-α inhibitors is often used initially for active Crohn disease and maintenance (see Table 57-7) (Friedman, 2018; Mahadevan, 2019).

Endoscopy or conservative surgery is indicated for complications (Killeen, 2017). Patients with small-bowel involvement are more likely to require surgery for complications that include fistulas, strictures, obstruction, abscesses, and intractable disease. In an earlier study, an abdominal surgical procedure was required during 5 percent of pregnancies (Woolfson, 1990). Parenteral nutrition has been used successfully during severe recurrences. Those with an ileal loop colostomy may have significant problems. Unless there is a perianal fistula or active perianal disease, women with Crohn disease usually can undergo vaginal delivery without complications (Foulon, 2017; Mahadevan, 2019).

As discussed, Crohn disease compared with ulcerative colitis is associated with higher adverse pregnancy outcome rates. Outcomes are probably related to disease activities. In a case-control Danish study, Norgård (2007) reported a twofold risk of preterm births. Dominitz (2002) reported a two- to threefold increased risk for preterm delivery, low birthweight, fetal-growth restriction, and cesarean delivery in 149 women with Crohn disease. Recall, however, that the ECCO-EpiCom study found pregnancy outcomes to be similar to those in unaffected women.

■ Ostomy and Pregnancy

A colostomy or an ileostomy can be problematic during pregnancy because of its location (Hux, 2010). In a report of 82 pregnancies in 66 women with an ostomy, *stomal dysfunction* was common, but it responded to conservative management in most cases (Gopal, 1985). Surgical intervention was necessary, however, in three of six women who developed *bowel obstruction* and in another four with *ileostomy prolapse*—almost 10 percent overall. In this older study, only a third of 82 women underwent cesarean delivery, but Takahashi (2007) described six of seven cesarean deliveries in women with Crohn disease and a stoma. Although adhesions usually are involved with an obstructed ileostomy, the enlarging uterus may act to cause obstruction (Porter, 2014). Last, Farouk and coworkers (2000) reported that pregnancy did not worsen long-term ostomy function.

■ Intestinal Obstruction

The incidence of bowel obstruction is not increased during pregnancy, although it generally is more difficult to diagnose. Meyerson (1995) reported a 20-year incidence of 1 case in

17,000 deliveries at two Detroit hospitals. Of acute abdomen cases in pregnancy, adhesive disease leading to small-bowel obstruction was second only to appendicitis—15 versus 30 percent, respectively (Unal, 2011). Approximately half of cases are due to adhesions from previous pelvic surgery that includes cesarean delivery (Andolf, 2010; Lyell, 2011). Another 25 percent of bowel obstruction is caused by volvulus, which may involve sigmoid colon, cecum, or small bowel. These have been reported in late pregnancy or early puerperium (Al Maksoud, 2015; Bade, 2014). Bokslag (2014) and Wax (2013) and their colleagues described small-bowel obstruction in pregnancy following the currently popular Roux-en-Y gastric bypass, which is performed for weight loss. Intussusception is occasionally encountered (Bosman, 2014; Moliere, 2019). Bowel obstruction subsequent to colorectal surgery for cancer was increased threefold in women who had open versus laparoscopic surgery (Haggar, 2013). Last, Serra and coworkers (2014) described a massive ventral hernia with intestinal obstruction.

Most cases of intestinal obstruction during pregnancy result from pressure of the growing uterus on intestinal adhesions. This is more likely around midpregnancy when the uterus becomes an abdominal organ; in the third trimester when the fetal head descends; or immediately postpartum when uterine size acutely shrinks (Davis, 1983). Perdue (1992) reported that 98 percent of affected pregnant women had either continuous or colicky abdominal pain, and 80 percent had nausea and vomiting. Abdominal tenderness was found in 70 percent, and abnormal bowel sounds noted in only 55 percent. Plain abdominal radiographs following soluble contrast showed evidence of obstruction in 90 percent of affected women. Plain radiographs, however, are less accurate for diagnosing small-bowel obstruction, and we and others have found that CT and MR imaging can be diagnostic (Essilfie, 2007; Moliere, 2019). Colonoscopy can be both diagnostic and therapeutic for colonic volvulus (Dray, 2012; Khan, 2012).

During pregnancy, mortality rates with obstruction can be excessive because of difficult and thus delayed diagnosis, reluctance to operate during pregnancy, and the need for emergency surgery (Firstenberg, 1998; Shui, 2011). In an older report of 66 pregnancies, Perdue and associates (1992) described 6-percent maternal and 26-percent fetal mortality rates. Two of the four women who died were in late pregnancy, and they had bowel perforation from sigmoid or cecal volvulus caused by adhesions.

Colonic Pseudo-Obstruction

Also known as *Ogilvie syndrome*, pseudo-obstruction is caused by adynamic colonic ileus. It is characterized by massive abdominal distention with cecal and right-hemicolonic dilation (Fig. 57-3). Approximately 10 percent of all cases are associated with pregnancy, and its reported frequency is 1 case in 1500 births (Reeves, 2015). The syndrome usually develops postpartum—90 percent after cesarean delivery—but it has been reported antepartum. In a review, perforation was common, especially if the cecal diameter exceeded 12 cm (Jayaram, 2017). More recently, treatment with an IV infusion of neostigmine, 2 mg, given during cardiac monitoring usually results in prompt decompression (Song, 2018). In some cases, colonoscopic decompression is performed, and in others, laparotomy is needed for perforation (Rawlings, 2010).

Appendicitis

The lifetime incidence for appendicitis ranges from 7 to 10 percent (Flum, 2015). Thus, evaluation for possible appendicitis is relatively common during pregnancy. Theilen and colleagues (2017) studied 171 such women during a 5-year period, but only 14 women ultimately were found to have pathologically confirmed appendicitis. After clinical and imaging evaluation, the frequency of suspected appendicitis drops and that of confirmed appendicitis in more than 8 million women ranged from 1 case in 1000 to 5500 births (Abbasi, 2014; Hée, 1999; Mazze, 1991).

It is repeatedly—and appropriately—emphasized that pregnancy makes the diagnosis of appendicitis more difficult. Nausea

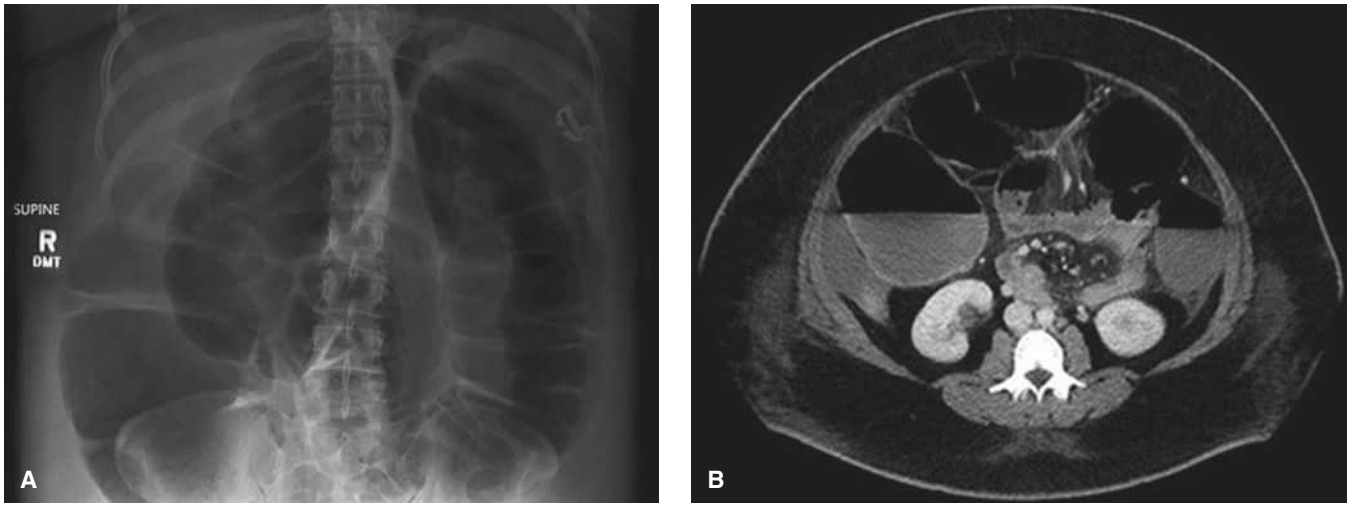

FIGURE 57-3 Ogilvie syndrome. Massive dilation of colon due to pseudo-obstruction in a woman following cesarean delivery. **A.** Abdominal radiograph. **B.** Axial image from computed tomography.

and vomiting accompany normal pregnancy, but also, as the uterus enlarges, the appendix commonly moves upward and outward from the right lower quadrant (Baer, 1932; Erkek, 2015; Pates, 2009). Another often-stated reason for late diagnosis is that some degree of leukocytosis accompanies normal pregnancy. That said, Theilen and coworkers (2017) observed that a white cell count >18,000/μL made the diagnosis tenfold more likely. Neutrophilic shift is another (Gentles, 2020). Pregnant women—especially in late gestation—frequently do not have clinical findings "typical" for appendicitis. Thus, it commonly is confused with cholecystitis, labor, pyelonephritis, renal colic, placental abruption, or uterine leiomyoma degeneration.

Most reports indicate increasing morbidity and mortality rates with advancing gestational age. And, as the appendix is progressively deflected upward by the growing uterus, omental containment of infection becomes increasingly unlikely. It is indisputable that appendiceal perforation is more common during later pregnancy (Abbasi, 2014). In the studies by Andersson (2001) and Ueberrueck (2004), the incidence of perforation was approximately 8, 12, and 20 percent in successive trimesters.

Diagnosis

Persistent abdominal pain and tenderness are the most reproducible findings. Right lower quadrant pain is the most frequent, although pain migrates upward with appendiceal displacement (Mourad, 2000). For initial evaluation, sonographic abdominal imaging is reasonable in suspected appendicitis, even if to exclude an obstetrical cause of pain (Butala, 2010). That said, *graded compression sonography* is difficult because of cecal displacement and uterine imposition (Pedrosa, 2009). *Appendiceal computed tomography* is more sensitive and accurate than sonography to confirm suspected appendicitis (Katz, 2012; Raman, 2008). Specific views can be designed to diminish fetal radiation exposure (Chap. 49, p. 873).

When available, MR imaging is the preferred modality for evaluation of suspected appendicitis in pregnancy (Fig. 57-4).

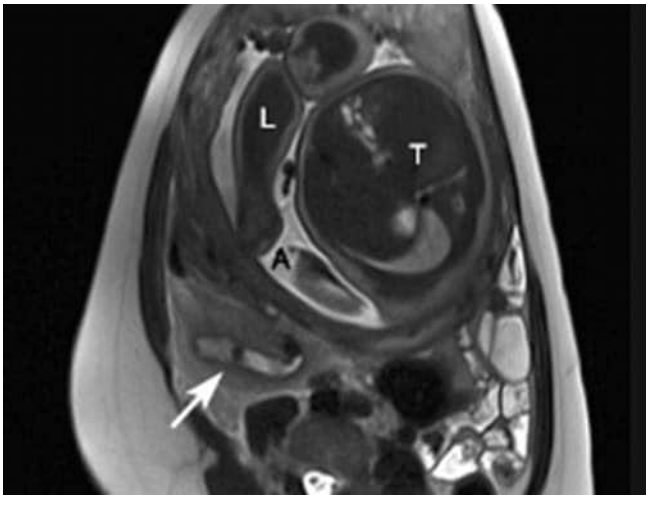

FIGURE 57-4 Magnetic resonance T2 flair image of acute appendicitis in a midtrimester pregnancy. The bright signal is inflammation and the block dot is a fecalith that can be seen in the midappendix (*arrow*). The fetal trunk (*T*) and leg (*L*) and amnionic fluid (*A*) are seen within the gravid uterus superior to the appendix. (Reproduced with permission by Dr. Christina Herrera.)

MR imaging has high diagnostic yield and accuracy, and it also provides alternative diagnoses (Fonseca, 2014; Theilen, 2015). One metaanalysis of 30 studies cited positive- and negative-predictive values of 96 and 99.5 percent, respectively, for MR imaging (Duke, 2016). Others report similar findings (Burke, 2015; Kave, 2019). However, Aguilera and colleagues (2018) found a sensitivity of only 18 percent in pregnant women.

Management

When appendicitis is suspected, most recommend prompt surgical exploration. Although diagnostic errors may lead to removal of a normal appendix, surgical evaluation is preferable to postponed intervention and generalized peritonitis (Abbasi, 2014). In earlier reports, the diagnosis was verified in only 60 to 70 percent of pregnant women. As indicated above, however, with CT and MR imaging, these figures have improved (Duke, 2016; Theilen, 2015). Still and importantly, the accuracy of diagnosis is inversely proportional to gestational age.

Currently, laparoscopic resection is almost always used to treat suspected appendicitis during the first two trimesters. In a report from a Swedish database of nearly 2000 laparoscopic appendectomies, perinatal outcomes were similar to those of more than 1500 open laparotomies done before 20 weeks' gestation (Reedy, 1997). Conversely, in their review, Wilasrusmee and coworkers (2012) reported a higher rate of fetal loss with laparoscopy. Authors of three more recent systematic reviews indicate that the level of evidence is not strong enough to demonstrate a preferred approach to appendectomy (Frountzas, 2019; Lee, 2019b; Walker, 2014). It has evolved that in many centers, laparoscopic appendectomy is also performed in most cases during the third trimester (Donkervoort, 2011). This is encouraged by others, including the Society of American Gastrointestinal and Endoscopic Surgeons (Pearl, 2017; Sekar, 2019; Soper, 2011).

Before exploration, IV antimicrobial therapy is begun, usually with a second-generation cephalosporin or third-generation penicillin. Unless there is gangrene, perforation, or a periappendiceal phlegmon, antimicrobial therapy can usually be discontinued after surgery. Without generalized peritonitis, the prognosis is excellent. Seldom is cesarean delivery indicated at the time of appendectomy. Uterine contractions are common, and although some clinicians recommend tocolytic agents, we do not. de Veciana (1994) reported that tocolytic use substantially increased the risk for pulmonary-permeability edema caused by sepsis (Chap. 50, p. 883).

Antimicrobial versus Surgical Treatment

Because of European studies, some advocate that many cases of appendicitis can be treated successfully with IV antimicrobials alone (Flum, 2015; Talan, 2019). In one study, 6 percent of pregnant women with appendicitis were treated medically, and these gravidas had "considerably" elevated risks for septic shock, peritonitis, and VTE compared with surgically managed cases (Abbasi, 2014). In another study of 20 women, failure rate was 25 percent (Joo, 2017). At this time, we discourage this practice until appropriate studies have been done with pregnant women. Certainly, if elected, such treatment should exclude women with obstructive appendicitis, and the threshold to convert to surgical treatment must be low.

Pregnancy Outcomes

Appendicitis increases the likelihood of preterm labor, especially if peritonitis has developed. Spontaneous labor after 23 weeks ensues with greater frequency following surgery for appendicitis compared with surgery for other indications (Ibiebele, 2019; Won, 2017). In one study, the fetal loss rate was 22 percent if surgery was performed after 23 weeks' gestation. Three large population-based studies attest to the adverse outcomes from appendicitis in pregnancy. From the California State Inpatient Database, the fetal loss rate was 20 percent (Won, 2017). A nationwide study from Taiwan found that risks for low birthweight and preterm delivery rose 1.5- to 2-fold when outcomes in 908 women with acute appendicitis were compared with those of controls (Wei, 2012). Last, an Australian population-based study reported an almost twofold increased incidence of preterm birth following appendectomy (Ibiebele, 2019).

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CHAPTER 58

Hepatic, Biliary, and Pancreatic Disorders

Disorders of the liver, gallbladder, and pancreas together constitute a formidable list of complications that may arise in pregnancy. Some stem from preexisting conditions, and some are unique to gestation. The relationships of several of these with pregnancy can be intriguing and challenging.

HEPATIC DISORDERS

Liver diseases complicating pregnancy are placed into three general categories. The first includes those specific to pregnancy and resolve either spontaneously or following delivery. Hyperemesis gravidarum, intrahepatic cholestasis, acute fatty liver, and *HELLP syndrome*—which is characterized by hemolysis, elevated liver enzyme levels, and low platelet counts, are examples. The second category involves acute hepatic disorders that are coincidental to pregnancy, such as acute viral hepatitis. Last are chronic liver diseases that predate pregnancy, such as chronic viral or autoimmune hepatitis, cirrhosis, or esophageal varices.

Laboratory testing can aid differentiation of these disorders. Hepatic dysfunction from hyperemesis gravidarum may manifest as mildly elevated serum bilirubin and transaminase levels (Chap. 57, p. 1014). Others listed in Table 58-1 can show more marked findings. One example, severe preeclampsia syndrome, discussed in Chapter 40 (p. 689), can be further complicated by the HELLP syndrome, which can rarely cause liver failure (Casey, 2020).

Importantly, several normal pregnancy-induced physiological changes induce appreciable liver-related clinical and laboratory manifestations (Chap. 4, p. 70 and Appendix, p. 1229). Abnormalities such as increased serum alkaline phosphatase levels, palmar erythema, and spider angiomas are common during normal pregnancy. In addition, higher levels of estrogen, progesterone, and other pregnancy hormones alter expression of the cytochrome P450 system. For example, hepatic CYP1A2 expression declines, but that of CYP2D6 and CYP3A4 rises. The latter pair possibly affects metabolism of commonly used therapeutic agents in pregnancy (Dallmann, 2018; Ornoy, 2019). Cytochrome enzymes are also expressed in the placenta. The net effect is complex and likely influenced by gestational age and organ of expression (Isoherranen, 2013). Despite these functional changes, no major hepatic histological changes are induced by normal pregnancy.

Acute Liver Failure in Pregnancy

Fortunately, liver failure is uncommon during pregnancy. Of the various causes, drug-induced liver injury (DILI) is probably the most frequent non-pregnancy-related etiology (Hoofnagle, 2019). Acetaminophen toxicity is the most prevalent cause in the United States (Lee, 2018). Other sources of liver failure include acute fatty liver of pregnancy (AFLP), fulminant viral hepatitis, environmental toxins, autoimmune hepatitis, shock liver, and alternative medicines. In a highly selective study of 70 referred women with a hepatic encephalopathy, half were caused by AFLP and half were associated with HELLP syndrome (Casey, 2020).

The treatment of acute liver failure in pregnancy mirrors that for nonpregnant individuals. Therapy targets the underlying etiology, and a team of obstetricians, maternal-fetal medicine and critical care specialists, hepatologists, and transplant surgeons is

TABLE 58-1. Clinical Findings with Liver Diseases in Pregnancy

Diagnosis	Onset	Symptoms	AST (U/L)	Bili (mg%)	Cr (mg%)	Hematological	Comments
Hyperemesis gravidarum	Early	N&V	<300	1–4	NL or elevated (prerenal)	NL	Common, infant vitamin K deficiency, Wernicke encephalopathy, Boerhaave syndrome
ICP	Late	Pruritus ± jaundice	<200	1–5	NL	NL	Common (0.5–2%), bile acids (>10 μmol/L), normal hepatic function
AFLP	Late	N&V (70%), HTN/ preeclampsia, RUQ pain	145–565	2–8	>0.9	Thrombocytopenia, coagulopathy ± DIC, nucleated red cells, hemolysis, echinocytosis	Low glucose, cholesterol <220 mg/dL, fibrinogen <300 mg/dL
HELLP	Late	Preeclampsia, RUQ pain	75–250 (initial)	1–2	<1.0	Thrombocytopenia, mild hemolysis	Common (7–10% of preeclampsia), normal hepatic function
Hepatitis							
Viral	Variable, chronic, episodic	Jaundice, RUQ pain, fatigue	400–5000	20	NL	Coagulopathy if cirrhotic, thrombocytopenia	Common (1–3%), serological tests for hepatitis A, B, C, E
Autoimmune	Variable, chronic, episodic	Jaundice, RUQ pain, fatigue	100–1000	3–10	NL	Coagulopathy if cirrhotic, thrombocytopenia	Uncommon, ANA+, anti-LKM1, anti–smooth muscle
NAFLD	Variable, chronic, episodic	Obese, diabetes, ± RUQ pain	NL to slightly elevated	NL	NL	NL	Common (6–8%), sonographic findings, MR imaging/ CT findings, ± metabolic syndrome, NASH, cirrhosis

AFLP = acute fatty liver of pregnancy; ANA = antinuclear antibodies; AST = aspartate transaminase; Bili = bilirubin; BP = blood pressure; Cr = creatinine; CT = computed tomography; DIC = disseminated intravascular coagulation; HELLP = hemolysis, elevated liver enzymes, low platelets; HTN = hypertension; ICP = intrahepatic cholestasis of pregnancy; LKM1 = liver, kidney microsome 1; MR = magnetic resonance; NAFLD = nonalcoholic fatty liver disease; NASH = nonalcoholic steatohepatitis; NL = normal; N&V = nausea and vomiting; RUQ = right upper quadrant.

assembled. Laboratory studies initially include serum levels of transaminases, bilirubin, amylase, lipase, electrolytes, creatinine, albumin, fibrinogen, lactate, and total cholesterol; complete blood count; and coagulation studies (Bacak, 2016). Etiology-targeted testing is described fully in later sections but broadly includes viral and autoimmune serological assays and testing for acetaminophen, iron, and copper toxicity. Computed tomography (CT) and magnetic resonance (MR) imaging may be needed to investigate hepatic structure. For a pregnancy-related etiology, delivery is undertaken. Because of comorbid coagulopathy, vaginal delivery is preferable if it can be achieved expeditiously and fetal condition allows. Hepatotoxic agents are avoided, coagulopathy is corrected, and monitoring for cerebral edema and increased intracranial pressure is necessary (Brown, 2018). Liver transplantation is problematic during pregnancy, but delivery before transplantation is considered if necessary (Bacak, 2016).

Intrahepatic Cholestasis of Pregnancy

Characterized by pruritus, jaundice, or both, this condition has been called recurrent jaundice of pregnancy, cholestatic hepatosis, and icterus gravidarum. Intrahepatic cholestasis of pregnancy (ICP) is more common in multifetal pregnancy, and genetic influences are significant (Sticova, 2018). Because of this, its incidence varies by population. In North America, the overall incidence approximates 1 case in 500 to 1000 pregnancies, but its rate nears 5.6 percent among pregnant Latina women in Los Angeles (Lee, 2006). Historically, indigenous women from Chile and Bolivia also have a relatively high incidence of ICP. For unknown reasons, this incidence has decreased since the 1970s and is now less than 2 percent (Reyes, 2016). In Sweden, China, and Israel, the incidence varies from 0.25 to 1.5 percent (Luo, 2015).

Pathogenesis

The cause of ICP is unclear, but changes in various sex steroid hormone levels are implicated. In one study, women treated with vaginal progesterone for preterm labor prophylaxis showed a fourfold increase in the ICP rate (Zipori, 2020). Current research focuses on the numerous mutations in the many genes that control hepatocellular transport systems. One example is mutations of the *ABCB4* gene, which encodes multidrug resistance protein 3 (MDR3) associated with *progressive familial intrahepatic cholestasis.* Another is error in the *ABCB11* gene, which encodes a bile-salt export pump (Reichert, 2018). Other potential gene products are the farnesoid X receptor and transporting ATPase encoded by *ATP8B1* (Abu-Hayyeh, 2016; Sticova, 2018). The latter predisposes to drug-induced cholestasis. In this regard, we have encountered impressive cholestatic jaundice in gravidas taking azathioprine following renal transplantation.

Following the inciting cause(s), bile acids are incompletely cleared and accumulate in plasma. Hyperbilirubinemia results from retention of conjugated pigment, but total plasma concentrations rarely exceed 4 to 5 mg/dL. Alkaline phosphatase levels are usually elevated even more than for normal pregnancy. Serum transaminase levels are normal to moderately elevated but seldom exceed 200 U/L (see Table 58-1). Liver biopsy shows mild cholestasis with bile plugs in the hepatocytes and canaliculi of the centrilobular regions. Inflammation or necrosis is absent. These changes disappear after delivery but often recur in subsequent pregnancies or with estrogen-containing contraceptives.

Clinical Presentation

Generalized pruritus that shows predilection for the palms and soles usually develops in late pregnancy or occasionally earlier. Constitutional symptoms are absent, and skin changes are limited to excoriations from scratching.

Serum transaminase and bile acid levels are measured in women with suspected ICP. As a threshold for comparison, total serum bile acid levels typically remain <10 μmol/L throughout normal pregnancy (Egan, 2012). Elevated total serum bile acid or transaminase levels plus pruritus supports an ICP diagnosis. Biochemical tests may be abnormal at presentation or may follow initial pruritus after several weeks. Moreover, a rise in transaminase levels may precede an increase in serum bile acid levels (Wood, 2018b). Approximately 10 percent of women have concurrent jaundice.

With normal liver enzyme levels or with specific skin findings, pruritus may instead reflect other dermatological disorders (Chap. 65, p. 1155). Sonography may be warranted to exclude cholelithiasis and biliary obstruction (p. 1042). Moreover, *acute viral hepatitis* is an unlikely diagnosis because of the usually low serum transaminase levels seen with ICP. Conversely, underlying *chronic hepatitis C* is associated with a significantly greater risk of developing ICP, which may be as much as 20-fold higher (Marschall, 2013).

Management

Pruritus may be troublesome and is thought to result from elevated serum bile salt concentrations. Antihistamines and topical emollients usually provide some relief. Cholestyramine is reported to be effective, but this compound also lowers absorption of fat-soluble vitamins. This may lead to vitamin K deficiency and fetal coagulopathy. Subsequent fetal intracranial hemorrhage and stillbirth have been reported (Matos, 1997).

Currently, the most popular treatment is with ursodeoxycholic acid (Actigall), which relieves pruritus and reduces serum levels of bile salts and liver enzymes (Bacq, 2012; Parízek, 2016). It is available as 300-mg capsules. Oral dosing is 10 to 15 mg/kg maternal body weight daily, which is divided into two or three doses (Tran, 2016). In a large randomized trial, the maternal "itch score" was not significantly lower with ursodeoxycholic acid compared with placebo (Chappell, 2019). From our experiences at Parkland Hospital, however, pruritus typically improves after 2 to 3 weeks of ursodeoxycholic acid therapy (Yule, 2021). Such treatment has also been reported to lower risks for stillbirth and fetal distress and is discussed subsequently.

Other described treatments include therapeutic plasma exchange and rifampin (Liu, 2018; Ovadia, 2018). A randomized trial comparing ursodeoxycholic acid and rifampicin is underway (Australian New Zealand Clinical Trials Registry, 2019).

Perinatal Outcomes

Early reports describe excessive adverse fetal outcomes in women with ICP. However, data from the past two decades are ambiguous concerning increased perinatal mortality rates and whether close fetal surveillance is preventive. Sheiner and coworkers (2006) described no differences in perinatal outcomes in 376 affected pregnancies compared with their overall obstetrical population. However, rates of labor induction and cesarean delivery in affected women were significantly higher. In a study of 5477 women with ICP from a database of 1.2 million births, neonates had a lower 5-minute Apgar score, but the stillbirth rate was not greater (Wikström Shemer, 2013). The latter rate was thought to reflect a higher labor induction rate, which at the time of the study was recommended to avoid stillbirth.

In some studies, complications developed more frequently in women with higher total bile acid levels (Di Mascio, 2019; Herrera, 2018; Ovadia, 2019). These studies described stillbirths

despite normal findings during antenatal testing. One study of 693 Swedish women found a greater perinatal mortality rate in women with bile acids levels >40 μmol/L (Glantz, 2004). In others, an increased stillbirth risk was noted in women whose serum bile acid levels were >100 μmol/L (Brouwers, 2015; Chappell, 2019, Kawakita, 2015). Chappell and associates (2019) also found that ursodeoxycholic acid treatment did not lower perinatal death rates. The use of antenatal fetal testing was not described. In a metaanalysis of 5557 women with ICP, Ovadia and colleagues (2019) concluded that serum bile acid levels >100 μmol/L were associated with stillbirth.

Other adverse perinatal outcomes also have been described. Brouwers and colleagues (2015) found higher rates of spontaneous preterm birth (19 percent) and meconium-stained amniotic fluid (48 percent), despite active management leading to earlier delivery. Novel associations of ICP with preeclampsia, gestational diabetes, and large for gestational age also are reported (Wikström Shemer, 2013).

In summary, management is directed at early delivery to mitigate the relatively uncommon incidence of fetal death. Treatment with ursodeoxycholic acid does not always improve maternal symptoms or protect against stillbirth. It is problematic that antenatal testing does not reliably forecast impending fetal death. We do not routinely employ these for uncomplicated ICP. The precise gestational age for labor induction is uncertain, but many authors recommend 37 weeks' gestation (Wood, 2018b). At Parkland Hospital, we routinely induce labor at 38 weeks if symptoms worsen or if serum bile acid levels exceed 40 μmol/L.

Fetal Effects of Bile Acids

As noted, evidence supports that maternal serum bile acid levels >100 μmol/L contribute to fetal death and meconium passage. Fetal death may be related to the cardiotoxicity of bile acids, which causes cardiac dysfunction and presumably cardiac arrest. In an ex-vivo preparation of cardiac myocytes, cholic acid lowered beating rates in a dose-dependent fashion, while elevating intracellular calcium concentration (Gao, 2014). Prolongation of the fetal cardiac PR interval and successful reversal with ursodeoxycholic acid has been described (Rodríguez, 2018; Strehlow, 2010). Last, Ozel and coworkers (2018) demonstrated impaired global ventricular function in fetuses of pregnancies complicated by ICP.

■ Acute Fatty Liver of Pregnancy

The most frequent cause of acute liver failure during pregnancy is acute fatty liver—also called *acute fatty metamorphosis* or *acute yellow atrophy.* It is characterized by accumulation of microvesicular fat that literally "crowds out" normal hepatocytic function (Fig. 58-1). Grossly, the liver is small, soft, yellow, and greasy. In its worst form, the incidence approximates 1 case per 10,000 births (Nelson, 2013). AFLP recurring in subsequent pregnancy is rare (Usta, 1994).

Etiopathogenesis

Although the underlying cause remains unclear, many cases of AFLP are associated with recessively inherited mitochondrial

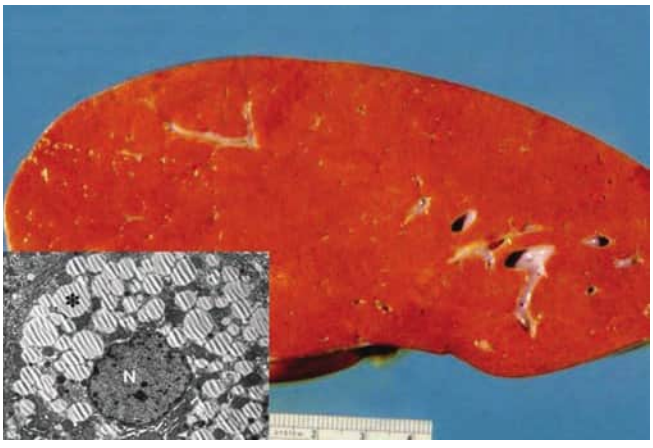

FIGURE 58-1 Acute fatty liver of pregnancy. Cross section of the liver from a woman who died as the result of pulmonary aspiration and respiratory failure. The liver has a greasy yellow appearance. Inset: Electron photomicrograph of a swollen hepatocyte containing numerous microvesicular fat droplets (*). The nucleus (*N*) remains centered within the cell in contrast to the case with macrovesicular fat deposition. (Reproduced with permission from Dr. Don Wheeler.)

abnormalities of fatty acid oxidation. Several mutations for the mitochondrial trifunctional protein enzyme complex that catalyzes the last oxidative steps in the pathway are implicated. The most common are the *G1528C* and *E474Q* missense mutations of the gene on chromosome 2 that codes for long-chain-3-hydroxyacyl-CoA dehydrogenase (LCHAD) (Liu, 2017a). Mutations for medium-chain acyl-CoA dehydrogenase (MCAD) and for carnitine palmitoyltransferase 1 (CPT1) deficiency are others. These are similar to mutations in children with Reye-like syndromes.

Sims and colleagues (1995) observed that some *homozygous* LCHAD-deficient children with Reye-like syndromes had *heterozygous* mothers with AFLP. This was also seen in women with a compound heterozygous fetus. Although some conclude that *only* heterozygous LCHAD-deficient mothers are at risk for ALFP when their fetus is homozygous, this is not always true (Liu, 2017a). An association between fatty acid β-oxidation enzyme defects and severe preeclampsia, especially in women with HELLP syndrome, is also controversial (Chap. 40, p. 693). Most observations derive from retrospective study of mothers with a child who later developed Reye-like syndrome. One case-control study compared 50 mothers of children with a fatty acid oxidation defect and 1250 mothers of matched control infants (Browning, 2006). During their pregnancy, 12 percent of mothers with an affected child developed HELLP syndrome and 4 percent developed AFLP. Comparatively, only 0.9 percent of control women developed liver problems. Despite these findings, the clinical, biochemical, and histopathological findings are sufficiently disparate and support that severe preeclampsia, with or without HELLP syndrome, and AFLP are distinct syndromes (American College of Obstetricians and Gynecologists, 2012; Byrne, 2020).

Clinical Findings

AFLP almost always manifests in the last trimester and rarely midpregnancy (Wong, 2020). From Parkland Hospital,

TABLE 58-2. Comparison of Clinical Findings at the Time of Admission in 67 Women with Acute Fatty Liver of Pregnancy and 67 with HELLP Syndrome

Factor	AFLP	HELLP	*p* Value
Clinical findings (%)			
Hypertension	62	94	<0.001
Abdominal pain	34	46	0.18
Nausea/vomiting	63	19	<0.001
Laboratory values			
AST (u/L)	278 [146, 564]	135 [77, 250]	<0.001
Creatinine (mg/dL)	1.6 [1, 2]	0.6 [1, 1]	<0.001
Fibrinogen (mg/dL)	200 [95, 298]	455 [367, 519]	<0.001
Bilirubin (mg/dL)	2.9 [1, 6]	0.6 [0, 1]	<0.001
Platelets (per μL)	163,000 [121, 205]	115,000 [78, 150]	<0.001
LDH (u/L)	464 [361, 749]	552 [439, 759]	0.19
Glucose (mg/dL)	88 [68, 102]	98 [83, 114]	0.011

AFLP = acute fatty liver of pregnancy; AST = aspartate transaminase; HELLP = hemolysis, elevated liver enzymes, and low platelets; LDH = lactic acid dehydrogenase.
Data from Byrne, 2020; Nelson, 2020.

Nelson and colleagues (2013) described 51 women with AFLP at a mean gestational age of 37 weeks (range 31.7 to 40.9 weeks). Approximately 41 percent were nulliparous and 20 percent were delivered at 34 weeks' gestation or earlier. Women with a multifetal gestation account for 20 percent of cases (Vigil-De Gracia, 2011).

AFLP has a broad spectrum of clinical features and severity, and symptoms usually advance over several days. Persistent nausea and vomiting are major complaints. Degrees of malaise, anorexia, epigastric pain, and progressive jaundice vary. In almost all severe cases, acute liver injury causes profound endothelial cell activation, capillary leakage, and hemoconcentration; acute kidney injury; ascites; and sometimes pulmonary permeability edema (Bernal, 2013). Half of affected women have hypertension, proteinuria, and edema, alone or in combination. Notably, these signs also suggest preeclampsia.

As shown in Tables 58-1 and 58-2, degrees of moderate to severe liver dysfunction are manifest by hypofibrinogenemia, hypocholesterolemia, and prolonged clotting times. Serum bilirubin levels usually are <10 mg/dL, and serum transaminase levels are modestly elevated and usually <1000 U/L. An AFLP diagnosis is arrived at by clinical and laboratory findings. Biopsy is unnecessary. The Swansea criteria proposed by Ch'ng and associates (2002) as a screening tool and predictor of severity shows suitable sensitivity (Table 58-3) (Morton, 2018; Wang, 2017).

Hemolysis can be severe and is thought to stem from effects of hypocholesterolemia on erythrocyte membranes (Cunningham, 1985). Laboratory evidence includes leukocytosis, nucleated red cells, mild to moderate thrombocytopenia, and increased serum levels of lactic acid dehydrogenase (LDH) or decreased haptoglobin levels. The peripheral blood smear demonstrates echinocytosis. However, the hematocrit is often high or within the normal range because of hemoconcentration. With severe hemoconcentration, uteroplacental perfusion is reduced and this, along with maternal acidosis, can cause fetal death. Likewise, maternal and fetal acidemia are associated with a high incidence of fetal jeopardy and a concordantly high cesarean delivery rate.

The degree of clotting dysfunction varies and can be potentially life threatening, especially if cesarean delivery is undertaken. Coagulopathy is caused by diminished hepatic procoagulant synthesis, although some evidence supports

TABLE 58-3. Swansea Criteria for AFLP Diagnosis[a]

Clinical features
Vomiting
Abdominal pain
Encephalopathy
Polydipsia/polyuria

Laboratory features

Bilirubin >0.8 mg/dL	AKI or Cr >1.7 mg/dL
Glucose <72 mg/dL	Ammonia >47 μmol/L
WBC >11,000/μL	Coagulopathy or PT >14 s
AST or ALT >42U/L	Urea >340 μmol/L

Ultrasound features
Ascites or echogenic liver

Histologic features
Microvesicular steatosis

[a]The presence of six or more features without another explanation for them supports a diagnosis of AFLP.
AFLP = acute fatty liver of pregnancy; AKI = acute kidney injury; ALT = alanine transaminase; AST = aspartate transaminase; PT = protime; WBC = white blood cell count.

increased consumption from disseminated intravascular coagulopathy. As shown in Table 58-2, hypofibrinogenemia can be profound. Of 51 women cared for at Parkland Hospital, almost one third had a plasma fibrinogen level nadir below 100 mg/dL (Nelson, 2014). Elevated levels of serum D-dimers or fibrin-split products also indicate an element of consumptive coagulopathy (Lisman, 2017). Although usually modest, occasionally thrombocytopenia is marked. Among the women from Parkland Hospital, 20 percent had platelet counts <100,000/μL, and 10 percent had platelet counts <50,000/μL (Byrne, 2020).

Because liver dysfunction and kidney injury are central to AFLP, Byrne and colleagues (2020) have proposed the acronym FaCCT to differentiate AFLP from HELLP syndrome using levels of commonly available laboratory analytes: fibrinogen (<300 mg/dL) and cholesterol (<220 mg/dL), creatinine (>0.9 mg/dL), and total bilirubin (>1 mg/dL). To emphasize, the clinical features and sequelae of AFLP are attributed to liver dysfunction, whereas in HELLP syndrome the procoagulant production and function of the liver appears relatively preserved.

AFLP typically continues to worsen after diagnosis. Hypoglycemia is common, and hepatic encephalopathy, severe coagulopathy, and some degree of renal failure each develop in approximately half of women. Delivery fortunately arrests liver function deterioration, but recovery may require substantial supportive care.

Various liver imaging techniques can help confirm the diagnosis, but none is particularly reliable (Liu, 2017a). In a prospective evaluation of the Swansea criteria, only a quarter of women with AFLP had classic sonographic findings that included maternal ascites or an echogenic hepatic appearance (Knight, 2008). Although Châtel and coworkers (2016) described greater liver fat detected by MR imaging, this has not been our experience.

We have encountered several women with an underdeveloped form of AFLP. Clinical involvement is relatively minor and laboratory aberrations—usually only hemolysis and a decreased plasma fibrinogen level—herald the syndrome. Thus, the spectrum of liver involvement can include unnoticed milder cases, findings that are instead attributed to preeclampsia, or a severe form displaying overt hepatic failure and associated encephalopathy.

Management

Intensive supportive measures and sound obstetrical care are essential. Delivery of the fetus is necessary in the treatment of AFLP, and significant procrastination increases maternal and fetal risks. We prefer a trial of labor induction with close fetal surveillance. Although some recommend cesarean delivery to hasten hepatic healing, this raises maternal bleeding complication risks when coagulopathy is severe. Nonetheless, cesarean delivery is common due to fetal intolerance of labor, and rates approach 90 percent. In some cases, the fetus has already died when AFLP is diagnosed, and the delivery route is less problematic. To correct coagulopathy, transfusions with whole blood or packed red cells, along with fresh-frozen plasma, cryoprecipitate, and platelets, are usually necessary for surgery or vaginal laceration repair (Chap. 44, p. 772).

Hepatic function usually returns to normal within a week postpartum, but in the interim, intensive medical support may be required. Two associated conditions can be seen during this time. Perhaps a fourth of women have evidence for *transient diabetes insipidus.* This presumably stems from elevated vasopressinase concentrations caused by diminished hepatic production of its inactivating enzyme. Second, *acute pancreatitis* develops in approximately 20 percent.

With supportive care, recovery usually is complete. Maternal deaths are caused by liver failure, sepsis, hemorrhage, aspiration, renal failure, pancreatitis, and gastrointestinal bleeding. Two women died in the series from Parkland Hospital. One had associated encephalopathy and aspirated before intubation during transfer to our care. The other was a woman with profound liver failure and nonresponsive hypotension (Nelson, 2013). Other treatment measures have included plasma exchange and liver transplantation (Ringers, 2016; Wu, 2018).

Maternal and Perinatal Outcomes

Maternal mortality rates with AFLP approached 75 percent in the past, but the contemporaneous outlook is much better. From his review, Sibai (2007) cites an average mortality rate of 7 percent. He also cited a 70-percent preterm delivery rate and a 15-percent perinatal mortality rate, which in the past was nearly 90 percent. During the past four decades at Parkland Hospital, the maternal and perinatal mortality rates have been 4 percent and 12 percent, respectively (Byrne, 2020).

■ Viral Hepatitis

Most viral hepatitis syndromes are asymptomatic, and acute symptomatic infections are becoming less common in the United States. There are at least five distinct types of viruses causing hepatitis: A (HAV), B (HBV), D (HDV) caused by the hepatitis B–associated delta agent, C (HCV), and E (HEV). The clinical presentation of acute infection is similar in all, and although the viruses themselves probably are not hepatotoxic, the immunological response to them causes hepatocellular necrosis (Dienstag, 2018a,b). Several other viral agents can infect the liver, and two examples are cytomegalovirus and herpes simplex virus (Calix, 2020; McCormack, 2019).

Acute infections are most often subclinical and anicteric. When they are clinically apparent, nausea and vomiting, headache, and malaise may precede jaundice by 1 to 2 weeks. By the time jaundice develops, symptoms usually are improving. Low-grade fever is more common with hepatitis A. Serum transaminase levels vary, and their peaks do not correspond with disease severity. Peak levels that range from 400 to 4000 U/L are usually reached by the time jaundice develops (see Table 58-1). Serum bilirubin values typically continue to rise, and peak at 5 to 20 mg/dL, despite falling serum transaminase levels.

Severe features should prompt hospitalization. These include persistent nausea and vomiting, prolonged prothrombin time, low serum albumin level, hypoglycemia, high serum bilirubin level, or central nervous system symptoms. In most cases, clinical and biochemical recovery is complete within 1 to 2 months in all cases of hepatitis A, in most cases of hepatitis B, but in only a small proportion of those caused by hepatitis C.

Patient's feces, secretions, bedpans, and other articles in contact with the intestinal tract should be handled with glove-protected hands. In hospitals, extra precautions, such as double gloving during delivery and surgical procedures, are recommended. Due to significant exposure of health-care personnel to hepatitis B, the Centers for Disease Control and Prevention (CDC) recommend active and passive vaccination, as described later (p. 1037) (Schillie, 2018). For hepatitis C, although direct antiviral regimens have been developed, there is no vaccine. Guidelines instead recommend postexposure serosurveillance only.

Acute hepatitis has a case-fatality rate of 0.1 percent. For those requiring hospitalization, it may reach 1 percent. Most fatalities are due to *fulminant hepatic necrosis*, which in later pregnancy may resemble AFLP. In these cases, hepatic encephalopathy is the usual presentation, and the mortality rate is 80 percent. Approximately half of patients with fulminant disease have hepatitis B infection, and co-infection with the delta agent is common.

Chronic hepatitis is more prevalent than acute infection. The CDC (2019) estimates that almost 3.5 million persons in the United States are living with chronic viral hepatitis. Although most are asymptomatic, approximately 20 percent develop cirrhosis within 10 to 20 years (Dienstag, 2018a). When present, symptoms are nonspecific and usually include fatigue. In some patients, cirrhosis with liver failure or bleeding varices may be the initial finding. Also, asymptomatic chronic viral hepatitis remains the leading cause of liver cancer and the most frequent reason for liver transplantation.

Chronic viral hepatitis is usually diagnosed serologically (Table 58-4). With persistently abnormal biochemical tests, liver biopsy usually discloses active inflammation, continuing necrosis, and fibrosis that may lead to cirrhosis. Chronic hepatitis is classified by cause; grade, defined by histological activity; and stage, which is the degree of progression (Dienstag, 2018a).

Most young women with chronic viral hepatitis either are asymptomatic or have only mild liver disease. For asymptomatic women, pregnancies are usually uncomplicated. With *symptomatic* chronic active hepatitis, pregnancy outcome depends primarily on disease severity, and especially on the presence of portal hypertension (p. 1040). The few women whom we have managed have done well, but their long-term prognosis is poor. Accordingly, they should be counseled regarding possible liver transplantation as well as contraceptive and sterilization options.

TABLE 58-4. Laboratory Features of Chronic Hepatitis

Disorders	Tests	Autoantibodies
Hepatitis B	HBsAg, IgG anti-HBc, HBeAg, HBV DNA	Uncommon
Hepatitis C	Anti-HCV, HCV RNA	Anti-LKM1
Hepatitis D	Anti-HDV, HDV RNA, HBsAg, IgG anti-HBc	Anti-LKM3
Autoimmune	ANA, anti-LKM1, anti-SLA, hyperglobulinemia	ANA, anti-LKM1, anti-SLA
Cryptogenic	All negative	None

HBc = hepatitis core; HBeAg = hepatitis B e antigen; HBsAg = hepatitis B surface antigen; LKM = liver, kidney microsome; SLA = soluble liver antigen.
Modified with permission from Jameson JL, Fauci AS, Kasper DL, et al: Harrison's Principles of Internal Medicine, 20th ed. New York, NY: McGraw Hill; 2018.

Hepatitis A

Vaccination has reduced the incidence of hepatitis A by 95 percent. In 2019, the rate was 6 cases per 100,000 individuals in the United States (Centers for Disease Control and Prevention, 2021). HAV is an RNA picornavirus and is transmitted by the fecal–oral route and usually by contaminated food or water ingestion. The incubation period approximates 4 weeks. Individuals shed virus in their feces, and during the relatively brief period of viremia, their blood also is infectious. Signs and symptoms are often nonspecific and usually mild, although jaundice develops in most patients. Symptoms usually last less than 2 months, but 10 to 15 percent of patients may remain symptomatic or relapse for up to 6 months (Dienstag, 2018b). Early serological testing identifies immunoglobulin M (IgM) anti-HAV antibody, which may persist for several months. During convalescence, IgG antibody predominates, and it provides subsequent immunity. Hepatitis A lacks a chronic stage.

Vaccination during childhood with inactivated hepatitis viral vaccine is more than 90-percent effective. The American College of Obstetricians and Gynecologists (2018) and the Advisory Committee on Immunization Practices recommends HAV vaccination for high-risk adults (Freedman, 2020). This includes pregnant women at risk (Nelson, 2020). Candidates are persons with chronic liver disease, human immunodeficiency virus (HIV) infection, homelessness, or illegal drug use. Those working in group facilities with at-risk persons, conducting research with HAV, or traveling to or adopting from endemic areas also are included. High-risk countries are listed in the CDC (2020b) "Yellow Book"—Health Information for International Travel.

For an unvaccinated gravida who is recently exposed by close personal or sexual contact with a person with hepatitis A, passive immunization is provided by a 0.1-mL/kg dose of immune globulin. Concurrently, the first dose of the hepatitis A vaccine series is given in a separate arm (Nelson, 2020).

Pregnancy and Hepatitis A. Management of hepatitis A in pregnancy includes a balanced diet and diminished physical activity. Women with mild illness may be managed as outpatients. In developed countries, the effects of hepatitis A on pregnancy outcomes are not dramatic (American College of Obstetricians and Gynecologists, 2012, 2018). However, in resource-poor countries, both perinatal and maternal mortality rates are substantively higher. HAV is not teratogenic, and transmission to the fetus is negligible. The risk of preterm birth may be higher, and neonatal cholestasis has been reported (Urganci, 2003). Although HAV RNA has been isolated in breast milk, no cases of neonatal hepatitis A have been reported secondary to breastfeeding (Daudi, 2012).

Hepatitis B

This infection stems from a double-stranded DNA virus that is found worldwide. HBV is endemic in Africa, Central and

Southeast Asia, China, Eastern Europe, the Middle East, and certain areas of South America. In all these, infection prevalence reaches 5 to 20 percent. An estimated 1.6 million people in the United States have chronic hepatitis B (Lim, 2020). HBV is carcinogenic, and chronic infection is a known risk for hepatocellular carcinoma. For others, cirrhosis can be a long-term sequela.

HBV is transmitted by exposure to blood or other body fluids from infected individuals. In endemic countries, vertical transmission, that is from mother to fetus or newborn, accounts for at least 35 to 50 percent of chronic HBV infections. In low-prevalence countries such as the United States, which has a prevalence below 2 percent, the more frequent transmission mode is sexual contact or shared contaminated needles.

Acute hepatitis B develops after an incubation period that ranges from 40 to 150 days (Schillie, 2018). At least half of acute infections are asymptomatic. Symptoms completely resolve within 3 to 4 months in most. However, acute hepatitis B accounts for half of fulminant hepatitis cases.

Figure 58-2 details the sequence of the various HBV antigens and antibodies in acute infection. The first serological marker is hepatitis B surface antigen (HBsAg), which often precedes the rise in transaminase levels. As HBsAg disappears, antibodies to the surface antigen develop (anti-HBs), and this marks complete disease resolution. Hepatitis B core antigen (HBcAg) is an intracellular antigen and not detectable in serum. However, antibodies against this core antigen (anti-HBc) are detectable and found within weeks of HBsAg appearance. The hepatitis B e antigen (HBeAg) is present during times of high viral replication and often correlates with detectable HBV DNA. After acute hepatitis, at least 90 percent of adults recover completely, and the remainder are considered to have chronic hepatitis B.

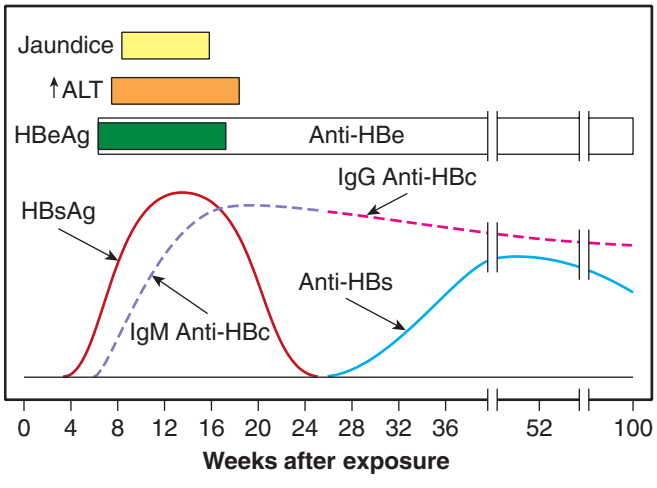

FIGURE 58-2 Sequence of various antigens and antibodies in acute hepatitis B. ALT = alanine transaminase; anti-HBc = antibody to hepatitis B core antigen; anti-HBe = antibody to hepatitis B e antigen; anti-HBs = antibody to hepatitis B surface antigen; HBeAg = hepatitis B e antigen; HBsAg = hepatitis B surface antigen. (Redrawn from Dienstag JL: Acute viral hepatitis. In Jameson JL, Fauci AS, Kasper DL, et al (eds): Harrison's Principles of Internal Medicine, 20th ed. New York, NY: McGraw Hill; 2018b, p 2347.)

Chronic HBV infection is often asymptomatic but may cause persistent anorexia, weight loss, fatigue, and hepatosplenomegaly. Extrahepatic manifestations include arthritis, generalized vasculitis, glomerulonephritis, pericarditis, myocarditis, transverse myelitis, and peripheral neuropathy. One risk factor for chronic disease is age at acquisition. Pertinent to the obstetrician, this risk exceeds 90 percent in newborns. The risk is 50 percent in young children and is less than 10 percent in immunocompetent adults (Schillie, 2018). An immunocompromised state such as with HIV infection, organ transplantation, or chemotherapy creates vulnerability.

Those with chronic HBV infection have serum test results that show HBsAg persistence. These infected persons may be asymptomatic carriers or may have chronic liver disease with or without cirrhosis or hepatocellular cancer. The presence of HPV DNA in serum tests is a marker of HBV replication. Those with high HBV replication, which is reflected in high HBV DNA levels with or without HBeAg, have the greatest likelihood of developing cirrhosis and hepatocellular carcinoma.

Pregnancy and Hepatitis B. The US Preventive Services Task Force (2019) recommends that all pregnant women be screened for HBV. This practice identifies asymptomatic cases and later allows neonatal intervention. At the first prenatal care visit, a serologic HBsAg level is obtained, and this is repeated in high-risk women again at the time of delivery. All states require cases of HBV infection to be reported, and 26 mandate that pregnant women be screened (Culp, 2016). HBV infection does not cause excessive rates of maternal morbidity or mortality (Stewart, 2013). In one regional study in the United States, 14 percent of women with HBV infection had a worsening of disease, sometimes termed a *flare*, either antepartum or in the 6 months postpartum (Kushner, 2018). A review of data from the National Inpatient Sample reported a modest rise in preterm birth rates in HBV-positive mothers but no effect on fetal-growth restriction or preeclampsia rates (Reddick, 2011). Others have shown similar results (Cui, 2017; Liu, 2017b).

Transplacental HBV infection is uncommon, and Towers and associates (2001) reported that viral DNA is rarely found in amnionic fluid or cord blood. The highest HBV DNA levels are found in women who transmitted the virus to their fetuses (Dunkelberg, 2014; Society for Maternal-Fetal Medicine, 2016).

To curb vertical transmission, newborns of seropositive mothers are given hepatitis B immune globulin (HBIG) plus the first of a three-dose hepatitis B recombinant vaccine series very soon after birth. In the absence of HBV immunoprophylaxis, 10 to 20 percent of women positive for HBsAg transmit viral infection to their infant. This rate rises to almost 90 percent if the mother is HBsAg and HBeAg positive. Administration of immunoprophylaxis and hepatitis B vaccine shortly after birth has lowered transmission dramatically and prevented approximately 90 percent of infections (Smith, 2012). But, women with high HBV viral loads—10^6 to 10^8 copies/mL—or those who are HBeAg positive still have at least a 10-percent vertical transmission rate, regardless of immunoprophylaxis (Rogan, 2019; Yi, 2016). Hill and colleagues (2002) reported

that the 2.4-percent transmission rate was not increased with breastfeeding if neonatal vaccination was completed. Although virus is present in breast milk, the incidence of transmission is not diminished by formula feeding (Shi, 2011). The American Academy of Pediatrics and the American College of Obstetricians and Gynecologists (2018) do not consider maternal HBV infection a contraindication to breastfeeding.

As a second transmission-prevention practice, the CDC and numerous societies now recommend antiviral therapy to decrease viral levels in gravidas whose viral load exceeds 10^6 to 10^8 copies/mL (Schillie, 2018). Newer drugs include tenofovir, an adenosine nucleoside analogue, and telbivudine, a thymidine analogue. Tenofovir is the first-line agent during pregnancy, and no dose adjustments are necessary (Cressey, 2018). These antiviral medications appear safe in pregnancy and are not associated with greater rates of congenital malformations or adverse obstetrical outcomes (Sylvester-Armstrong, 2019). Follow-up of children at age 6 to 7 years found no related problems (Wen, 2020).

Regarding efficacy, one randomized trial in Thailand showed that tenofovir compared with placebo beginning at 28 weeks' gestation did not reduce the low rate of vertical transmission if both active and passive immunoprophylaxis were given at birth to the neonate (Jourdain, 2018). In another similar randomized trial, vertical transmission rates were significantly lowered (Pan, 2016).

For high-risk mothers who are seronegative, HBV vaccine can be given during pregnancy. Candidates are persons with chronic liver disease, diabetes, HIV or HCV infection, injection drug use, occupational exposure risk, household contacts, or long-term travel to endemic areas. Those requiring dialysis, living in a long-term-care or correctional facility, or engaging in sex with multiple or HBV-infected partners also are included (Schillie, 2018).

Vaccine efficacy is similar to that for nonpregnant adults, and overall seroconversion rates approach 95 percent after three doses (Stewart, 2013). The traditional vaccination schedule of 0, 1, and 6 months may be difficult to complete during pregnancy, and compliance rates decline postpartum. Sheffield and coworkers (2006) reported that an accelerated three-dose regimen—given initially and at 1 and 4 months—resulted in seroconversion rates of 56, 77, and 90 percent, respectively. This regimen was usually easily completed during prenatal care.

Hepatitis D

Also called *delta hepatitis*, this is a defective RNA virus that is a hybrid particle with an HBsAg coat and a delta core. The HDV must co-infect with HBV either simultaneously or secondarily, and transmission is similar to HBV.

Hepatitis C

This infection stems from a single-stranded RNA virus. Transmission is via blood and other body fluids, although sexual transmission is inefficient. In the United States, adult prevalence of HCV was reported to be 2 to 5 cases per 1000 births (Prasad, 2020; Rossi, 2020). Up to a third of anti-HCV positive persons have no identifiable risk factors (Dienstag, 2018b).

Until recently, screening for HCV was encouraged only for high-risk individuals. But in 2020, the CDC recommended HCV screening for all adults at least once in a lifetime, and more regularly for those with risk factors (Schillie 2020). These are injection drug use, hemodialysis, or exposure to blood-contaminated items. The CDC also recommended prenatal HCV screening for all women regardless of risk factors. The US Preventive Services Task Force (2020) has published similar recommendations.

Chronic hepatitis C is diagnosed by identification of anti-HCV antibodies detected with a serum immunoassay. Acute HCV infection is usually asymptomatic or yields mild symptoms. Only 10 to 15 percent of patients develop jaundice. The incubation period ranges from 15 to 160 days, with a mean of 7 weeks. Transaminase levels are elevated episodically during the acute infection. HCV RNA testing confirms clinical suspicion of active or acute HCV infection. RNA levels may be found even before rises in transaminase and anti-HCV levels. Anti-HCV antibody is not detected for an average of 15 weeks and in some cases up to 1 year (Dienstag, 2018b).

Nearly 80 to 90 percent of patients with acute HCV will be chronically infected. Although most remain asymptomatic, approximately 20 to 30 percent progress to cirrhosis within 20 to 30 years. Transaminase and HCV RNA values fluctuate over time. Liver biopsy reveals chronic disease and fibrosis in up to 50 percent, however, these findings are often mild. Overall, the long-term prognosis for most patients is good.

Pregnancy and Hepatitis C. As expected, most pregnant women diagnosed with HCV have chronic disease. Aggregate reports have chronicled modestly greater fetal risks of low birthweight, neonatal intensive-care admission, preterm delivery, and mechanical ventilation (Rossi, 2020; Society for Maternal-Fetal Medicine, 2017). In some women, these adverse outcomes may have been influenced by concurrent high-risk behaviors associated with HCV infection.

The primary adverse perinatal outcome is vertical transmission of HCV infection to the fetus-neonate. This is higher in mothers with viremia (Indolfi, 2014). Airoldi and Berghella (2006) cited a rate of 1 to 3 percent in HCV-positive, RNA-negative women compared with 4 to 6 percent in those who were RNA-positive. In a report from Dublin, the vertical transmission rate in 545 women with HCV infection was 7 percent in RNA-positive women compared with none in those who were RNA-negative (McMenamin, 2008). Some have found an even higher risk when the mother is co-infected with HIV (Snidjewind, 2015; Tovo, 2016). Approximately two thirds of prenatal transmission cases occur peripartum. HCV genotype, invasive prenatal procedures, breastfeeding, and delivery mode are not associated with vertical transmission. That said, invasive procedures such as scalp-electrode fetal heart rate monitoring are avoided. HCV infection is not a contraindication to breastfeeding (Post, 2017).

No licensed vaccine is available for HCV prevention. In 2011, the first direct-acting antiviral drugs against HCV became available. Since then, second-generation prototypes with fewer adverse effects have been developed and are given as combinations to nonpregnant individuals. They are currently

not recommended for use in pregnancy except in clinical trials (Society for Maternal-Fetal Medicine, 2017). The combination of ledipasvir plus sofosbuvir shows efficacy and reassuring safety data in early clinical trials.

Hepatitis E

This infection stems from a water-borne RNA virus, which usually is enterically transmitted by contaminated water supplies. Hepatitis E is found worldwide, but the Centers for Disease Control (2020a) lists Mexico, Asia, and Africa as endemic areas. In these regions, seroprevalence rates vary by age and geography, but overall rates of 10 percent have been reported. In Mexico, Durango State has the highest rate—37 percent (Fierro, 2016).

Hepatitis E is the most common cause of acute hepatitis worldwide but rarely causes liver failure in the United States (Fontana, 2016). Epidemic outbreaks in third-world countries result in substantial morbidity and mortality rates. Pregnant women have a greater case-fatality rate than nonpregnant individuals (Li, 2020). In a metaanalysis of nearly 4000 women from Asia and Africa, maternal and fetal case-fatality rates were 21 and 34 percent, respectively (Jin, 2016a). Fulminant hepatitis, although rare, is more common in gravidas and contributes to the increased mortality rates.

A recombinant HEV vaccine has been developed and licensed in China (Zaman, 2020). It is >95 percent effective for 12 months after vaccination. Long-term efficacy is 87 percent, and protective titers are maintained for up to 4.5 years (Zhang, 2015). Preliminary data from inadvertently vaccinated pregnant women show no adverse maternal or fetal events (Wu, 2012).

Autoimmune Hepatitis

This generally progressive chronic hepatitis is more common in women and western countries. Autoimmune hepatitis frequently coexists with other types of autoimmune disease, particularly autoimmune thyroid disease and Sjögren syndrome. It is characterized by multiple autoimmune antibodies such as antinuclear (ANA), anti-smooth muscle, and anti-liver, kidney microsome 1 (LKM1) antibodies (see Table 58-1). Rates of subsequent cirrhosis vary worldwide. The less common type 2 autoimmune hepatitis has an even higher prevalence in females and typically a more aggressive presentation. The incidence peaks in childhood and adolescence.

Symptoms are typical of acute and chronic hepatitis, but a fourth of patients may be asymptomatic. Treatment employs corticosteroids, alone or combined with azathioprine (Dienstag, 2018a). Failure to respond to these two agents is more frequent in those with type 2 disease. Nearly all women with type 2 disease require long-term intensive therapy. In some patients with progressive disease and cirrhosis, hepatocellular carcinoma develops.

In general, autoimmune hepatitis—especially when severe—increases the risk of adverse pregnancy outcomes. Westbrook and coworkers (2012) reported the outcomes of 81 pregnancies in 53 women. A third had a flare, and these were more common in those not taking medication and those with active disease in the year before conception. Women with cirrhosis had more maternal and fetal complications. From a Swedish national database of 171 births, the frequencies of preterm birth, low birthweight, and diabetes were elevated, but not those of preeclampsia or cesarean delivery (Stokkeland, 2016). Another study reported delivery before 38 weeks' gestation in 25 percent of cases and development of a postpartum flare in a third (Danielsson Borssén, 2016). However, adverse outcomes were not greater in women with cirrhosis. Given the important role of procoagulant production, surveillance of coagulation indices is advised to minimize obstetrical hemorrhage complications. Also, the usual vaccines, along with pneumococcal vaccine, should be given (Furer, 2020).

Iron and Copper Overload

Chronic hepatitis and cirrhosis can result from iron and copper overload. Iron overload may stem from a primary cause, such as hereditary hemochromatosis, or from secondary complications of erythrocyte disorders (Chap. 56 p. 1052). Many gene mutations underlying hereditary hemochromatosis involve hepcidin and result in dysregulated iron transport. Some of these mutations are more common in certain populations from northern Europe (Pietrangelo, 2016; Salgia, 2015). Cardiomyopathy, diabetes, joint disease, and skin changes can coexist with liver disease. Diagnosis is made by identifying an *HFE* gene mutation and elevated serum ferritin and transferrin saturation levels. An abnormal *HFE* gene alone is not diagnostic because the mutation has low penetrance. Pregnancy outcomes are driven by the degree of liver dysfunction, although higher iron levels may affect birthweight (Dorak, 2009).

A form of neonatal hemochromatosis that does not affect the mother is now thought to be alloimmune and is called *gestational alloimmune liver disease* (Anastasio, 2016; Ibrahim, 2020). With this, maternal autoantibodies cross to the fetus and mediate dysfunction of iron homeostasis, although the antigenic target of these alloantibodies remains unclear. It is associated with significant neonatal morbidity and mortality and frequently recurs in subsequent pregnancies. In these cases, antepartum treatment with intravenous immunoglobulin (IVIG) may improve outcomes (Feldman, 2013; Roumiantsev, 2015).

Wilson disease is caused by copper overload leading to chronic hepatitis and cirrhosis. Autosomal recessive mutations of the *ATP7B* gene underlie this disorder. This gene codes for the P-type ATPase involved in copper transport to ceruloplasmin and bile (Bandman, 2015). This systemic condition can also manifest with cardiomyopathy, renal disease, neuropsychiatric symptoms, and certain endocrine abnormalities. Serum ceruloplasmin, slit-lamp examination, and 24-hour urinary copper excretion are used to identify this disease. A Kayser-Fleischer ring surrounding the iris is highly specific, but a suspected diagnosis generally requires subsequent genetic analysis confirmation.

With Wilson disease, infertility may be present, but pregnancy outcomes among affected women are influenced by disease severity (Malik, 2013). In one multicenter study of 282 pregnancies, the miscarriage rate was 26 percent, and 6 percent of the women had worsening liver disease (Pfeiffenberger, 2018).

Birth defects were not increased with chelation treatment. Maternal and neonatal outcomes were good. The American College of Gastroenterology states that few data guide which of the various chelating agents is best (Tran, 2016). These include penicillamine, zinc, and trientine, and any theoretical risks are outweighed by the risks of discontinuing therapy. The latter include not only hepatic decompensation, but also injury to the placenta and fetal liver. Accordingly, the American College of Gastroenterology recommends that pregnant women should continue their chelation therapy, although a dose reduction of 25 to 50 percent should be considered to promote wound healing in the event of a surgical delivery.

■ Nonalcoholic Fatty Liver Disease

This is the most common chronic liver disease in the United States. Unsurprisingly, because it is frequently comorbid with obesity, it is demonstrable in 25 percent of American adults (Abdelmalek, 2018). Nonalcoholic fatty liver disease (NAFLD) is a macrovesicular fatty liver condition that resembles alcohol-induced liver injury but is seen without ethanol abuse. Its most severe form—*nonalcoholic steatohepatitis (NASH)*—is an increasingly recognized condition that may occasionally progress to hepatic cirrhosis. Currently, this is the third most common indication for liver transplantation in the United States (Diehl, 2017).

Obesity, type 2 diabetes, and hyperlipidemia—*syndrome X*—frequently coexist with NAFLD (Chap. 51, p. 904). The current hypothesis suggests that these conditions may interact with other unknown etiological agents to cause multiple insults that lead to hepatic injury (Buzzetti, 2016). In one study of individuals with type 2 diabetes and normal liver enzyme levels, half had NAFLD, and those with NAFLD showed greater insulin resistance (Portillo-Sanchex, 2015). In a study of obese adolescents undergoing bariatric surgery and intraoperative core liver biopsy, more than a third had fatty liver without hepatitis. An additional 20 percent had borderline or definite NASH (Xanthakos, 2015).

Liver damage follows a progressive continuum from NAFLD to NASH and then to hepatic fibrosis that may progress to cirrhosis (Goh, 2016). The disease is usually asymptomatic, and it is a frequent explanation for elevated serum transaminase levels found during routine screening. When other liver disease is excluded, NAFLD is the cause of elevated asymptomatic transaminase levels in up to 90 percent of cases. Currently, weight loss along with control of diabetes and dyslipidemia is the only recommended treatment.

Pregnancy

During the past decade, we have encountered an increasing number of obese and diabetic gravidas with fatty liver infiltration. These women appear to have no greater rates of adverse outcomes relative to liver involvement compared with pregnant women of similar weight. However, some emerging data indicate potential concerns. In one patient registry, risks of gestational diabetes, preeclampsia, preterm birth, and low-birthweight newborns were two- to threefold higher than in unaffected women (Hagström, 2016). Yarrington and colleagues (2016) reported a high rate of gestational diabetes among nonobese women who had elevated alanine transaminase levels in the first trimester. Somewhat related, in another study, almost a fourth of women with prior gestational diabetes had NAFLD (Foghsgaard, 2017). Last, some evidence suggests that the fetus of an affected mother is at increased risk for NAFLD in adulthood (Baker, 2018).

■ Cirrhosis

Irreversible chronic liver injury with extensive fibrosis and regenerative nodules is the final common pathway for several disorders. *Laënnec cirrhosis* from chronic alcohol exposure is the most frequent cause in the general population. However, in young women, most cases are caused by *postnecrotic cirrhosis* from chronic hepatitis B or C. As discussed, many cases of *cryptogenic cirrhosis* are now known to be caused by NAFLD (Ge, 2016; Goh, 2016). Clinical manifestations of cirrhosis include jaundice, edema, coagulopathy, and metabolic abnormalities. Of associated conditions, portal hypertension can lead to gastroesophageal varices, and splenomegaly may cause thrombocytopenia. Also, the incidence of venous thromboembolism is increased. The prognosis is poor, and 75 percent have progressive disease that leads to death in 1 to 5 years.

The incidence in pregnancy was reported to be 1 case in 3300 births (Palatnik, 2017). Common complications include transient hepatic failure, variceal hemorrhage, preterm delivery, fetal-growth restriction, spontaneous bacterial peritonitis, and maternal death (Tan, 2008). Outcomes generally are poor, especially if esophageal varices coexist. Another potentially fatal cirrhosis complication arises from associated splenic artery aneurysms. Up to 20 percent of aneurysm ruptures occur during pregnancy, and 70 percent of these rupture in the third trimester (Tan, 2008). The 20-percent maternal mortality rate is likely related to the emergent diagnosis of these aneurysms (Ha, 2009).

■ Portal Hypertension and Esophageal Varices

In pregnant women, the causes of esophageal varices are equally divided between cirrhosis and extrahepatic portal vein obstruction (Andrade, 2018). Of the extrahepatic cases, some develop following portal vein thrombosis associated with one of the *thrombophilia syndromes* (Chap. 55, p. 976). Others follow thrombosis related to umbilical vein catheterization when the woman was a neonate, especially if she was born preterm. Last, the rare *Budd-Chiari syndrome* results from hepatic vein thrombosis that causes extrahepatic portal hypertension. Of 16 pregnancies complicated by this syndrome, one observational study reported favorable outcomes (Khan, 2017).

With either intrahepatic or extrahepatic resistance to flow, portal vein pressure rises from its normal range of 5 to 10 mm Hg, and values may exceed 30 mm Hg. Collateral circulation develops that carries portal blood to the systemic circulation. Blood drains into the gastric, intercostal, and other veins to reach the esophageal system, where varices develop. In rare cases, abdominal wall varices develop (Wood, 2018a). Bleeding is usually from varices near the gastroesophageal junction, and

hemorrhage can be severe. Bleeding during pregnancy from varices occurs in a third to half of affected women and is the major cause of maternal mortality in this group (Tan, 2008).

Maternal prognosis with esophageal varices largely depends on whether these rupture. The mortality rate is 18 percent if varices are associated with cirrhosis compared with 2 percent for varices without cirrhosis. Similarly, perinatal mortality rates are high in women with varices and are worse if cirrhosis caused the varices. Increased rates of neonatal demise, preterm birth, low birthweight, preeclampsia, and postpartum hemorrhage have been reported (Puljic, 2016).

Treatment is the same as for nonpregnant patients. Preventively, all patients with cirrhosis, including pregnant women, should undergo endoscopic screening for variceal dilation (Bacon, 2015). Beta-blocking drugs such as propranolol are given to decrease portal pressure and bleeding risk (Ge, 2016; Tran, 2016).

For acute bleeding and for prophylaxis, endoscopic band ligation is preferred to sclerotherapy because it avoids any potential risk of injecting sclerotherapeutic chemicals. Acute medical management for bleeding varices verified endoscopically includes the intravenous vasoconstrictors octreotide or somatostatin along with endoscopic banding. Vasopressin is less often used. If endoscopy is not available, *balloon tamponade* using a triple-lumen Sengstaken-Blakemore tube, which is placed into the esophagus and stomach to compress bleeding varices, can be lifesaving. An interventional radiology procedure—*transjugular intrahepatic portosystemic stent shunting (TIPSS)*—also can control bleeding from gastric varices that is unresponsive to other measures (Ge, 2016; Tan, 2008). We have had good outcomes with this procedure done electively during pregnancy in women with prior variceal hemorrhage (Chandramouli, 2020).

Acetaminophen Hepatotoxicity

As discussed earlier (p. 1030), acetaminophen is the most frequent cause of acute liver failure in the United States (Lee, 2018). This commonly used medication can be associated with hepatotoxicity at doses above 4 g/d, and even less in certain populations (Clark, 2012). The drug is often used during pregnancy, and overdose–either accidentally or by attempted suicide–may lead to hepatocellular necrosis and acute liver failure (Taney, 2017). Massive necrosis causes a cytokine storm and multiorgan dysfunction. Early overdose symptoms are nausea, vomiting, diaphoresis, malaise, and pallor. After a latent period of 24 to 48 hours, liver failure ensues, and it usually begins to resolve in 5 days. In a prospective Danish study, only 35 percent of patients who were treated for fulminant hepatic failure spontaneously recovered before being listed for liver transplantation (Schmidt, 2007).

The antidote is *N-acetylcysteine (NAC)*, which must be given promptly. The drug is thought to raise glutathione levels, which aid metabolism of the toxic metabolite, *N*-acetyl-*p*-benzoquinoneimine. The *Rumack-Matthew nomogram* uses serum acetaminophen levels to predict subsequent plasma hepatotoxic levels as a function of the time from acute ingestion (Rumack, 1975). The need for treatment is based on these projections, and online nomograms and calculators are available. If the plasma level exceeds 150 μg/mL 4 hours after ingestion, treatment is given. When plasma determinations are not available, empirical treatment is initiated if the ingested amount is >7.5 g. An oral loading dose of 140 mg/kg is given followed by 70 mg/kg every 4 hours for a total treatment duration of 72 hours (Heard, 2008). Both the oral and an equally efficacious intravenous dosing regimen have been reviewed by Hodgman and Garrard (2012). Although the drug reaches therapeutic concentrations in the fetus, any protective effects of NAC during acetaminophen overdose are unknown (Wiest, 2014).

After 14 weeks' gestation, the fetus has some cytochrome P450 activity necessary for metabolism of acetaminophen to the toxic metabolite. Riggs and associates (1989) reported follow-up data from the Rocky Mountain Poison and Drug Center in 60 women suffering overdose. The likelihood of maternal and fetal survival was better if the antidote was given soon after overdose. At least one 33-week fetus appears to have died as a direct result of hepatotoxicity 2 days after maternal ingestion. In another case, Wang and coworkers (1997) confirmed acetaminophen placental transfer and found maternal and cord blood levels measuring 41 μg/mL. Both the mother and the emergently delivered neonate died from hepatorenal failure.

Focal Nodular Hyperplasia

This benign lesion of the liver is characterized in most cases by a well-delineated accumulation of normal but disordered hepatocytes surrounding a central stellate scar. These usually can be differentiated from hepatic adenomas by MR and CT imaging. Except in rare situations of unremitting pain, surgery is rarely indicated, and most women remain asymptomatic during pregnancy. In one review of 20 cases, no woman had related complications during pregnancy (Rifai, 2013). Three women showed 20-percent tumor growth; in half, the tumor diminished in size; and the remaining seven tumors were unchanged across pregnancy. In another surveillance of 44 lesions with MR imaging in 30 gravidas, tumor size was unchanged in 80 percent and decreased in most of the remainder (Ramírez-Fuentes, 2013). Investigators concluded that size changes were unrelated to pregnancy, combination oral contraceptive use, or menopause. This lesion is not a contraindication to estrogen-containing contraceptives (Chap. 38, p. 673).

Hepatocellular Adenoma

This rare benign neoplasm develops most often in young women. Lesions are more common in individuals taking combination oral contraceptives or other steroid medications (Renzulli, 2019). Hepatic adenomas have a 5-percent risk of malignant transformation and a significant risk of rupture-associated hemorrhage, particularly in pregnancy. The rupture risk progresses with lesion size, and surgery is generally recommended for tumors measuring >5 cm (Agrawal, 2015). Thus, differentiation from focal nodular hyperplasia is important and can be achieved by MR or CT imaging.

Tran and associates (2016) recommend sonographic surveillance of hepatic adenomas during pregnancy. In a study of

51 pregnancies in women with an adenoma <5 cm, 25 percent of the lesions expanded approximately 14 mm (Gaspersz, 2020). In one review of 27 cases in pregnancy, 23 became apparent in the third trimester and puerperium (Cobey, 2004). No bleeding complications followed tumors measuring <6.5 cm. However, 60 percent presented with tumor rupture that resulted in seven maternal deaths and six fetal deaths. Of note, 13 of 27 women presented within 2 months postpartum, and in half, hemorrhage heralded rupture. Bleeding adenomas can be managed by angiographic embolization followed by resection (Tsilimigras, 2019).

Liver Transplantation

According to the Organ Procurement and Transplantation Network (2020) more than 177,000 liver transplantations have been performed in the United States. Analysis of the National Inpatient Sample database found 2 liver transplantations per 100,000 deliveries (Ghazali, 2017). In most studies, the 80-percent live-birth rate compares favorably with that of the general population. However, risks of preeclampsia, cesarean delivery, fetal-growth restriction, and preterm birth are significantly elevated (Coscia, 2010; Deshpande, 2012; Kanzaki, 2016). Although cesarean delivery is common, vaginal delivery is not contraindicated (Madej, 2018). Mattila and colleagues (2017) found that half of the women they cared for had maternal complications, including acute graft rejection. Importantly, 4 percent of mothers had died within a year after delivery, but this rate is comparable to that in nonpregnant liver transplantation patients.

GALLBLADDER DISORDERS

Cholelithiasis and Cholecystitis

In the United States, 17 percent of women have gallstones. Most stones contain cholesterol, and its oversecretion into bile is thought to be a major factor in stone formation. The cumulative risk of all patients with gallstones to become symptomatic is 20 percent (Lammert, 2016). For this reason, prophylactic cholecystectomy is not warranted for *asymptomatic* stones.

Symptomatic cholelithiasis typically presents with right upper or epigastric abdominal pain, bloating, belching, nausea, and fatty food intolerance. Pain stems from gallbladder contraction, which forces a stone up into the sac's neck. With subsequent gallbladder relaxation, the stone falls back to relieve the obstruction. Laboratory values are normal, and leukocytosis or elevated liver and pancreatic enzymes should warn for acute cholecystitis or pancreatitis. Standard care for symptomatic cholelithiasis is laparoscopic cholecystectomy (Cafasso, 2014). Less often, oral ursodeoxycholic acid therapy or extracorporeal shock wave lithotripsy are used, but experience with these during pregnancy is lacking.

Acute cholecystitis usually develops when a stone obstructs the cystic duct, which connects the gallbladder to the common bile duct. Bacterial infection plays a role in 50 to 85 percent of cases. In more than half of patients with acute cholecystitis, a history of prior right upper quadrant pain from biliary colic is elicited. With acute disease, pain is accompanied by anorexia, nausea and vomiting, low-grade fever, and mild leukocytosis. As shown in Figure 58-3, sonography will display stones, and both false-positive and false-negative rates range from 2 to 4 percent (Greenberger, 2018). In acute cases, medical therapy consists of intravenous fluids, antibiotics, analgesics, and in some instances, nasogastric suction. Surgical therapy follows, and laparoscopic cholecystectomy is the preferred route for most.

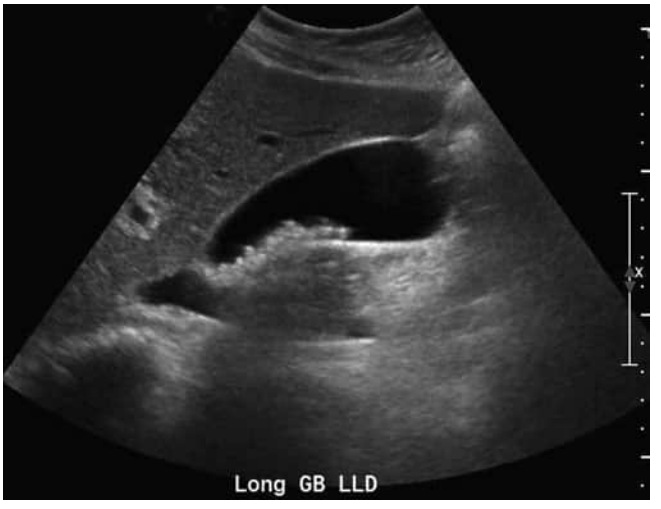

FIGURE 58-3 Sonogram shows multiple, hyperechoic gallstones collecting along the inferior wall of an anechoic gallbladder.

Gallbladder Disease During Pregnancy

After the first trimester, the gallbladder fasting volume and the residual volume after postprandial emptying are doubled. Incomplete emptying may result in retention of cholesterol crystals, a prerequisite for cholesterol gallstones. From studies, the combined incidence of biliary sludge and gallstones is 5 to 8 percent (Ko, 2005, 2014).

Postpartum, sludge frequently regresses, and occasionally gallstones will resorb. Still, gallbladder diseases are the most common cause of nonobstetrical admissions in the first year following delivery (Lydon-Rochelle, 2011). This is particularly true for women managed conservatively during pregnancy. Jorge and coworkers (2015) reported that half of 53 women with symptomatic cholelithiasis in pregnancy underwent later postpartum cholecystectomy. In 80 percent of these women, recurrent symptoms had developed prior to surgery.

Medical versus Surgical Management

Symptomatic cholelithiasis is common in pregnancy. Othman and colleagues (2012) showed that gravidas managed conservatively had greater pain, more recurrent emergency department visits, more hospitalizations, and higher cesarean delivery rate. Dhupar and associates (2010) reported more complications with conservative management of gallbladder disease compared with laparoscopic cholecystectomy in pregnancy. These included multiple admissions, prolonged total parenteral nutrition (TPN), and unplanned labor induction for worsening gallbladder symptoms. Therefore, operative and

endoscopic interventions are increasingly favored over conservative measures.

Acute cholecystitis during pregnancy or the puerperium is also common. Acute disease in pregnancy may be complicated by sepsis, pancreatitis, venous thromboembolism, and bowel obstruction (El-Messidi, 2018). Cholecystitis is initially managed similarly to that for nonpregnant women. In the distant past, most favored medical therapy. However, the recurrence rate during the same pregnancy is high, and 25 to 50 percent of women ultimately require cholecystectomy for persistent symptoms (Dhupar, 2010). Moreover, if cholecystitis recurs later in gestation, preterm labor is more likely and cholecystectomy is technically more difficult.

Cholecystectomy can be performed safely in all trimesters (Kwon, 2018). A metaanalysis found that cholecystectomy does not raise the risk of preterm labor or of maternal or fetal mortality (Athwal, 2016). Of surgical routes, laparoscopic cholecystectomy has evolved as the favored approach (Pearl, 2017; Shigemi, 2019). This is discussed further in Chapter 49 (p. 867). Management at Parkland Hospital favors a surgical approach, especially if biliary pancreatitis, as subsequently discussed, is comorbid (Juo, 2018).

Endoscopic Retrograde Cholangiopancreatography

Approximately 10 percent of patients with symptomatic stone disease have common duct stones (Stinton, 2012). Symptomatic biliary duct gallstones during pregnancy can be retrieved by endoscopic retrograde cholangiopancreatography (ERCP) (Fogel, 2014; Greenberger, 2018). The procedure is performed if common duct obstruction is suspected or proven. ERCP can be modified in many cases so that radiation exposure from fluoroscopy is avoided (Sethi, 2015). If standard fluoroscopy is used, a lead apron shield is placed between the radiation source and the fetus.

In 68 ERCP procedures performed in pregnant women at Parkland Hospital, all but two women had gallstones, and common duct stones were identified in half of 65 women (Tang, 2009). Stones were successfully removed in all but one woman. A biliary stent was placed in 22 percent of cases and removed after delivery. Complications were minimal, but post-ERCP pancreatitis developed in 16 percent. Pregnancy outcomes were not different from those in the general obstetrical population. As a less invasive approach, MR cholangiopancreatography (MRCP) in pregnancy has been reported (Oto, 2009).

Ascending cholangitis can complicate acute biliary obstruction. Nearly 70 percent of affected patients develop *Charcot triad*—jaundice, abdominal pain, and fever. The diagnosis is aided by sonography, and treatment is broad-spectrum antibiotics and biliary drainage by ERCP (Greenberger, 2018).

PANCREATIC DISORDERS

Pancreatitis

Acute pancreatic inflammation is triggered by factors that cause activation of pancreatic trypsinogen followed by autodigestion. It is characterized by cell-membrane disruption and proteolysis, edema, hemorrhage, and necrosis (Conwell, 2018). Up to 10 percent of patients develop necrotizing pancreatitis, which carries a mortality risk of 15 percent. This rate rises if infection develops (Cain, 2015).

The incidence of pancreatitis varies with the population studied. At Parkland Hospital, with a predominant Mexican-American population, acute pancreatitis complicated approximately 1 in 3300 pregnancies (Ramin, 1995). From other reviews, the incidence is 1 case in 3500 to 6000 pregnancies (Eddy, 2008; Hacker, 2015; Hernandez, 2007).

In nonpregnant patients, acute pancreatitis is almost equally associated with gallstones and alcohol abuse. During pregnancy, however, cholelithiasis is almost always the predisposing condition. Other causes are hyperlipidemias, usually hypertriglyceridemia; hyperparathyroidism; congenital ductal anomalies; recent ERCP; some drugs; and rarely autoimmune pancreatitis (Conwell, 2018; Tang, 2018). Nonbiliary pancreatitis occasionally develops postoperatively, or it is associated with trauma, drugs, or some viral infections. Certain metabolic conditions, including acute AFLP and familial hypertriglyceridemia, also predispose to pancreatitis (Nelson, 2013). Cases of acute and chronic pancreatitis have been linked to numerous mutations of the cystic fibrosis transmembrane conductance regulator gene (Chang, 2015).

Diagnosis

Acute pancreatitis incites incapacitating epigastric pain, nausea and vomiting, and abdominal distention. Patients are usually distressed and have low-grade fever, tachycardia, hypotension, and abdominal tenderness. As many as 10 percent have sepsis, which causes endothelial activation and can lead to acute respiratory distress syndrome (Chap. 50, p. 887).

Serum lipase measurements are preferred for diagnosis, however, amylase levels also can be used. In 173 pregnant women with pancreatitis, the mean amylase value approximated 2000 IU/L, and the mean lipase value approached 3000 IU/L (Table 58-5). *Importantly, the degree of enzyme elevation and disease severity do not reliably correlate.* By 48 to 72 hours amylase levels may return to normal despite other evidence for continuing pancreatitis. Serum lipase activity typically remains increased with continued inflammation. Leukocytosis is usually found, and 25 percent of patients have hypocalcemia. Elevated serum bilirubin and aspartate transaminase levels may signify concomitant gallstone disease.

TABLE 58-5. Laboratory Values in 173 Pregnant Women with Acute Pancreatitis

Analyte	Mean	Range	Normal
Serum amylase (IU/L)	1980	111–8917	28–100
Serum lipase (IU/L)	3076	36–41,824	7–59
Total bilirubin (mg/dL)	1.7	0.1–8.71	0.2–1.3
Aspartate transaminase (U/L)	115	11–1113	10–35
Leukocytes (per μL)	10,700	1000–27,200	3900–10,700

From Ramin, 1995; Tang, 2010; Turhan, 2010.

Several prognostic scoring systems are used to classify pancreatitis severity. However, the Ranson criteria and the Apache II scoring system may be less relevant for pregnancy. In contrast, the Atlanta Classification incorporates the degree of organ failure as a measure of severity and may be more applicable in pregnancy (Cain, 2015; Conwell, 2018). With this last tool, *mild disease* lacks organ failure or systemic complications. *Moderately severe disease* shows organ failure lasting <48 h, with or without local or systemic complications. *Severe disease* is defined by persistent single- or multi-organ failure (Banks, 2013).

Management

Medical treatment mirrors that for nonpregnant patients. This includes analgesics, intravenous hydration, and measures to decrease pancreatic secretion by interdiction of oral intake. Nasogastric suction does not improve outcomes of mild to moderate disease. In a series by Ramin and colleagues (1995), all 43 affected pregnant women responded to conservative treatment and were hospitalized for a mean of 8.5 days. If bacterial superinfection, necrotizing pancreatitis, sepsis, or cholangitis is found, broad-spectrum antimicrobials are administered. If common duct stones are found, ERCP is indicated.

Enteral feeding may be helpful once pain improves and associated ileus resolves. For women with more severe pancreatitis and prolonged disease course, total enteral nutrition using nasojejunal feeding is superior to TPN (Cain, 2015; Conwell, 2018). Cholecystectomy is considered after inflammation subsides because women with gallstone pancreatitis carry a greater risk of recurrent inflammation (Cain, 2015). Juo and coworkers (2018) reported that a third of women with biliary pancreatitis not treated with cholecystectomy were readmitted, and 30 percent of these had recurrent pancreatitis. Of the initial group, those who instead did undergo cholecystectomy had only a 5-percent readmission rate.

Pregnancy Outcomes

Increasing severity of pancreatitis is associated with adverse maternal and fetal outcomes (Tang, 2018). In one review of 101 pancreatitis cases, Eddy and coworkers (2008) found a 30-percent preterm delivery rate, and 11 percent were delivered before 35 weeks' gestation. There were also 4 percent stillbirths. There were two pancreatitis-related maternal deaths. Importantly, almost a third of women had recurrent pancreatitis during pregnancy. In another study of 342 pregnancies complicated by pancreatitis, preterm delivery and fetal mortality rates were comparable to the data from Eddy (Hacker, 2015).

■ Pancreatic Transplantation

Few reports describe pregnancy following pancreas transplantation. Of 44 pregnancies in 73 women following pancreas-kidney transplantation, outcomes are encouraging, and vaginal delivery has been described (Mastrobattista, 2008). Although the incidence of hypertension, preeclampsia, preterm delivery, and fetal-growth restriction are high, there was only one perinatal death. Four rejection episodes developed during pregnancy and were treated successfully. Pancreatic islet autotransplantation and at least three subsequent successful pregnancies have been reported (Jung, 2007).

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CHAPTER 59

Hematological Disorders

Pregnant women are susceptible to several hematological abnormalities that may affect any woman of childbearing age. These include chronic disorders such as hereditary anemias, immunological thrombocytopenia, and hematological malignancies. Other disorders arise from pregnancy-induced demands. Two are iron deficiency and megaloblastic anemias. Pregnancy may also unmask underlying hematological conditions. Importantly, pregnancy induces physiological changes that often confuse diagnosis and assessment of these disorders (Chap. 4, p. 60).

ANEMIAS

Definition and Incidence

Normal values for concentrations of many cellular elements during pregnancy are listed in the Appendix (p. 1227). The Centers for Disease Control and Prevention (1998) defined anemia in iron-supplemented pregnant women using a cutoff of the 5th percentile, which is 11 g/dL in the first and third trimesters and 10.5 g/dL in the second trimester. Notably, these were not based on a U.S. population. Table 59-1 describes the distribution of hematocrit values of 480 iron-sufficient women at Parkland Hospital (Zofkie, 2020). Using these data, values below 30 percent seem reasonable to define anemia.

The modest fall in hemoglobin and hematocrit values during pregnancy stems from a relatively greater expansion of plasma volume compared with red cell volume (Georgieff, 2020). The disproportion between the rates at which plasma and erythrocytes add to the maternal circulation is greatest during the second trimester. Late in pregnancy, plasma expansion essentially ceases, while hemoglobin mass continues to accrue.

The causes of more common anemias encountered in pregnancy are listed in Table 59-2. Their frequency is dependent on

TABLE 59-1. Hematocrit Values in Pregnancy

	Percent		
	5th percentile	50th percentile	75th percentile
1st trimester	33.0	37.5	41.2
2nd trimester	30.5	35.7	39.2
Predelivery	30.7	36.5	40.5

TABLE 59-2. Causes of Anemia During Pregnancy

Acquired
Iron-deficiency anemia
Acute blood-loss anemia
Anemia of chronic disease
Megaloblastic anemia
Hemolytic anemias
Aplastic or hypoplastic anemia
Hereditary
Thalassemias
Sickle-cell hemoglobinopathies
Other hemoglobinopathies
Hemolytic anemias

multiple factors such as geography, ethnicity, socioeconomic level, nutrition, preexisting iron status, and prenatal iron supplementation (American College of Obstetricians and Gynecologists, 2021). In the United States, the prevalence of anemia in pregnancy is 3 to 38 percent (Centers for Disease Control and Prevention, 1989).

Initial evaluation of a pregnant woman with moderate anemia includes measurements of hemoglobin, hematocrit, red cell indices, and serum iron or ferritin levels; careful examination of a peripheral blood smear; and a sickle-cell preparation if the woman has African lineage (Appendix p. 1227).

Effects on Pregnancy Outcomes

Anemia is associated with several adverse pregnancy outcomes (American College of Obstetricians and Gynecologists, 2021; Rahmati, 2020). Most anemia studies during pregnancy describe large populations and nutritional anemias. In a Canadian study, 12 percent of more than 500,000 women had mild anemia defined by a hemoglobin concentration of 9.0 to 10.9 g/dL (Smith, 2019). These women had a 2.5-fold increased risk for blood transfusions. With moderate anemia, incidences of fetal-growth restriction, low 5-minute Apgar score, and perinatal mortality were increased. Ray and coworkers (2020) reported similar results. Correction of iron-deficiency anemia results in a lower transfusion rate with delivery (Ibinosa, 2020).

A seemingly paradoxical finding is that healthy pregnant women with higher hemoglobin concentrations also are at greater risk for adverse perinatal outcomes (von Tempelhoff, 2008). This may result from lower than average plasma volume expansion of pregnancy concurrent with normal red cell mass accrual. Scanlon and associates (2000) studied the relationship between maternal hemoglobin levels and rates of preterm or growth-restricted newborns. Women whose hemoglobin concentration was three standard deviations *above* the mean at 12 or 18 weeks' gestation had a 1.3- to 1.8-fold greater incidence of fetal-growth restriction. Placental weight correlates negatively with maternal hemoglobin concentration (Larsen, 2016). These findings have led some to the illogical conclusion that withholding iron to cause iron-deficiency anemia will improve pregnancy outcomes (Ziaei, 2007).

Iron-deficiency Anemia

The two most common causes of anemia during pregnancy and the puerperium are iron deficiency and acute blood loss (Vandevijvere, 2013). In a typical singleton gestation, the maternal need for iron averages nearly 1000 mg (Chap. 4, p. 60). Multifetal gestational requirements are considerably higher (Ru, 2016). These amounts exceed the iron stores of most women and result in iron-deficiency anemia unless supplementation is provided.

In the third trimester, additional iron is needed to augment maternal hemoglobin levels and for transport to the fetus. Because the amount of iron diverted to the fetus is similar in a normal and in an iron-deficient mother, the newborn of a severely anemic mother does not suffer from iron-deficiency anemia. Neonatal iron stores are related to maternal iron status and to timing of cord clamping.

Iron deficiency often manifests as an appreciable drop in hemoglobin concentration. Classic morphological evidence is erythrocyte hypochromia and microcytosis (Fig. 59-1). These may be less prominent in the pregnant woman. A mean corpuscular volume <80 fL is classically seen (Appendix, p. 1227) (James, 2021). Serum ferritin levels normally decline during pregnancy, and levels below 10 to 15 mg/L confirm iron-deficiency anemia. In addition, *hepcidin* levels drop in pregnancy. This hormone inhibits iron transport by binding to the iron-export channel ferroportin.

Routinely in pregnancy, daily oral supplementation with 30 to 60 mg of elemental iron and 400 μg of folic acid is recommended (World Health Organization, 2016). For iron-deficiency anemia, resolution and restitution of iron stores can be accomplished with simple iron salts that provide approximately 200 mg daily of *elemental iron*. These include ferrous sulfate, fumarate, or gluconate. If a woman cannot take oral iron preparations, parenteral therapy is given. Although both are administered intravenously, ferrous sucrose is safer than iron dextran (Auerbach, 2020; Pavord, 2020).

Moderate iron-deficiency anemia responds to adequate iron therapy, and the hematological response is an elevated

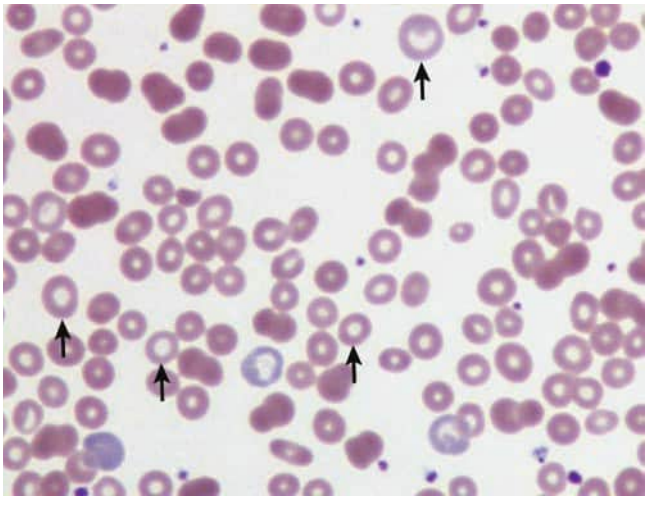

FIGURE 59-1 In this peripheral blood smear, iron-deficiency anemia is reflected by scattered microcytic and hypochromic red cells (*arrows*). (Reproduced with permission from Dr. Siayareh Rambally.)

reticulocyte count. In gravidas, the rise of hemoglobin concentration or hematocrit is typically slower than in nonpregnant women due to the larger plasma volumes of pregnancy. Hemoglobin and ferritin levels show equivalent rises in women treated with either oral or parenteral iron therapy (Breymann, 2017; Daru, 2016; Neogi, 2019).

Anemia from Acute Blood Loss

In early pregnancy, anemia caused by acute blood loss is common with abortion, ectopic pregnancy, and hydatidiform mole. Postpartum, anemia commonly stems from obstetrical hemorrhage. Massive hemorrhage demands immediate treatment and is described in Chapter 44 (p. 771). If a moderately anemic woman—defined by a hemoglobin value of approximately 7 g/dL—is hemodynamically stable, is able to ambulate without adverse symptoms, and is not septic, then blood transfusions are not indicated. Instead, oral iron therapy is provided for at least 3 months.

Anemia of Chronic Disease

Diseases associated with chronic inflammation can cause mild to moderate anemia. Anemia stems from several cytokines produced by inflammatory cells. These restrict erythropoiesis and shorten red cell lifespan. Hepcidin levels are elevated with chronic inflammation, and this inhibits iron-exporting activity from enterocytes (Ross, 2017). Anemia is usually characterized by slightly hypochromic and microcytic erythrocytes, low transferrin saturation, and a high serum ferritin level (Ganz, 2019). Along with iron deficiency, it is the most common form of anemia worldwide.

During pregnancy, women with chronic disorders may develop anemia for the first time. In those with preexisting anemia, it may worsen as plasma volume expands. Frequent causes include chronic renal insufficiency, inflammatory bowel disease, and connective tissue disorders. Others are granulomatous infections and malignant neoplasms.

Chronic renal insufficiency is the most common disorder that we have encountered during pregnancy as a cause of this anemia type. Some cases are accompanied by erythropoietin deficiency. During pregnancy in women with mild chronic renal disease, the degree of red cell mass expansion is inversely related to renal impairment (Chap. 56, p. 1004). At the same time, plasma volume expansion usually is normal, and thus anemia severity intensifies (Cunningham, 1990).

For treatment, adequate iron stores must be ensured. *Recombinant erythropoietin*, with or without intravenous iron, has been used to treat anemia stemming from chronic disease (Ganz, 2019). In pregnancies complicated by chronic renal insufficiency, recombinant erythropoietin is usually considered when the hematocrit approximates 20 percent (Cyganek, 2011). One side effect is hypertension, which is already prevalent in women with renal disease. Red cell aplasia and antierythropoietin antibodies also have been reported (McCoy, 2008).

Megaloblastic Anemia

Folic Acid Deficiency

Megaloblastic anemias are characterized by blood and bone marrow abnormalities from impaired DNA synthesis. This leads to large cells with arrested nuclear maturation, whereas the cytoplasm matures more normally. Worldwide, the pregnancy prevalence of this anemia varies considerably but is low in the United States.

Megaloblastic anemia developing during pregnancy almost always results from folic acid deficiency. In the past, this condition was called *pernicious anemia of pregnancy*. It usually is found in women who do not consume fresh green leafy vegetables, legumes, or animal protein. As folate deficiency and anemia worsen, anorexia often intensifies and further aggravates the dietary deficiency. Other causes are malabsorption syndromes that include tropical sprue, extensive jejunal resection, gastrectomy, and Crohn disease; hemolytic anemias; malignancy; and some antifolate drugs (Hoffbrand, 2018).

Nonpregnant women need 50 to 100 μg of folic acid daily. During pregnancy, requirements rise, and 400 μg/d is recommended. The earliest biochemical evidence is low plasma folic acid concentrations (Appendix, p. 1227). Early morphological changes usually include hypersegmented neutrophils and macrocytic erythrocytes. As the anemia worsens, peripheral nucleated erythrocytes appear, and bone marrow examination discloses megaloblastic erythropoiesis. Anemia may then become severe, and thrombocytopenia, leukopenia, or both may develop. The fetus and placenta effectively extract folate from maternal circulation, and the fetus is not anemic despite severe maternal anemia.

For treatment, 5 to 15 mg of oral folic acid is provided with iron, and a nutritious diet is encouraged (Hoffbrand, 2018). At 4 to 7 days of treatment, the reticulocyte count is higher, and leukopenia and thrombocytopenia are corrected.

For anemia prevention, a diet should contain sufficient folic acid. Moreover, the role of folate deficiency in the genesis of neural-tube defects is well studied (Chap. 15, p. 276).

Vitamin B_{12} Deficiency

With pregnancy, vitamin B_{12} levels are lower than nonpregnant values because levels of binding proteins, namely, the transcobalamins decline. However, in most gravidas, megaloblastic anemia is rarely from vitamin B_{12} deficiency. Of predisposing conditions, vitamin B_{12} deficiency in pregnancy is more likely encountered following gastric resection. Women who have undergone total gastrectomy require 1000 μg of intramuscular vitamin B_{12} (cyanocobalamin) monthly. Those with a partial gastrectomy usually do not need supplementation, but adequate serum vitamin B_{12} levels should be ensured (Appendix, p. 1230). Other causes of megaloblastic anemia from vitamin B_{12} deficiency include Crohn disease, ileal resection, some drugs, and bacterial overgrowth in the small bowel (Hoffbrand, 2018). *Addisonian pernicious anemia* results from absent intrinsic factor that is requisite for dietary vitamin B_{12} absorption. This autoimmune disorder usually has its onset after age 40 years, which accounts for its uncommon occurrence in pregnancy (Govindappagari, 2019).

Hemolytic Anemia

Several conditions accelerate erythrocyte destruction. Hemolysis may be a primary disorder, and sickle-cell disease and

hereditary spherocytosis are examples. In others, hemolysis complicates an underlying condition such as systemic lupus erythematosus or preeclampsia. Microangiopathic hemolytic anemia from malignancy has been reported in pregnancy (Happe, 2016).

Autoimmune Hemolysis

The cause of aberrant antibody production is unknown. Typically, both the direct and indirect antiglobulin (Coombs) tests are positive. Anemias caused by these factors may be due to warm-active autoantibodies (80 to 90 percent), cold-active antibodies, or a combination. These syndromes may also be classified as primary (idiopathic) or secondary due to underlying diseases or other factors. Examples of the secondary group include lymphomas and leukemias, connective tissue diseases, infections, chronic inflammatory diseases, and drug-induced antibodies (Knuesel, 2018). *Cold-agglutinin disease* may be induced by infectious etiologies such as *Mycoplasma pneumoniae* or Epstein-Barr viral mononucleosis. Hemolysis and positive antiglobulin test results may be the consequence of either immunoglobulin M (IgM) or immunoglobulin G (IgG) antierythrocyte antibodies. When thrombocytopenia is comorbid, it is termed *Evans syndrome* (Wright, 2013).

In pregnancy, hemolysis can be markedly accelerated. Low-dose rituximab (Truxima)—100mg weekly for 4 weeks—coupled with prednisone, is first-line treatment (Luzzatto, 2018). Coincidental thrombocytopenia usually corrects with therapy. Transfusion of red cells is complicated by antierythrocyte antibodies, but warming the donor cells to body temperature may decrease their destruction by cold agglutinins. In rare cases, the fetus may be involved (Maroto, 2020).

Drug-induced Hemolysis

These hemolytic anemias must be differentiated from other causes of autoimmune hemolysis. In most cases, hemolysis is mild and resolves with drug withdrawal. Subsequently, avoiding the drug is preventive. One mechanism is hemolysis induced through drug-mediated immunological injury to red cells. If bound to a red cell protein, the drug may act as a high-affinity hapten to which antidrug antibodies attach. An example is IgM antipenicillin or anticephalosporin antibodies. Garratty and colleagues (1999) described seven women with severe Coombs-positive hemolysis stimulated by cefotetan given as prophylaxis for obstetrical procedures. Alpha-methyldopa can cause similar hemolysis (Grigoriadis, 2013). Some other drugs, which include probenecid, quinidine, and rifampin, act as low-affinity haptens and adhere to cell membrane proteins. A frequent mechanism for drug-induced hemolysis relates to a congenital erythrocyte enzymatic defect, such as glucose-6-phosphate dehydrogenase deficiency (p. 1052).

Pregnancy-associated Hemolysis

Unexplained severe hemolytic anemia can develop during early pregnancy and resolves within months postpartum. Clear immune mechanisms or red cell defects are not contributory. Because the fetus–neonate also may demonstrate transient hemolysis, an immunological cause is suspected. Maternal corticosteroid treatment is often—but not always—effective (Kumar, 2001). We have cared for a woman who during each pregnancy developed severe hemolysis with anemia that responded to prednisone. Her fetuses were not affected, and hemolysis abated spontaneously after delivery.

In some cases, hemolysis is induced by conditions unique to pregnancy. Mild microangiopathic hemolysis with thrombocytopenia is relatively common with severe preeclampsia and eclampsia (Cunningham, 2015; Kenny, 2015). This HELLP (hemolysis, elevated liver enzyme levels, low platelet count) syndrome is discussed in Chapter 40 (p. 699). Another example is acute fatty liver of pregnancy, which causes moderate to severe hemolytic anemia (Chap. 58, p. 1033).

Paroxysmal Nocturnal Hemoglobinuria

Although commonly regarded as a hemolytic anemia, this hemopoietic stem cell disorder is characterized by formation of defective platelets, granulocytes, and erythrocytes. Paroxysmal nocturnal hemoglobinuria is acquired and arises from one abnormal clone of cells, much like a neoplasm. In contrast, one mutated X-linked gene responsible for this condition is termed *PIG-A* because it codes for phosphatidylinositol glycan protein A. Resultant abnormal anchor proteins of the erythrocyte and granulocyte membrane make these cells unusually susceptible to lysis by complement. A serious complication is thrombosis, which is heightened in the hypercoagulable state of pregnancy.

Chronic hemolysis has an insidious onset, and its severity ranges from mild to lethal. Hemoglobinuria develops at irregular intervals and is not necessarily nocturnal. Hemolysis may be initiated by transfusions, infections, or surgery. Almost 40 percent of patients suffer venous thromboembolism (VTE) and may also experience renal failure, hypertension, and Budd-Chiari syndrome. To counter the VTE risk, prophylactic anticoagulation is recommended (Luzzato, 2018). The preferred treatment is eculizumab (Soliris), an antibody that inhibits complement activation (Kelly, 2015; Stefanovic, 2019). The drug is apparently safe in pregnancy (Sarno, 2019). Median survival after diagnosis of the syndrome is 10 years, and bone marrow transplantation is the definitive treatment.

During pregnancy, paroxysmal nocturnal hemoglobinuria can be serious and unpredictable. Complications may affect up to three fourths of affected women, and the maternal mortality rate in the past was 10 to 20 percent (de Guibert, 2011). Complications more often develop postpartum, and half of affected women develop VTE. Kelly and coworkers (2015) described 75 pregnancies in 61 affected women treated with eculizumab. They described no maternal deaths, but the stillbirth rate was 4 percent. Miyasaka and associates (2016) found similar results.

Bacterial Toxins

The most fulminant acquired hemolytic anemia encountered during pregnancy is caused by the exotoxin of *Clostridium perfringens* or by group A β-hemolytic streptococcus (Chap. 50, p. 890). In additional, endotoxin of gram-negative bacteria, that is, lipopolysaccharide, may be accompanied by hemolysis and mild to moderate anemia (Cox, 1991). For example, anemia often accompanies acute pyelonephritis. With normal erythropoietin production, red cell mass is restored following infection resolution (Cavenee, 1994; Dotters-Katz, 2013).

Inherited Erythrocyte Membrane Defects

The normal erythrocyte is a flexible biconcave disc that allows numerous cycles of reversible deformations. Several genes encode erythrocyte structural membrane proteins and intraerythrocytic enzymes. Various mutations can destabilize the lipid bilayer. The loss of lipids from the cell membrane causes a surface area deficiency and poorly deformable erythrocytes that undergo hemolysis (Iolascon, 2019). Anemia severity depends on the degree of rigidity. Erythrocyte morphology similarly is dependent on these factors, and these disorders are usually named after the most dominant red cell shape. Three examples are *hereditary spherocytosis*, *pyropoikilocytosis*, and *ovalocytosis*.

Hemolytic anemias that compose this group of inherited membrane defects are among the most common complicating pregnancy. Mutations are usually an autosomally dominant, variably penetrant α- and β-spectrin deficiency. Others are dominant or recessive gene mutations that result from deficiency of ankyrin, band 3, 4.1, and 4.2, or combinations of these (Luzzato, 2018; Rencic, 2017). The degrees of anemia and jaundice vary, and diagnosis is confirmed by identification of abnormal erythrocytes on peripheral smear and their increased osmotic fragility.

Spherocytic anemias may be associated with a crisis typified by severe anemia from accelerated hemolysis, and it develops in patients with an enlarged spleen. Infection can also accelerate hemolysis or suppress erythropoiesis to worsen anemia. An example of the latter is parvovirus B19 infection (Chap. 67, p. 1191). In severe cases, splenectomy reduces hemolysis, anemia, and jaundice.

In general, women with inherited erythrocyte membrane defects do well during pregnancy. Oral folic acid supplementation of 4 mg daily is given to sustain erythropoiesis. Women with hereditary spherocytosis cared for at Parkland Hospital had hematocrits ranging from 23 to 41 percent, with a mean of 31 (Maberry, 1992). Reticulocyte counts varied from 1 to 23 percent. Among 50 pregnancies in 23 women, eight women miscarried. Four of 42 infants were born preterm, but none was growth restricted. Infection in four women intensified hemolysis, and three of these required transfusions. Similar results were reported by Pajor and colleagues (1993).

Because these disorders are inherited, the newborn may be affected. Preconceptional counseling emphasizes folic acid supplementation and provides an opportunity to discuss prenatal diagnosis. Celkan and Alhaj (2008) report prenatal diagnosis via cordocentesis at 18 weeks' gestation and testing for osmotic fragility. Although fetal anemia is uncommon, newborns with hereditary spherocytosis may manifest hyperbilirubinemia and anemia shortly after birth.

Erythrocyte Enzyme Deficiencies

An intraerythrocytic deficiency of enzymes that permit anaerobic glucose metabolism may cause *hereditary nonspherocytic anemia*. Most of these mutations are autosomal recessive traits. Most episodes of severe anemia with these enzyme deficiencies are induced by drugs or infections.

Pyruvate kinase deficiency has a frequency of 1:10,000 persons and is associated with variable degrees of anemia (Luzzatto, 2018). Recurrent transfusions in homozygous carriers can lead to iron overload, and associated myocardial dysfunction should be monitored (Dolan, 2002). The fetus that is homozygous for this mutation may develop *hydrops fetalis* from anemia and heart failure (Chap. 18, p. 360).

Glucose-6-phosphate dehydrogenase (G6PD) deficiency is complex because there are more than 200 enzyme variants. The most common stem from a base substitution that leads to an amino acid replacement and a broad range of phenotypic severity (Luzzatto, 2018; Puig, 2013). In the homozygous or A variant, both X chromosomes are affected, and erythrocytes are markedly deficient in G6PD activity. Approximately 2 percent of African-American women are affected, and the heterozygous variant is found in 10 to 15 percent. In both cases, random X-chromosome inactivation—*lyonization*—results in variable enzyme activity.

During pregnancy, hemolysis severity in G6PD-deficient heterozygotes or homozygotes is related to enzyme activity. Anemia is usually episodic, but some variants induce chronic nonspherocytic hemolysis. Because young erythrocytes contain more enzyme activity, anemia stabilizes and corrects soon after the inciting cause is resolved.

These women are offered preconceptional counseling to discuss risks of adverse pregnancy outcomes, precipitating factors of hemolysis such as pyelonephritis and pneumonia, and the limited list of safe medications available for treatment during pregnancy. For example, macrodantin is used for pyelonephritis suppression in pregnancy but can induce hemolysis in those with G6PD deficiency. Because fetal and neonatal manifestations are possible, these patients should undergo genetic counseling, with possible partner testing, to assess fetal transmission risk.

■ Aplastic and Hypoplastic Anemia

Aplastic anemia is a grave complication characterized by pancytopenia and markedly hypocellular bone marrow (Young, 2018). The functional defect is a marked decline in the number of committed marrow stem cells. Etiologies are multiple, and the inciting cause can be identified in approximately a third of cases. These include immunological disorders, drugs, other chemicals, infection, irradiation, leukemia, and inherited conditions such as *Fanconi anemia* and *Diamond-Blackfan syndrome* (Green, 2009).

Immunosuppressive therapy is given, and in some nonresponders, eltrombopag (Promacta) is successful (Townsley, 2017; Young, 2018). Definitive treatment is bone marrow transplantation, and approximately three fourths of patients have a good response and long-term survival (Tichelli, 2020). Umbilical cord blood–derived stem cells also can serve as a potential transplant source (Moise, 2005; Pinto, 2008).

Pregnancy

Hypoplastic or aplastic anemia complicating pregnancy is rare. A study of 60 pregnancies complicated by aplastic anemia found that half were diagnosed during pregnancy (Bo, 2016). In another series of 19 pregnancies, the complication rate was 79 percent, but no women died (McGowan, 2019). *Pregnancy-*

induced hypoplastic anemia is rare, and the anemia and other cytopenias improve or remit following delivery or pregnancy termination (Choudhry, 2002; Edahiro, 2020). In some cases, anemia recurs in a subsequent pregnancy.

Diamond-Blackfan anemia is rare form of pure red cell hypoplasia. Approximately 40 percent of cases are familial and have autosomal dominant inheritance (Orfali, 2004). The response to glucocorticoid therapy is usually good. Continuous treatment is necessary, and most become at least partially transfusion dependent (Gansner, 2017). In a study of 64 pregnancies complicated by this syndrome, two thirds had problems related to placental vascular etiologies that included miscarriage, preeclampsia, preterm birth, fetal-growth restriction, or stillbirth (Faivre, 2006).

Gaucher disease is an autosomally recessive lysosomal enzyme deficiency characterized by deficient activity of *acid β-glucosidase*. Affected women have anemia and thrombocytopenia that usually worsens in pregnancy. Elstein and colleagues (1997) described six pregnant women whose disease improved with alglucerase enzyme replacement. Imiglucerase (Cerezyme) is human recombinant enzyme replacement therapy.

The major risks with hypoplastic anemia are hemorrhage and infection. Rates of preterm labor, preeclampsia, fetal-growth restriction, and stillbirth are increased (Bo, 2016). Management depends on gestational age, and supportive care includes continuous infection surveillance and prompt antimicrobial therapy. Granulocyte transfusions are given only during infections. Red cells are transfused to improve symptomatic anemia and routinely to maintain the hematocrit above 20 volumes percent. Platelet transfusions may be needed to control hemorrhage. Mortality rates reported since 1960 have averaged nearly 50 percent but have declined more recently (Giri, 2017).

Bone Marrow Transplantation

Several reports describe successful pregnancies in women who have undergone bone marrow transplantation. In their review, Sanders and coworkers (1996) reported 72 pregnancies in 41 such women. In the 52 pregnancies resulting in a liveborn neonate, almost half were complicated by preterm delivery or hypertension. Data from the National Cancer Institute regarding 102 pregnancies following transplantation showed 71 liveborns, of which 16 were preterm. Of all women, 20 percent had decreased hemopoiesis, and transfusions were required (Giri, 2017). Carter and associates (2006) reported decreased fertility but generally good pregnancy outcomes. Our experiences with a few of these women indicate that they have normal pregnancy-augmented erythropoiesis and total blood volume expansion. In pregnancy, cell-free DNA study results must account for donor DNA contributions (Duque-Afonso, 2018).

POLYCYTHEMIAS

Excessive erythrocytosis during pregnancy is usually secondary and related to chronic hypoxia. Etiologies include maternal congenital cyanotic cardiac disease or a chronic pulmonary disorder. In addition, we have encountered otherwise healthy pregnant women who were heavy smokers, had chronic bronchitis, and had hematocrits ranging from 55 to 60 volumes percent! If polycythemia is severe, the probability of a successful pregnancy outcome is low.

Polycythemia vera is a primary clonal myeloproliferative hemopoietic stem cell disorder characterized by excessive proliferation of erythroid, myeloid, and megakaryocytic precursors. Virtually all patients have a *JAK2* gene mutation (Spivak, 2018). Symptoms are related to greater blood viscosity, and thrombotic complications are common. Treatment of nonpregnant patients is with hydroxyurea or ruxolitinib.

Fetal loss rates are high in women with polycythemia vera, and pregnancy outcome may be improved with aspirin therapy (Bertozzi, 2018; Dewarrat, 2020). Women with a history of VTE are given prophylaxis with low-molecular-weight heparin (Stein, 2019). If cytoreduction is required during pregnancy, interferon alpha may be considered (Kreher, 2014).

HEMOGLOBINOPATHIES

■ Sickle-cell Hemoglobinopathies

Pathophysiology

Hemoglobin A is the most common hemoglobin tetramer and consists of two α- and two β-globin chains. Genes *HBA1* and *HBA2* each code for α-globin, whereas only *HBB* codes for β-globin. Sickle hemoglobin (hemoglobin S) originates from a single β-globin substitution of glutamic acid by valine, which stems from an A-for-T substitution. Hemoglobin C originates from a single β-globin substitution of glutamic acid by lysine, which stems from a T-for-C substitution. Hemoglobinopathies that can result in clinical features of the *sickle-cell syndrome* include sickle-cell anemia (Hb SS); sickle-cell hemoglobin C disease (Hb SC); sickle-cell β-thalassemia disease (either Hb S/B^0 or Hb S/B^+); and sickle-cell E disease (Hb SE). All are associated with higher pregnancy morbidity.

When deoxygenated, red cells containing hemoglobin S undergo sickling, and the hemoglobin aggregates (Fig. 59-2). Constant sickling and unsickling damages the cell membrane, and its shape may become irreversibly sickled. Events that slow

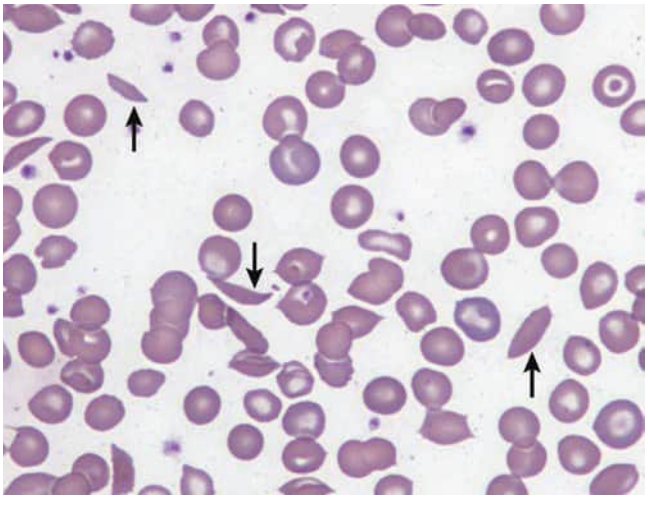

FIGURE 59-2 Peripheral smear of sickle cells (*arrows*) characteristic of sickle-cell anemia. (Reproduced with permission from Dr. Imran Hitto.)

erythrocyte transit through the microcirculation include adhesion to endothelial cells, erythrocyte dehydration, and vasomotor dysregulation.

Clinically, sickling episodes are marked by ischemia and infarction in various organs. The *sickle-cell crisis* produces pain, which is often severe. Aplastic, megaloblastic, sequestration, and hemolytic crises can develop.

Chronic and acute changes from sickling include bony abnormalities such as osteonecrosis of femoral and humeral heads, renal medullary damage, autosplenectomy in homozygous SS patients but splenomegaly in other variants, hepatomegaly, ventricular hypertrophy, pulmonary infarctions, cerebrovascular accidents, leg ulcers, and a propensity for infection and sepsis (Benz, 2018; Ware, 2017). Pulmonary hypertension can develop and is found in 20 percent of adults with SS hemoglobin (Gladwin, 2008). Other sequelae are cerebrovascular aneurysms and sickle-cell vasculopathy (Buonanno, 2016).

Treatment

Good supportive care is essential to prevent mortality. Specific therapies are evolving, and many are still experimental. One treatment is hemoglobin F induction with drugs that stimulate γ-globin synthesis. Remember that hemoglobin F is prominent in fetal life (Chap. 7, p. 129). This induction raises hemoglobin F levels, which inhibits hemoglobin S polymerization. One agent is hydroxyurea, which augments hemoglobin F production and reduces the number of sickling episodes (Tshilolo, 2019). Hydroxyurea is teratogenic in animals. A preliminary 17-year surveillance of antenatally exposed children was reassuring (Ballas, 2009; Briggs, 2017).

Other agents include biologic antibody drugs and l-glutamine (Ataga, 2017, Niihara, 2018; Stefanovic, 2019). Various forms of hemopoietic cell transplantation are emerging as "cures" for sickle-cell syndromes and severe thalassemias (Oringanje, 2013; Kanter, 2021). Last, gene therapy has been accomplished by viral vector–mediated addition of a β-globin gene into stem cells (Harrison, 2019; Ribeil, 2017).

■ Sickle-cell Syndromes During Pregnancy

Pregnancy is a serious burden to women with any major sickle hemoglobinopathy, particularly those with hemoglobin SS (Table 59-3) (Kuo, 2016; Villers, 2008). Maternal mortality rates have improved, but perinatal morbidity and mortality rates remain formidable (Bae, 2021; Oteng-Ntim, 2015). Thus, women with sickle-cell hemoglobinopathies require close prenatal observation. Specifically, any factor that impairs erythropoiesis or increases red cell destruction aggravates the anemia. Prenatal folic acid supplementation with 4 mg daily is needed to support rapid red blood cell turnover.

TABLE 59-3. Pregnancy Morbidity with Hemoglobin SS and SC Disease

Outcome	Odds Ratios	
	Hb SS	Hb SC
Preeclampsia	2–3.1	2.0
Stillbirth	6.5	3.2
Preterm delivery	2–2.7	1.5
Growth restriction	2.8–3.9	1.5
Maternal mortality	11–23	11

From Boafor, 2016; Oteng-Ntim, 2015.

One danger is that a symptomatic woman may categorically be considered to be suffering from a sickle-cell crisis. As a result, serious obstetrical or medical problems that cause pain, anemia, or both may be overlooked. Examples are ectopic pregnancy, placental abruption, pyelonephritis, or appendicitis. Thus, a diagnosis of sickle-cell crisis should be applied only after all other possible causes have been excluded. Pain with sickle-cell syndromes is caused by intense sequestration of sickled erythrocytes and infarction in various organs, particularly bone marrow. These episodes develop acutely, especially late in pregnancy, during labor and delivery, and early in the puerperium.

No randomized trials have evaluated treatment during pregnancy. At minimum, intravenous fluids are given, and opioids are administered promptly for severe pain. Oxygen via nasal cannula may decrease the sickling intensity at the capillary level. We have found that red cell transfusions after the onset of severe pain do not dramatically relieve pain intensity and may not shorten its duration. Conversely, as discussed later, prophylactic transfusions almost always prevent further vaso-occlusive episodes and pain crises. Antenatal epidural analgesia may offer benefits for pain (Verstraete, 2012; Winder, 2011). Long term, affected women can become habituated to narcotics. This problem is highlighted by the elevated rates of neonatal abstinence syndrome, which is a constellation of withdrawal symptoms (Shirel, 2016).

Rates of covert bacteriuria and acute pyelonephritis are elevated substantively, and screening and treatment for bacteriuria are essential. If pyelonephritis develops, sickle cells are extremely susceptible to bacterial endotoxin, which can incite dramatic, rapid red cell destruction and suppress erythropoiesis. Pneumonia, especially due to *Streptococcus pneumoniae,* is common. The Centers for Disease Control and Prevention (2020) recommends specific vaccination for those with sickle-cell disease and all asplenic patients. These are polyvalent pneumococcal, *Haemophilus influenzae* type B, and meningococcal vaccines (Table 10-7, p. 190).

Pulmonary complications are frequent. Of these, *acute chest syndrome* is characterized by pleuritic chest pain, fever, cough, lung infiltrates, hypoxia, and usually bone and joint pain (Vichinsky, 2000). It develops in approximately 6 percent of pregnant women (Inparaj, 2020). In addition to symptoms, radiographs show a new pulmonary infiltrate. The four precipitants are infection, marrow emboli, thromboembolism, and atelectasis (Medoff, 2005). Bacterial or viral infection causes approximately half of cases. When acute chest syndrome develops, the mean duration of hospitalization is 10.5 days. Mechanical ventilation is required in approximately 15 percent, and the mortality rate nears 3 percent (Gladwin, 2008).

For nonpregnant adults, some recommend rapid simple transfusion or exchange transfusions to remove the "trigger" for acute chest syndromes (Ramphul, 2020). In a study of nonpregnant patients, Turner and colleagues (2009) reported that

exchange transfusion offered no increased benefits compared with simple transfusions, and the former were associated with fourfold greater blood usage. These results notwithstanding, the American Society of Hematology *suggests* exchange transfusions instead of simple transfusions. However, they state this recommendation is conditional due to scarce high-quality evidence (Chou, 2020).

Women with sickle-cell disease usually have some degree of *cardiac dysfunction* from ventricular hypertrophy. Chronic hypertension worsens the dysfunction. During pregnancy, the basal hemodynamic state characterized by high cardiac output and increased blood volume is augmented (Veille, 1994). Although most women tolerate pregnancy without problems, complications such as severe preeclampsia or serious infections may result in ventricular failure (Cunningham, 1986). Heart failure caused by pulmonary hypertension also must be considered.

In 4352 pregnancies in women with sickle-cell syndromes, Chakravarty and associates (2008) reported significantly higher pregnancy complication rates. Compared with controls, women with sickling disorders had a 63-percent rate of nondelivery-related admissions. They had a 1.8-fold greater incidence of hypertensive disorders—19 percent; a 2.9-fold higher rate of fetal-growth restriction—6 percent; and a 1.7-fold increased cesarean delivery rate—45 percent.

With hemoglobin SC disease, morbidity and mortality rates are appreciably lower than those from sickle-cell anemia. Indeed, fewer than half of these women have symptoms before pregnancy. In our experiences, affected gravidas suffer attacks of severe bone pain and episodes of pulmonary infarction and embolization more commonly than when not pregnant (Cunningham, 1983). Some adverse pregnancy outcomes are shown in Table 59-3.

Prophylactic Red Cell Transfusions

Chronic transfusion therapy has the most dramatic benefit on maternal morbidity rates (Benites, 2016; Malinowski, 2015; Vianello, 2018). It is problematic for universal application because of complications from multiple transfusions. In an earlier 10-year prospective study at Parkland Hospital, we offered prophylactic transfusions to all pregnant women with sickle-cell syndromes. Transfusions were given throughout pregnancy to maintain the hematocrit above 25 volumes percent and the portion of hemoglobin S below 60 percent (Cunningham, 1979). Maternal morbidity was minimal, and erythropoiesis suppression was not problematic. Their outcomes were compared with historical controls who were not routinely transfused. Overall, maternal morbidity and hospitalization rates were reduced in the transfused group, but perinatal morbidity and mortality rates remained increased because of preterm birth and fetal-growth restriction (Cunningham, 1983).

In a multicenter trial, Koshy and coworkers (1988) randomly assigned 72 pregnant women with sickle-cell syndromes to prophylactic or indicated transfusions. They reported a significant decline in the incidence of painful sickle-cell crises with prophylactic transfusions but no differences in perinatal outcomes. Because of risks inherent with blood administration, they concluded that prophylactic transfusions were not indicated.

A metaanalysis of 12 studies found prophylactic transfusions improved rates of most adverse maternal and neonatal outcomes, including maternal mortality, pulmonary complications, and perinatal mortality (Malinowski, 2015). Undoubtedly, morbidity from multiple transfusions is significant. Up to 10 percent of women had a delayed hemolytic transfusion reaction, and infections are a major concern. Garratty (1997) reviewed 12 studies and found alloimmunization developed in a fourth of women. Last, from liver biopsies in these women, we found no evidence of transfusion-related iron overload, hemochromatosis, or chronic hepatitis (Yeomans, 1990).

Because of what some consider marginal benefits, routine prophylactic transfusions during pregnancy remain controversial (American College of Obstetricians and Gynecologists, 2019b). Current consensus is that their use should be individualized. With such a practice, approximately 60 percent of women will need transfusions during pregnancy (Sharif, 2018).

Fetal Assessment

Perinatal outcomes include increased risks for preterm birth, fetal-growth restriction, and perinatal mortality. Thus, beginning in the mid-second trimester, serial fetal-growth assessment with sonography is reasonable. At 32 to 34 weeks' gestation, weekly antepartum surveillance with biophysical profiles or nonstress test is considered (American College of Obstetricians and Gynecologists, 2019b). Anyaegbunam and colleagues (1991) reported nonreactive stress tests during sickling crises, which resumed reactivity with crisis resolution. They concluded that transient effects of sickle-cell crisis do not compromise umbilical blood flow. Of interest, placentas from sickle-cell pregnancies show abnormalities in 69 percent (Malinowski, 2020).

Labor and Delivery

Management is essentially identical to that for women with cardiac disease (Chap. 52, p. 920). Women are kept comfortable but not oversedated. Conduction analgesia is ideal. Compatible blood should be available. If a difficult vaginal or cesarean delivery is contemplated and the hematocrit is <20 volumes percent, packed erythrocyte transfusions are administered. Vaginal delivery is suitable, and cesarean delivery is reserved for obstetrical indications (Rogers, 2010).

In the puerperium, many clinicians do not recommend combination hormonal contraception because of potential adverse vascular and thrombotic effects. However, one systematic review found that complication rates were not higher with their use in women with sickle-cell syndromes (Haddad, 2012). The Centers for Disease Control and Prevention categorizes combination hormonal contraception, intrauterine devices, implants, and progestin-only methods as having no risk or as having advantages that generally outweigh theoretical or proven risks (Curtis, 2016).

■ Sickle-cell Trait

The frequency of sickle-cell trait among African Americans averages 8 percent. Carriers have occasional hematuria, renal papillary necrosis, and hyposthenuria, which is urine of low

specific gravity (Tsaras, 2009). Sickle trait may be associated with progression of end-stage renal disease in blacks (Olaniran, 2020). Although controversial, sickle-cell trait does not appear to be associated with increased rates of abortion, perinatal mortality, low birthweight, or pregnancy-induced hypertension (Pritchard, 1973; Wellenstein, 2019; Wilson, 2020). In one study of more than 5000 women, the incidence of gestational hypertension was significantly elevated, but that of preeclampsia was not (O'Hara, 2020). Of note, they did not control for chronic hypertension. One unquestioned relationship is the twofold greater incidence of asymptomatic bacteriuria and urinary infection. Sickle-cell trait is not considered a deterrent to pregnancy or to hormonal contraception.

Hemoglobin C and C-β-Thalassemia

Approximately 2 percent of African-Americans are heterozygous for hemoglobin C, but even if homozygous, hemoglobin C is innocuous (Nagel, 2003). Only when coinherited with sickle-cell trait to yield hemoglobin SC is the trait problematic. Pregnancy in women with homozygous hemoglobin CC disease or C-β-thalassemia carries relatively benign associations. Other than mild to moderate anemia, pregnancy outcomes were not abnormal (Maberry, 1990). Supplementation with folic acid and iron is indicated.

Hemoglobin E

Although uncommon in the United States, hemoglobin E is the second most frequent hemoglobin variant worldwide. The heterozygous E trait is common in Southeast Asia. In one study, homozygous hemoglobin E, hemoglobin E plus β-thalassemia, or hemoglobin E trait was identified in 36 percent of Cambodians and 25 percent of Laotians (Hurst, 1983). Homozygosity for hemoglobin E is associated with little or no anemia, hypochromia, marked microcytosis, or erythrocyte targeting. With hemoglobin E trait, another study found no increased pregnancy risks other than asymptomatic bacteriuria between 1073 women and 2146 controls (Kemthong, 2016).

Conversely, doubly heterozygous E-β-thalassemia is a common cause of severe childhood anemia in Southeast Asia (Taher, 2018). In a cohort study of 54 women with singleton pregnancies, a threefold greater risk of preterm birth and fetal-growth restriction was found in affected women (Luewan, 2009). It is unclear if hemoglobin SE disease is ominous during pregnancy.

Hemoglobinopathy in the Newborn

Neonates with homozygous SS, SC, and CC disease can be identified accurately at birth by cord blood electrophoresis. The United States Health Resources and Services Administration (2020) recommends that all newborns be tested for sickle-cell disease. In most states, such screening is mandated by law and performed routinely (Chap. 32, p. 594).

Prenatal Diagnosis

Inheritance is a concern for the fetus whenever a mother and father carry a gene for abnormal hemoglobins that include S, C, and D or for β-thalassemia trait. Sickle-cell anemia results from the inheritance of the gene for S hemoglobin from each parent. In the United States, 1 of 12 African-Americans has sickle-cell trait, which results from inheritance of one gene for hemoglobin S and one for normal hemoglobin A. The computed incidence of sickle-cell anemia among African-Americans is 1 in 576 (1/12 × 1/12 × 1/4 = 1/576). The disease is less common in adults because of earlier mortality. Approximately 1 in 40 African-Americans has the gene for hemoglobin C. Thus, the theoretical incidence for coinheritance of the gene for hemoglobin S and an allelic gene for hemoglobin C in an African-American child is 1 in 2000 (1/12 × 1/40 × 1/4). β-Thalassemia minor affects about 1 in 40, thus S-β-thalassemia also is found in approximately 1 in 2000 (1/12 × 1/40 × 1/4).

Many tests are available to detect sickle-cell disease antenatally. Most are DNA based and use chorionic villus samples or amnionic fluid specimens (American College of Obstetricians and Gynecologists, 2019b). Several mutations that encode hemoglobin S and other abnormal hemoglobins can be detected by targeted mutation analysis and polymerase chain reaction–based techniques (Chap. 18, p. 325).

THALASSEMIA SYNDROMES

Hundreds of mutations affect the genes that control hemoglobin production (Benz, 2018). Some of these impair synthesis of one or more of the normal globin peptides and may result in a clinical syndrome characterized by varying degrees of ineffective erythropoiesis, hemolysis, and anemia. Thalassemias are classified according to the globin that is deficient. The two major forms involve impaired production or instability of α-globin to cause α-thalassemia or of β-globin to cause β-thalassemia. Clinically, these can be divided into transfusion dependent and nontransfusion dependent (Taher, 2018).

Alpha Thalassemias

The two α-globin genes, *HBA1* and *HBA2*, are both found on chromosome 16. Because diploid chromosome sets contains four α-globin genes total, the inheritance of α-thalassemia is more complicated than for β-thalassemia (Piel, 2014). Some of the possible genotypes and phenotypes are shown in Table 59-4. The γ-globin genes are similarly duplicated. Correspondingly, the normal genotype for diploid cells can be expressed as αα/αα and γγ/γγ. Of the two main groups of α-thalassemia determinants, α^0-thalassemia is mutation of both genes from one chromosome (––/αα), whereas α^+-thalassemia is mutation of a single gene from one allele (–α/αα heterozygote) or from both alleles (–α/–α homozygote).

The relative frequency of the different α-thalassemia types varies remarkably among racial groups, and all are encountered in Asians. In those of African descent, although α-thalassemia minor has a frequency approximating 2 percent, hemoglobin H disease is rare and hemoglobin Bart disease is unreported. This is because Asians usually have α^0-thalassemia minor inherited with both gene deletions typically from the

TABLE 59-4. Genotypes and Phenotypes of α-Thalassemia Syndromes

Genotype	Genotype	Phenotype
Normal	αα/αα	Normal
α^+-Thalassemia heterozygote	−α/αα αα/−α	Normal; silent carrier
α^+-Thalassemia homozygote[a]	−α/−α	α-Thalassemia minor—mild hypochromic, microcytic anemia
α^0-Thalassemia heterozygote[b]	−−/αα	
Compound heterozygous α^0/α^+	−−/−α	Hb H (β_4) disease with moderate to severe hemolytic anemia
Homozygous α-thalassemia	−−/−−	Hb Bart (γ_4) disease, hydrops fetalis

[a]More common in African Americans.
[b]More common in Asian Americans.

same chromosome (−−/αα), whereas blacks usually have α^+-thalassemia minor in which one gene is deleted from each chromosome (−α/−α).

Pregnancy

Important obstetrical aspects of some α-thalassemia syndromes depend on the number of gene deletions in a given woman. Clinical severity closely correlates with the degree of impaired α-globin synthesis. The silent carrier state with one gene deletion may be associated with mild microcytic anemia (Andolina, 2020). Deletion of two genes resulting in α-thalassemia minor is characterized by minimal to moderate hypochromic microcytic anemia. This is due to either α^0- or α^+-thalassemia trait, and thus genotypes may be −−/αα or −α/−α, respectively. Differentiation is possible only by DNA analysis (Piel, 2014). Because no other clinical abnormalities accompany either form of α-thalassemia minor, it often goes unrecognized and is usually of no maternal consequence (Hanprasertpong, 2013). The fetus with these forms of thalassemia minor will have hemoglobin Bart (γ_4) at birth, but as its levels drop, it is not replaced by hemoglobin H (β_4). Red cells are hypochromic and microcytic, and the hemoglobin concentration is normal to slightly depressed.

Hemoglobin H disease (β_4) results from the compound heterozygous state for α^0- plus α^+-thalassemia with deletion of three of four alpha genes (−−/−α). With only one functional α-globin gene per diploid genome, the newborn will have abnormal red cells containing a mixture of hemoglobin Bart (γ_4), hemoglobin H (β_4), and hemoglobin A. Of these three, fetal hemoglobin Bart (γ_4) and hemoglobin H (β_4) transport oxygen poorly. The neonate appears normal but soon develops hemolytic anemia as most of the hemoglobin Bart (γ_4) is replaced by hemoglobin H (β_4). In adults, their low hemoglobin A production leads to anemia that is moderate to severe and usually worsens during pregnancy.

Inheritance of all four abnormal α-globin genes causes homozygous α-thalassemia, which is also called Hb Bart disease and alpha thalassemia major. Hemoglobin Bart (γ_4) is predominantly produced. This hemoglobin Bart has an appreciably increased affinity for oxygen, transfers oxygen to end organs poorly, and is incompatible with extended survival. These fetuses are stillborn or are hydropic and usually die soon after birth.

Sonographic measurement of the fetal cardiothoracic ratio at 12 to 13 weeks' gestation can be used to identify affected fetuses (Lam, 1999; Zhen, 2015). Sonographic assessment of myocardial performance—the *Tei index*—in the first half of pregnancy has been evaluated. Changes predate hydrops in affected fetuses (Luewan, 2013). These noninvasive tests may aid pregnancy counseling.

■ Beta Thalassemias

The β-thalassemias stem from impaired β-globin production or α-globin instability. Genes that encode control of β-globin synthesis are in the δγβ-gene cluster on chromosome 11 (Chap. 7, p. 129). More than 150 point mutations in the β-globin gene have been described (Weatherall, 2010). In β-thalassemia, β-globin production is decreased, and excess α-globin precipitate to damage cell membranes. Other forms of β-thalassemias derive from α-globin instability (Kihm, 2002).

The heterozygous trait is β-thalassemia minor, and those most commonly encountered have elevated hemoglobin A_2 levels. This hemoglobin is composed of two α- and two δ-globins, and concentrations are usually more than 3.5 percent. Hemoglobin F—composed of two α- and two γ-globins—also usually has increased concentrations that exceed 2 percent. Some patients with heterozygous β-thalassemia minor do not have anemia, and others have mild to moderate anemia characterized by hypochromia and microcytosis.

Homozygous β-thalassemia—also called β-thalassemia major or Cooley anemia—is a serious and frequently fatal disorder. Hemolysis is intense and leads to severe anemia. Many patients become transfusion dependent, and the subsequent iron load, along with abnormally greater gastrointestinal iron absorption, leads to hemochromatosis, which is fatal in many cases. A heterozygous form of β-thalassemia that clinically manifests as *thalassemia intermedia* produces moderate anemia.

Several treatment schemes treat β-thalassemia. Stem cell transplantation has been used to treat β-thalassemia major (Jagannath, 2014). Preliminary observations indicate that a combination of thalidomide and hydroxyurea—both contraindicated in pregnancy—may be beneficial to boost hemoglobin

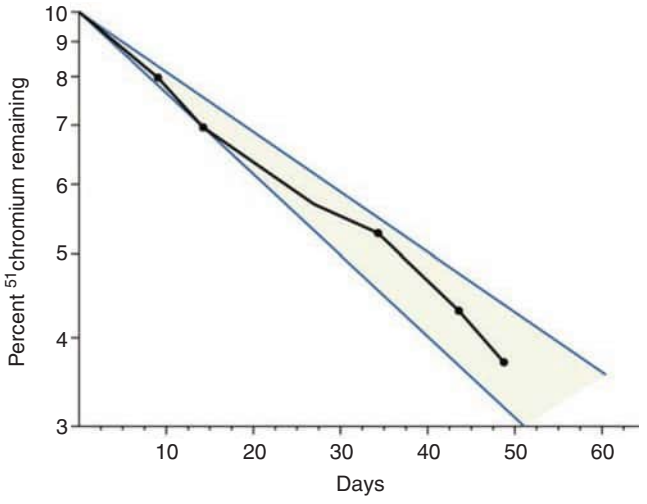

FIGURE 59-3 Erythrocyte-survival times with β-thalassemia minor (*black solid line*) are comparable to those of normal red cells (*shaded area*).

production (Shah, 2020). Inserting a gene with a lentiviral vector into β-globin has been used to transfect harvested bone marrow stem cells (Harrison, 2019). Last, luspatercept—a recombinant fusion protein—may enhance erythroid maturation to reduce transfusion requirements (Cappellini, 2020).

Pregnancy

Iron and folate supplements are given to all affected women. Those with β-thalassemia minor may have mild anemia during pregnancy (Charoenboon, 2016). This is caused by ineffective erythropoiesis and not hemolysis. Shown in Figure 59-3 are comparable red cell survival times in women with β-thalassemia minor compared with those from normally pregnant women. In some women, anemia will worsen because slightly subnormal erythropoiesis accompanies normal plasma volume expansion. Fetal-growth restriction has been associated with thalassemia minor (Vafaei, 2020).

Thalassemia major and some of the other severe forms were uncommonly encountered during pregnancy before the advent of transfusion and iron-chelation therapy. In reviews, 63 pregnancies with such management were reported and suffered no serious complications (Aessopos, 1999; Daskalakis, 1998). Pregnancy is considered reasonably safe if maternal cardiac function is normal. Transfusions are provided throughout pregnancy to maintain the hemoglobin concentration at 10 g/dL. This is coupled with surveillance of fetal growth (American College of Obstetricians and Gynecologists, 2019b).

■ Prenatal Diagnosis

Diagnosis of α-thalassemia major in the fetus can be accomplished by DNA analysis using molecular techniques (Piel, 2014). Fetal diagnosis of hemoglobin Bart (γ_4) has been described using capillary electrophoresis or high-performance liquid chromatography techniques (Sirichotiyakul, 2009). Molecular genetic testing for *HBA1* and *HBA2* identifies 90 percent of deletions and 10 percent of point mutations in affected individuals (Galanello, 2011b).

Because β-thalassemia major is caused by numerous mutations, prenatal diagnosis is difficult. For a given individual, targeted mutation analysis requires prior identification of the familial mutation. The analysis is done using chorionic villus sampling and other techniques discussed in Chapter 17 (p. 344). Noninvasive testing using cell-free fetal DNA for β-thalassemia diagnosis has been described (Xiong, 2015; Zhang, 2019). Preimplantation genetic testing allows for identification of affected offspring prior to blastocyst transfer.

PLATELET DISORDERS

■ Thrombocytopenia

Platelet abnormalities are common and may precede pregnancy, develop coincidentally during pregnancy, or be induced by pregnancy. Thrombocytopenia—defined by a platelet count <150,000/μL—is identified in nearly 10 percent of gravidas (American College of Obstetricians and Gynecologists, 2019c). Of these cases, 75 percent are *gestational thrombocytopenia.* The remainder is due to other causes, and HELLP syndrome is a common one (Eslick, 2020). Thrombocytopenia may be inherited or idiopathic, acute or chronic, and primary or associated with other disorders (Table 59-5). Of recent importance is thrombocytopenia in pregnancy complicated by COVID-19 infection (Tang, 2020; Zitiello, 2020).

■ Gestational Thrombocytopenia

In two studies of pregnant women, platelet counts falling below the 2.5th percentile were 116,000 and 123,000/μL (American

TABLE 59-5. Some Causes of Thrombocytopenia in Pregnancy

Gestational thrombocytopenia: 75 percent
Preeclampsia and HELLP syndromes: 20 percent
Obstetrical coagulopathies: DIC, MTP
Immune thrombocytopenic purpura
Systemic lupus erythematosus and APS
Infections: viral and bacterial
Drugs
Hemolytic anemias
Thrombotic microangiopathies
Malignancies
Pseudothrombocytopenia
Renal or liver diseases
Aplastic anemia
Genetic causes
COVID-19

APS = antiphospholipid syndrome; DIC = disseminated intravascular coagulopathy; HELLP = hemolysis, elevated liver enzyme levels, low platelet count; MTP = massive transfusion protocol.
From American College of Obstetricians and Gynecologists, 2019c; Cooper, 2019; Tang, 2020.

College of Obstetricians and Gynecologists, 2019c). Approximately 1 percent have values <100,000/μL. Bleeding is only encountered with drastically lower values. It seems reasonable that a platelet count of <80,000/μL should trigger an evaluation for etiologies other than incidental or gestational thrombocytopenia, which is unlikely to have a platelet count <50,000/μL.

Platelet counts decline normally across pregnancy (Fig. 4-7, p. 62). With gestational thrombocytopenia, the platelet concentration nadir is usually evident in the third trimester and is thought to stem from hemodilution. The normal increased splenic mass of pregnancy also may contribute (Maymon, 2006; Reese, 2018).

Inherited Thrombocytopenias

Bernard-Soulier syndrome and *Glanzmann thrombasthenia* lack a platelet membrane glycoprotein, which leads to severe dysfunction (Grainger, 2018). Moreover, women exposed to fetal platelets carrying this glycoprotein can develop antibodies against this fetal GPIb/IX antigen to cause alloimmune fetal thrombocytopenia (Poon, 2018). In 30 pregnancies in 18 women from one review, the primary postpartum hemorrhage rate was 33 percent, and half of women with bleeding required blood transfusion (Peitsidis, 2010). The reviewers also described six cases of neonatal alloimmune thrombocytopenia and two perinatal deaths. Close monitoring throughout pregnancy and 6 weeks postpartum is critical to avoid potential life-threatening hemorrhage (Prabu, 2006).

May-Hegglin anomaly is an autosomal dominant disorder characterized by thrombocytopenia, giant platelets, and leukocyte inclusions. In one review of 26 studies containing 75 pregnancies, there were four cases of postpartum hemorrhage, 34 cases of neonatal thrombocytopenia, and two fetal deaths (Hussein, 2013).

Immune Thrombocytopenic Purpura

The primary form—also termed *idiopathic thrombocytopenic purpura (ITP)*—is usually caused by a cluster of IgG antibodies directed against one or more platelet glycoproteins. Antibody-coated platelets are destroyed prematurely in the reticuloendothelial system, especially the spleen (Baucom, 2019; Cooper, 2019). With ITP, platelet counts range from 10,000 to 100,000/μL (George, 2014). Although not proven, ITP is probably mediated by autoantibodies directed at platelet-associated immunoglobulins—PAIgG, PAIgM, and PAIgA.

ITP classification is shown in Table 59-6 (Rodeghiero, 2009). In adults, it usually is a chronic disease that rarely resolves spontaneously. Secondary forms of immune-mediated chronic thrombocytopenia appear in association with systemic lupus erythematosus, lymphomas, leukemias, and several systemic diseases. Approximately 2 percent of thrombocytopenic patients have positive serological tests for lupus, and in some cases, levels of anticardiolipin antibodies are high. Last, approximately 10 percent of patients with human immunodeficiency virus (HIV) have associated thrombocytopenia.

TABLE 59-6. Classification of Immune Thrombocytopenia (ITP)

Etiology	
Primary ITP: acquired immune-mediated disorder characterized by isolated thrombocytopenia in the absence of obvious initiating or underlying cause	
Secondary ITP: thrombocytopenia due to underlying cause/drug exposure	
Duration	
Newly diagnosed: persistent 3–12 months	
Chronic: 12 months or more	

Pregnancy

Pregnancy does not raise the risk of relapse or worsen active disease. The estimated incidence of ITP complicating pregnancy approximates 1 case in 10,000 births (Care, 2018). However, it is not unusual for women who have been in clinical remission for several years to have recurrent thrombocytopenia during pregnancy. Although this may be from closer surveillance, hyperestrogenemia is also implicated.

Therapy is considered if the woman has symptomatic bleeding and the platelet count is below 30,000/μL. The corrected target level is 50,000/μL (American College of Obstetricians and Gynecologists, 2019c). Primary treatment is corticosteroids, intravenous immune globulin (IVIG), or both (Cooper, 2019). Initially, prednisone, 1 mg/kg daily, helps suppress the phagocytic activity of the splenic monocyte–macrophage system. IVIG given in a total dose of 2 g/kg over 2 to 5 days also is effective.

Some immunomodulating agents are avoided in pregnancy due to teratogenicity risks. Azathioprine (Imuran) and rituximab (Truxima), however, which are used in nonpregnant persons with ITP, have been used for other conditions in pregnancy. Last, the thrombopoietin-receptor agonists romiplostim (Nplate) and eltrombopag (Promacta) have stimulated responses in some patients (Patras, 2020; Rosa María, 2020).

Prospective observations from the UK Obstetric Surveillance System (UKOSS) of 107 pregnancies were described by Care and associates (2018). Postpartum hemorrhage occurred in half, and in 20 percent it was severe. No neonate needed therapy for thrombocytopenia, and no cases of intracranial hemorrhage were noted. Comont and coworkers (2018) reported on 50 pregnancies in 39 women with ITP. Half had a platelet count <50,000/μL, but 84 percent were treated. They concluded that a third of these women were overtreated.

In pregnant women with no response to corticosteroid or IVIG therapy, open or laparoscopic splenectomy may be effective. In late pregnancy, cesarean delivery may be necessary for surgical exposure. Improvement usually follows splenectomy in 1 to 3 days and peaks at approximately 8 days.

Fetal and Neonatal Effects

Pregnancy complications that are increased with ITP include stillbirth, fetal loss, and preterm birth (Wyszynski, 2016). Platelet-associated IgG antibodies cross the placenta, and fetal death from hemorrhage occurs occasionally. Studies that included more than 800 neonates born to women with ITP cite an intracranial hemorrhage rate <1 percent (American College of Obstetricians and Gynecologists, 2019c). Hemorrhage was not associated with route of delivery.

Investigators concur that fetal and maternal platelet counts lack strong correlation (George, 2009; Hachisuga, 2014). Because of this, maternal IgG free platelet antibody levels and platelet-associated antibody levels have been evaluated to predict fetal platelet counts. Again, however, little concurrence with these was found. Measuring fetal platelet counts by direct sampling is not recommended (American College Obstetricians and Gynecologists, 2019c).

Alloimmune Thrombocytopenia

Disparity between maternal and fetal platelet antigens can stimulate maternal production of antiplatelet antibodies. Such platelet alloimmunization can be severe, and its pathophysiology mirrors that caused by red cell antigens. This is discussed in Chapter 18 (p. 352).

■ Thrombocytosis

Also called *thrombocythemia*, thrombocytosis generally is defined as persistent platelet counts >450,000/μL. Common causes of *secondary* or *reactive thrombocytosis* are infection, iron deficiency, trauma, inflammatory diseases, and malignant tumors (Tefferi, 2019). Platelet counts seldom exceed 1 million/μL in these secondary disorders, and prognosis depends on the underlying disease. Instead, *primary* or *essential thrombocytosis* accounts for most cases in which platelet counts exceed 1 million/μL. It is a clonal disorder often due to an acquired mutation in the *JAK2* gene (Spivak, 2018). Thrombocytosis usually is asymptomatic, but arterial and venous thromboses may develop, and thrombosis is associated with pregnancy complications (Rabinerson, 2007; Randi, 2014). First-line treatment is aspirin and possibly hydroxyurea.

Normal pregnancies have been described in women whose mean platelet counts were >1.25 million/μL. However, in a report of 40 pregnancies in 16 women with essential thrombocythemia, almost half had a spontaneous abortion, fetal demise, or preeclampsia (Niittyvuopio, 2004). In 63 pregnancies in 36 women cared for at the Mayo Clinic, a third had a miscarriage, but other pregnancy complications were uncommon (Gangat, 2009). In this observational study, aspirin therapy was associated with a significantly lower abortion rate than that in untreated women—1 versus 75 percent, respectively. Suggested treatments during pregnancy include aspirin, low-molecular-weight heparin, and interferon α (Finazzi, 2012; Vantroyen, 2002). Interferon α therapy during pregnancy was successful in a review of 11 women. One women had transient blindness at midpregnancy when her platelet count was 2.3 million/μL (Delage, 1996).

THROMBOTIC MICROANGIOPATHIES

Although not a primary platelet disorder, some degree of thrombocytopenia accompanies the thrombotic microangiopathies, which include *thrombotic thrombocytopenic purpura (TTP)* and *hemolytic uremic syndrome (HUS).* These are characterized by thrombocytopenia, microangiopathic hemolysis, and microvascular thrombosis (Konkle, 2018). Their similarities to HELLP syndrome allude to their obstetrical ramifications.

■ Etiopathogenesis

Although different causes account for the variable findings within these syndromes, clinically, they frequently are indistinguishable. Inherited or idiopathic TTP is thought to be caused by antibodies to or a plasma deficiency of ADAMTS13 (Konkle, 2018). This endothelium-derived metalloprotease cleaves von Willebrand factor (vWF) to decrease its activity. Conversely, HUS is usually from endothelial damage incited by viral or bacterial infections and is seen primarily in children (George, 2014). Secondary thrombotic microangiopathies are the most common—94 percent (Bayer, 2019). A substantial number of all cases are pregnancy related. Other common causes are malignancies, drugs, transplantations, and autoimmune diseases. COVID-19 infection has been reported to precipitate TTP (Futterman, 2020; Makatsariya, 2020).

With TTP, intravascular platelet aggregation stimulates a cascade that leads to end-organ failure. There is endothelial activation and damage, but it is unclear whether this is a consequence or a cause. Elevated levels of unusually large multimers of vWF are identified with active TTP. Various defects in the *ADAMTS13* gene create differing clinical presentations. In another mechanism, antibodies raised against ADAMTS13 neutralize its action to cleave vWF multimers during an acute episode. The result is microthrombi of hyaline material containing platelets and fibrin within arterioles and capillaries. When sufficient in number or size, these aggregates produce ischemia or infarction.

■ Manifestations

Thrombotic microangiopathies are characterized by thrombocytopenia, fragmentation hemolysis, and organ dysfunction. TTP has the pentad of thrombocytopenia, hemolytic anemia, fever, renal impairment, and neurological abnormalities. HUS typically has more profound renal involvement and fewer neurological aberrations (Gaggl, 2018).

Thrombocytopenia is usually severe, but fortunately, even with very low platelet counts, spontaneous severe hemorrhage is uncommon. Microangiopathic hemolysis is associated with moderate to marked anemia, and erythrocyte transfusions are frequently necessary. The blood smear shows erythrocyte fragmentation and schizocytosis. Reticulocytes and nucleated red blood cells counts are increased, lactate dehydrogenase (LDH) levels are high, and haptoglobin concentrations are decreased (Konkle, 2018). Consumptive coagulopathy, although common, is usually subtle and clinically insignificant.

■ Treatment

The cornerstone of treatment for TTP is plasmapheresis with fresh-frozen plasma replacement along with glucocorticoids. Plasma exchange removes inhibitors and replaces the ADAMTS13 enzyme (George, 2014; Scully, 2019). Treatment with caplacizumab (Cablivi), the anti-vWF immunoglobulin, inhibits the interaction between ultra-large vWF multimers and platelets (Peyandi, 2016). These treatments have remarkably improved outcomes in patients with these formerly fatal syndromes. Red cell transfusions are imperative for life-threatening anemia.

Treatment is usually continued until the platelet count is normal for 2 days. Unfortunately, relapses are common. Additionally, long-term sequelae such as renal impairment can develop (Dashe, 1998; Vesely, 2015). Treatment for pregnancy-associated HUS, which is complement mediated, is eculizumab (Soliris), the anti-C5 humanized monoclonal antibody (Fakhouri, 2016; Gupta, 2020).

Pregnancy

As shown in the Appendix (p. 1228), ADAMTS13 enzyme activity declines across pregnancy by up to 50 percent (Sánchez-Luceros, 2004). Levels drop even further with preeclampsia, and especially HELLP syndrome. This is consonant with prevailing opinions that TTP is more commonly seen during pregnancy. In the Parkland Hospital experience, 11 pregnancies were complicated by these syndromes among nearly 275,000 gravidas—a frequency of 1 in 25,000 (Dashe, 1998).

Some of the disparately higher incidence in pregnancy reported by others may be from the inclusion of women with severe preeclampsia and eclampsia (Hsu, 1995; Magann, 1994). Differences that usually allow appropriate diagnosis are listed in Table 59-7. For example, moderate to severe hemolysis is a rather constant feature of thrombotic microangiopathies. This is seldom severe with preeclampsia, even when complicated by HELLP syndrome (Chap. 40, p. 699). Moreover, although hyaline microthrombi are seen in the liver with thrombotic microangiopathy, hepatocellular necrosis and elevated serum hepatic transaminase levels, which are characteristic of preeclampsia, are not a common feature (Ganesan, 2011; Sadler, 2010).

The diagnosis of thrombotic microangiopathies, rather than severe preeclampsia, should be clear before initiating therapy. Unfortunately, recall that determination of ADAMTS13 enzyme activity may be difficult to interpret with HELLP syndrome (Franchini, 2007). *Plasmapheresis is not indicated for preeclampsia-eclampsia complicated by hemolysis and thrombocytopenia.* Importantly, delivery is imperative to reverse the preeclampsia syndrome, but thrombotic microangiopathy is not improved by delivery (Dashe, 1998; Letsky, 2000).

TABLE 59-7. Some Differential Factors between HELLP Syndrome and Thrombotic Microangiopathies[a]

	HELLP Syndrome	Thrombotic Microangiopathies
Thrombocytopenia	Mild/mod.	Mod./severe
Microangiopathic hemolysis (schizocytosis)	Mild	Severe
ADAMTS13 deficiency	Mild/mod.	Severe
DIC	Mild	Mild
Transaminitis (AST, ALT)	Mod./severe	None/mild
Treatment	Delivery	Plasmapheresis

[a]Includes thrombotic thrombocytopenia purpura (TTP) and hemolytic uremic syndrome (HUS).
ADAMTS13 = ADAM metallopeptidase with thrombospondin type 1 motif, 13; AST = aspartate transaminase; ALT = alanine transaminase; DIC = disseminated intravascular coagulopathy; HELLP = hemolysis, elevated liver enzyme levels, low platelet count; Mod. = moderate.

Thrombotic microangiopathy was previously fatal in up to half of mothers. However, during the past two decades, and coincidental with plasmapheresis and plasma exchange, maternal survival rates have improved dramatically (Go, 2018; Gupta, 2020). Hunt and associates (2013) reported that TTP accounted for 1 percent of maternal deaths in the United Kingdom from 2003 to 2008. In a systematic review of 60 cases of pregnancy-associated HUS, two mothers died (Gupta, 2020).

Microangiopathic syndromes are usually recurrent and frequently unassociated with pregnancy. For example, seven of the 11 women described earlier at Parkland Hospital had recurrent disease either when not pregnant or within the first trimester of a subsequent pregnancy. George (2009) reported recurrent TTP in only five of 36 subsequent pregnancies. In 17 women with nonpregnant atypical HUS, recurrence developed in five of 32 pregnancies.

Long-term Prognosis

Women who are diagnosed with thrombotic microangiopathy during pregnancy are at risk for serious long-term complications (Gaggl, 2018; George, 2018). The relapse rate is as high as 40 percent in nonpregnant patients (Konkle, 2018). The described Parkland experience included a mean 9-year surveillance period (Dashe, 1998). These women had multiple recurrences; renal disease requiring dialysis, transplantation, or both; severe chronic hypertension; and transfusion-acquired infection. Two women died remote from pregnancy—one from dialysis complications and one from transfusion-acquired HIV infection. In the review by Gupta (2020) cited earlier, 15 percent of mothers with atypical HUS had long-term renal failure. In 19 women with primary atypical HUS, eight progressed to end-stage renal disease (Timmermans, 2020).

INHERITED COAGULATION DEFECTS

Hemophilias A and B

Obstetrical hemorrhage may infrequently be the consequence of an inherited defect in a protein that controls coagulation (Majluf-Cruz, 2020). Hemophilia and von Willebrand disease are examples.

Hemophilia A is an X-linked recessively transmitted disorder characterized by a marked deficiency of factor VIII. Severity reflects plasma factor levels and is categorized as mild—levels of 6 to 30 percent; moderate—2 to 5 percent; or severe—less than 1 percent (Arruda, 2015). It is rare among women compared with men, in whom the heterozygous state is responsible for the disease. Heterozygous women have diminished factor VIII levels, but almost invariably, the homozygous state is requisite for hemophilia A. In a few instances, it appears in

women spontaneously from a newly mutated gene. Pregnancy-associated acquired hemophilia A from antibodies may result in severe bleeding-related morbidity (Tengborn, 2012). *Christmas disease* or *hemophilia B* is caused by severe deficiency of factor IX and has similar genetic and clinical features.

Pregnancy

The risk of obstetrical bleeding with hemophilia is directly related to factor VIII or IX levels. Affected women have a range of activity that is determined by random X-chromosome inactivation—lyonization—although activity is expected to average 50 percent (Letsky, 2000). Levels below 10 to 20 percent pose hemorrhage risks. If levels fall to near zero, this risk is substantial. Pregnancy does afford some protection, however, because concentrations of both these clotting factors rise appreciably during normal pregnancy (Appendix, p. 1228). Treatment with desmopressin can stimulate factor VIII release. Risks are further reduced by avoiding lacerations, minimizing episiotomy use, and maximizing postpartum uterine contractions. Operative vaginal delivery and cesarean delivery pose bleeding risks.

A few articles describe pregnancy courses. Kadir and colleagues (1997) reported that 20 percent of carriers had postpartum hemorrhage. Guy and associates (1992) reviewed five pregnancies in women with hemophilia B, and in all, outcomes were favorable. They recommended factor IX administration if levels are below 10 percent. Desmopressin in selected cases has reduced obstetrical bleeding complications (Trigg, 2012). If a male fetus has hemophilia, the risk of hemorrhage increases after delivery in the neonate. This is especially true if circumcision is attempted.

Related to preconceptional counseling, most women with hemophilia A or B carry one affected allele and the other X chromosome is normal. These individuals will have all sons affected by the disease, and half of her daughters will be carriers. Rarely, a woman may carry two abnormal alleles, in which case all daughters will be carriers and all of her sons will inherit the disease. Prenatal diagnosis of hemophilia is possible in some families using chorionic villus biopsy (Chap. 17, p. 346). Preimplantation genetic testing for hemophilia was reviewed by Lavery (2009).

Factor VIII or IX Inhibitors

Rarely, antibodies directed against factor VIII or IX are acquired and may lead to life-threatening hemorrhage. Patients with hemophilia more commonly develop antibodies, and their acquisition in patients without hemophilia is extraordinary. It has been identified rarely in women during the puerperium (Santoro, 2009). The prominent clinical feature is severe, protracted, repetitive hemorrhage from the reproductive tract starting a week or so after an apparently uncomplicated delivery (Gibson, 2016). The activated partial thromboplastin time is markedly prolonged. Treatment has included multiple blood-component transfusions, immunosuppressive therapy, and attempts at various surgical procedures, especially curettage and hysterectomy. A recombinant activated factor VII (NovoSeven) stops bleeding in up to 75 percent of patients with these inhibitors (Arruda, 2015; Gibson, 2016).

Von Willebrand Disease

At least 20 heterogeneous clinical disorders involve aberrations of factor VIII complex and platelet dysfunction and collectively are termed *von Willebrand disease (vWD)*. These abnormalities are the most frequently inherited bleeding disorders, and their prevalence is as high as 1 to 2 percent (Arruda, 2015; Punt, 2020). Most von Willebrand disease variants are inherited as autosomal dominant traits. Types I and II are the most common, and type I accounts for 75 percent. Type III, which is the most severe, is a recessive trait. Although most cases of acquired vWD develop after age 50 years, some have been reported in pregnant women (Lipkind, 2005).

Pathogenesis

The *von Willebrand factor (vWF)* is a series of large, plasma multimeric glycoproteins that form part of the factor VIII complex. It is essential for normal platelet adhesion to subendothelial collagen and formation of a primary hemostatic plug. It also plays a major role in stabilizing the coagulant properties of factor VIII. Factor VIII, a glycoprotein, is synthesized by the liver. The von Willebrand precursor, which is present in platelets and plasma, is instead synthesized by endothelium and megakaryocytes. The von Willebrand factor antigen (vWF:Ag) is the antigenic determinant measured by immunoassays.

Symptomatic women typically present with easy bruising, epistaxis, mucosal hemorrhage, heavy menses, and excessive bleeding with trauma or surgery. The classic autosomal dominant forms usually cause symptoms in the heterozygous state. With vWD, laboratory features often include a prolonged bleeding time, prolonged partial thromboplastin time, decreased vWF antigen levels, decreased factor VIII immunological and coagulation-promoting activity, and inability of platelets from an affected person to react to various stimuli.

Although most patients with vWD have heterozygous variants and associated minor bleeding complications, the disease can be severe. Moreover, homozygous offspring develop serious clotting dysfunction. Chorionic villus sampling with DNA analysis to detect the missing genes has been described, but the specific genetic mutation must be known. Some authorities recommend cesarean delivery to avoid trauma to a possibly affected fetus if the mother has severe disease.

Pregnancy

During normal pregnancy, maternal levels of both factor VIII and vWF antigen increase substantively (Appendix, p. 1228). Because of this, pregnant women with vWD often develop normal levels of factor VIII coagulant activity and vWF antigen, although their measured bleeding time still may be prolonged (Delbrück, 2019). If factor VIII activity is very low or if there is bleeding, treatment is recommended. Desmopressin by infusion transiently increases factor VIII and vWF levels (Arruda, 2015). With significant bleeding, 15 or 20 units of cryoprecipitate are transfused every 12 hours. Alternatively, factor VIII concentrates (Alphanate, Humate-P) that contain high-molecular-weight vWF multimers may be given. Lubetsky and colleagues (1999) described continuous infusion with Humate-P in a woman during a vaginal delivery. According to Chi and

coworkers (2009), conduction analgesia can be provided safely if coagulation defects have corrected or if hemostatic agents are administered prophylactically.

Pregnancy outcomes in women with vWD are generally good, but postpartum hemorrhage is common. In one systematic review, with more than 800 deliveries, the postpartum hemorrhage incidence was 33 percent (Punt, 2020). In a database review of more than 2200 deliveries complicated by vWD, this incidence was only about 5 percent (O'Brien, 2020). From two reviews, postpartum hemorrhage may be primary and at the time of delivery, or it may have a delayed onset (Makhamreh, 2021a,b).

■ Other Factor Deficiencies

In general, the activity of most procoagulant factors rises across pregnancy (Appendix, p. 1228). *Factor VII deficiency* is a rare autosomal recessive disorder. Levels of this factor increase during normal pregnancy, but these may rise only mildly in women with factor VII deficiency (Fadel, 1989). A systematic review of 94 births found no difference in postpartum hemorrhage rates with or without prophylaxis with recombinant factor VIIa (Baumann Kreuziger, 2013).

Factor X or *Stuart-Prower factor* deficiency is rare and inherited as an autosomal recessive trait. Factor X levels typically rise by 50 percent during normal pregnancy. Despite this, adverse pregnancy outcome are common. Spiliopoulos and coworkers (2019) reported 31 pregnancies in 19 women. They described a high rate of preterm birth, perinatal mortality, and postpartum hemorrhage. Conversely, Nance and colleagues (2012) described 24 pregnancies, of which 18 resulted in a healthy baby. Treatment is with plasma-derived factor X, fresh-frozen plasma, or prothrombin complex concentrates.

Factor XI deficiency is inherited as an autosomal recessive trait in most families. It manifests as severe disease in homozygotes but only as a minor defect in heterozygotes. It is most prevalent in Ashkenazi Jews and is rarely seen in pregnancy. In one review of 105 pregnancies from 33 affected women, 70 percent had an uneventful pregnancy and delivery (Myers, 2007). Authors recommended peripartum treatment with factor XI concentrate for cesarean delivery and advised against epidural analgesia unless factor XI is given. From another review, factor XI levels and bleeding severity correlated poorly in women with severe deficiency (Martin-Salces, 2010). Wiewel-Verschueren and associates (2016) performed a systematic review of 27 studies with 372 women and reported that 18 percent had postpartum hemorrhage.

Factor XII deficiency is another autosomal recessive disorder that rarely complicates pregnancy. A greater incidence of thromboembolism is encountered in nonpregnant patients with this deficiency.

Factor XIII deficiency is an autosomal recessive trait and may be associated with maternal intracranial hemorrhage (Bouttefroy, 2020). In their review, Kadir and associates (2009) cited an increased risk of recurrent miscarriage and placental abruption. It has also been reported to cause umbilical cord bleeding (Odame, 2014). Treatment is fresh frozen plasma. Naderi and colleagues (2012) described 17 successful pregnancies in women receiving weekly prophylaxis with factor XIII concentrate.

Fibrinogen abnormalities—either qualitative or quantitative—also may cause coagulation abnormalities. Autosomally inherited abnormalities usually involve the formation of a functionally defective fibrinogen—commonly referred to as *dysfibrinogenemia*. Familial *hypofibrinogenemia* and sometimes *afibrinogenemia* are infrequent recessive disorders. Our experience suggests that hypofibrinogenemia represents a heterozygous autosomal dominant state. The thrombin-clottable protein level in these patients typically ranges from 80 to 110 mg/dL when nonpregnant. Cai and coworkers (2018) described successful outcomes in affected women in whom fibrinogen or plasma infusions were given throughout pregnancy.

THROMBOPHILIAS

Several important regulatory proteins act as inhibitors at strategic sites in the coagulation cascade to maintain blood fluidity. Inherited deficiencies of these inhibitory proteins are caused by gene mutations. Because they may be associated with recurrent thromboembolism, they are collectively referred to as *thrombophilias.* These are discussed in Chapter 55 (p. 976) and reviewed by the American College of Obstetricians and Gynecologists (2020).

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CHAPTER 60

Diabetes Mellitus

According to the Centers for Disease Control and Prevention (2020), nearly 27 million adults in the United States have been diagnosed with diabetes. Another 7.3 million are suspected to be undiagnosed, and an estimated 88 million have prediabetes. Reasons for these substantial rates include an aging population, which is more likely to develop type 2 diabetes; population growth within minority groups at particular risk for type 2 diabetes; and a dramatic rise in obesity rates. In 2019, almost three in 10 women were considered obese prior to becoming pregnant (Driscoll, 2020). The strong relationship between diabetes and the current obesity epidemic in the United States underlines the critical need for diet and lifestyle interventions to change the trajectory of both.

TYPES OF DIABETES

In nonpregnant individuals, the type of diabetes is based on its presumed pathogenesis and its manifestations. Absolute insulin deficiency, which generally is autoimmune in etiology, characterizes *type 1 diabetes*. In contrast, insulin resistance, relative insulin deficiency, or elevated glucose production characterizes *type 2 diabetes* (Table 60-1). Both types are generally preceded by a period of abnormal glucose homeostasis often referred to as prediabetes. Pancreatic β-cell destruction can begin at any age, but type 1 diabetes is clinically apparent most often before age 30. Type 2 diabetes usually develops with advancing age but is increasingly identified in younger obese adolescents. Etiological overlap in diabetes subtypes is well established and has led to the proposal of a single classification system centered on β-cell function along with the concept of individualized treatment strategies (World Health Organization, 2020). Other forms of diabetes include *maturity-onset diabetes of the young (MODY)*. The more common MODY type is in obese adolescents (TODAY Study Group, 2021). The less common form is an autosomal dominant condition and characterized by mild diabetes diagnosed in adolescence or young adulthood (Udler, 2020).

Classification During Pregnancy

Diabetes is the most common medical complication of pregnancy. Women can be separated into those diagnosed with diabetes before pregnancy—*pregestational* or *overt diabetes*, and those diagnosed during pregnancy—*gestational diabetes*.

The proportion of pregnancies complicated by diabetes more than doubled between 1994 and 2008, after which rates have leveled (Deputy, 2018; Jovanovič, 2015). In 2018, 7.6 percent of pregnant women in this country had some form of diabetes (Martin, 2019). Prevalence is highest among non-Hispanic

TABLE 60-1. Etiological Classification of Diabetes Mellitus

Type 1: β-Cell destruction, usually absolute insulin deficiency
Immune-mediated
Idiopathic

Type 2: Ranges from predominantly insulin resistance to predominantly an insulin secretory defect with insulin resistance

Other types
Genetic mutations of β-cell function: MODY 1–6, others
Genetic defects in insulin action
Genetic syndromes: Down, Klinefelter, Turner, others
Diseases of the exocrine pancreas: pancreatitis, cystic fibrosis
Endocrinopathies: Cushing syndrome, pheochromocytoma, others
Drug or chemical induced: glucocorticosteroids, thiazides, β-adrenergic agonists, others
Congenital infections: rubella, cytomegalovirus, coxsackievirus

Gestational diabetes (GDM)

MODY = maturity-onset diabetes of the young.
Adapted from American Diabetes Association, 2020; Powers, 2018.

blacks, Mexican-Americans, Puerto Rican-Americans, and Native Americans (Powers, 2018).

White Classification

Until the mid-1990s, the classification system of Priscilla White (1978) for diabetic pregnant women was the linchpin of management. Today, the White classification is used less often but still provides simple, useful information on pregnancy risks and prognosis (Bennett, 2015). Because most currently cited literature also contains data from these older classifications, the one previously recommended by the American College of Obstetricians and Gynecologists (1986) is shown in Table 60-2.

The American College of Obstetricians and Gynecologists (2019a) no longer recommends the White classification. The current focus is whether diabetes *antedates* pregnancy or is first diagnosed *during* pregnancy. Many now recommend the system proposed by the American Diabetes Association (Table 60-3).

PREGESTATIONAL DIABETES

Considering the previously mentioned high percentage of undiagnosed diabetes, many women identified with gestational diabetes likely have previously unrecognized type 2 diabetes. Indeed, 5 to 10 percent of women with gestational diabetes are diagnosed with overt diabetes immediately after pregnancy.

Diagnosis

Women with high plasma glucose levels, glucosuria, and ketoacidosis present no diagnostic challenge. Women with a random plasma glucose level >200 mg/dL plus classic signs and symptoms such as polydipsia, polyuria, and unexplained weight loss, those with a fasting glucose level >125 mg/dL, or those with a first-trimester glycosylated hemoglobin (HbA_{1c}) level of ≥6.5 percent are considered by the American Diabetes Association

TABLE 60-2. Modified White Classification Scheme Used from 1986 Through 1994 for Diabetes Complicating Pregnancy

		Plasma Glucose Level		
Class	**Onset**	**Fasting**	**2-Hour Postprandial**	**Therapy**
A_1	Gestational	<105 mg/dL	<120 mg/dL	Diet
A_2	Gestational	>105 mg/dL	>120 mg/dL	Insulin
Class	**Age of Onset (yr)**	**Duration (yr)**	**Vascular Disease**	**Therapy**
B	Over 20	<10	None	Insulin
C	10 to 19	10 to 19	None	Insulin
D	Before 10	>20	Benign retinopathy	Insulin
F	Any	Any	Nephropathy[a]	Insulin
R	Any	Any	Proliferative retinopathy	Insulin
H	Any	Any	Heart	Insulin

[a]When diagnosed during pregnancy: proteinuria ≥500 mg/24 hr before 20 weeks' gestation.

TABLE 60-3. Proposed Classification System for Diabetes in Pregnancy

Gestational diabetes: diabetes diagnosed during pregnancy that is not clearly overt (type 1 or type 2) diabetes

Type 1 Diabetes:
Diabetes resulting from β-cell destruction, usually leading to absolute insulin deficiency
a. Without vascular complications
b. With vascular complications (specify which)

Type 2 Diabetes:
Diabetes from inadequate insulin secretion in the face of increased insulin resistance
a. Without vascular complications
b. With vascular complications (specify which)

Other types of diabetes: genetic in origin, associated with pancreatic disease, drug-induced, or chemically induced

Data from American Diabetes Association, 2017a; Powers, 2018.

(2019) and the World Health Organization (2019) to have overt diabetes first detected in pregnancy.

Women with only minimal metabolic derangement may be more difficult to identify. To diagnose overt diabetes in pregnancy, the International Association of Diabetes and Pregnancy Study Groups (IADPSG) Consensus Panel (2010) recognizes the threshold values found in Table 60-4 for fasting or random plasma glucose and HbA_{1c} levels at prenatal care initiation. The American Diabetes Association (2020) and the World Health Organization (2019) now also consider a plasma glucose level >200 mg/dL measured 2 hours after a 75-g oral glucose load to be diagnostic. No consensus has been reached as to whether such testing should be universal or limited to those women classified as high risk.

Regardless, a presumed diagnosis of overt diabetes in pregnancy based on these thresholds should be confirmed postpartum. Risk factors for impaired carbohydrate metabolism in pregnant women include a strong familial history of diabetes, prior delivery of a large newborn, persistent glucosuria, or unexplained fetal losses.

Harm in Pregnancy

With overt diabetes, the embryo, fetus, and mother frequently experience serious complications directly attributable to diabetes (Egan, 2020). Many of these complications might be prevented each year by preconceptional care for improved glycemic control (Peterson, 2015). Using HbA_{1c} values as objective risk quartiles, Finneran and Kiefer (2020) reported that glycemic control throughout pregnancy and a late-pregnancy HbA_{1c} level <6.5 percent leads to reduced rates of adverse obstetrical and neonatal outcomes. The likelihood of successful outcomes with overt diabetes, however, is not simply related to glucose control. The degree of underlying cardiovascular or renal disease may be more important. Thus, advancing stages of the White classification, seen in Table 60-2, are inversely related to favorable pregnancy outcomes. Shown in Table 60-5 are data that chronicle the adverse pregnancy outcomes with overt diabetes, and many are described next (Battarbee, 2020b).

Fetal Effects

Spontaneous Abortion

Up to 25 percent of overtly diabetic mothers have an early miscarriage, and poor glycemic control is an associated factor. In one study, those whose HbA_{1c} concentrations were >12 percent or whose preprandial glucose concentrations persisted above 120 mg/dL had an elevated miscarriage risk (Galindo, 2006). In a large Chinese population-based study, those with a history of diabetes had an increased risk of miscarriage, and the risk rose 8 percent for each 20-mg/dL incremental rise in fasting glucose (Wei, 2019). In 89 pregnancies in women with the monogenic form of MODY, only women with the causative *glucose kinase (GCK)* mutation were more likely to miscarry (Bacon, 2015). Another analysis of 128 GCK-MODY pregnancies showed that the observed miscarriage rate was comparable to the background rate (Dickson, 2019). These women have hyperglycemic variability that can be difficult to control.

Preterm Delivery

Overt diabetes is an undisputed risk factor for preterm birth. In an analysis of more than 500,000 pregnancies in Ontario,

TABLE 60-4. Diagnosis of Overt Diabetes in Pregnancy[a]

Measure of Glycemia	Threshold
Fasting plasma glucose	At least 7.0 mmol/L (126 mg/dL)
Hemoglobin A_{1c}	At least 6.5%
Random plasma glucose	At least 11.1 mmol/L (200 mg/dL) plus confirmation

[a]Apply to women without known diabetes antedating pregnancy. The decision to perform blood testing for evaluation of glycemia on all pregnant women or only on women with characteristics indicating a high risk for diabetes is based on the background frequency of abnormal glucose metabolism in the population and on local circumstances.
Data from International Association of Diabetes and Pregnancy Study Groups Consensus Panel, 2010.

TABLE 60-5. Selected Maternal and Perinatal Outcomes in Percent in Women with Gestational and Overt Diabetes Compared with Nondiabetic Women[a]

Factor	Normal 182,464[b] (%)	GDM 10,549[b] (%)	Overt DM 2993[b] (%)
Maternal			
Chronic HTN	1.5	5.0	11.5
Renal disease	0.5	0.6	2.7
Gestational HTN	8.0	12.9	22.9
Chorioamnionitis	4.1	4.0	5.2
Cesarean birth	42	59	69
Neonatal			
RDS	3.8	4.7	11.0
Ventilation	2.8	3.1	7.0
NICU admit	12.8	19.8	41.9
Macrosomia	7.7	18.1	29.9
Death[c]	0.2	0.1	0.4

[a]Unless specified, all comparisons $p < 0.001$.
[b]Number of women in group.
[c]$p < 0.05$.
DM = diabetes mellitus; GDM = gestational diabetes mellitus; HTN = hypertension; NICU = neonatal intensive care unit; RDS = respiratory distress syndrome.

almost 20 percent of women with diabetes were delivered preterm compared with 5.6 percent of women without diabetes, obesity, or hypertension (Berger, 2020). More than 60 percent were indicated preterm births, that is, due to obstetrical or medical complications. Notably, more than 37 percent of women with diabetes and chronic hypertension delivered preterm. In a review of California births, 19 percent of women with pregestational diabetes delivered before 37 weeks' gestation compared with 9 percent of controls (Yanit, 2012). In a study from the United Kingdom, the preterm delivery rate was 42 percent for 8690 type 1 diabetic women and 3 percent for those with type 2 diabetes (Murphy, 2021).

Malformations

The incidence of major malformations in fetuses of women with type 1 diabetes approximates 11 percent and is at least double the rate in fetuses of nondiabetic mothers (Jovanovič, 2015). This risk is present for all women with pregestational diabetes, including those with type 2 disease (Tinker, 2020). Congenital anomalies constitute almost half of perinatal deaths in diabetic pregnancies.

Cardiovascular malformations account for more than half of the anomalies, and Table 60-6 lists selected malformations reported by the National Birth Defects Prevention Study (Tinker, 2020). In a study of more than 2 million births in Canada, the risk of an isolated cardiac defect was fivefold higher in women with type 1 diabetes compared with nondiabetic mothers (Liu, 2013). The *caudal regression sequence*, described in Chapter 15 (p. 280), is a rare malformation that, according to the National Birth Defects Prevention Study, is 80 times more likely in women with pregestational diabetes.

TABLE 60-6. Selected Congenital Malformations in Pregnancies Complicated by Overt Diabetes

Birth Defect	OR (95% CI)
Cardiovascular	
Fallot tetralogy	5.3 (3.5–8.0)
AV septal defect	10.5 (6.2–17.9)
Aortic coarctation	4.5 (2.8–7.1)
Neural-tube defect	
Anencephaly	3.5 (1.9–6.4)
Encephalocoele	5.4 (2.5–11.7)
Hydrocephaly	8.2 (5.0–13.5)
Cleft palate	4.3 (2.9–6.5)
Esophageal	3.4 (1.9–6.1)
Hypospadias	2.8 (1.7–4.8)
Renal	8.1 (3.9–16.9)
Sacral agenesis	80.2 (46.1–139.3)

CI = confidence interval; OR = odds ratio.

Poorly controlled diabetes, both preconceptionally and early in pregnancy, is thought to underlie this elevated risk for major malformation. In one study of mothers with type 1 diabetes, a periconceptional HbA_{1c} <6.5 percent carried a twofold risk for a fetal major cardiac defect, and a HbA_{1c} >9 percent carried a sixfold risk (Ludvigsson, 2018). Others cite similar frequencies (Murphy, 2021). Figure 60-1 shows the association between HbA_{1c} levels and fetal congenital malformation rates in a Parkland Hospital cohort of women with overt diabetes (Martin, 2021).

The etiological mechanisms that explain this link include excess production of toxic superoxide radicals, altered cell signaling pathways, upregulation of some genes by hyperglycemia, and

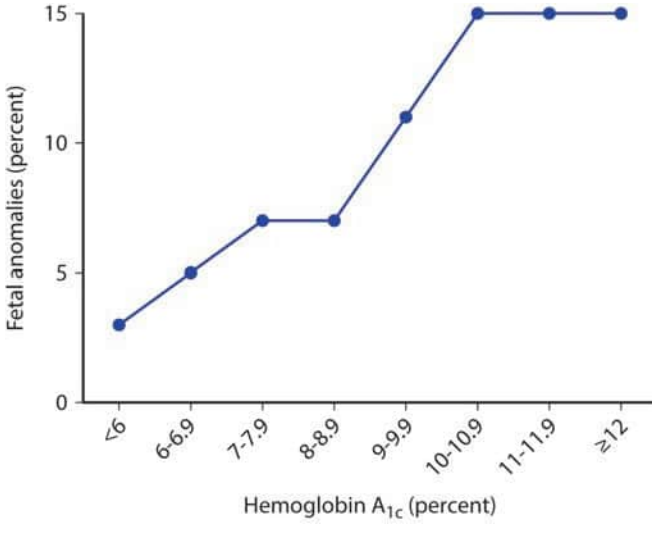

FIGURE 60-1 Association between fetal malformation rates and HbA_{1c} values determined at initiation of prenatal care in 1573 pregnancies in women with pregestational diabetes.

activation of programmed cell death (Basu, 2018; Reece, 2012). One review of potential molecular mechanisms suggests that cellular responses to oxidative stress represent possible therapeutic targets to prevent diabetes-induced embryopathy (Yang, 2015).

Altered Fetal Growth

Diminished fetal growth may result from congenital malformations or from substrate deprivation due to advanced maternal vascular disease. That said, fetal overgrowth is more typical of pregestational diabetes. Maternal hyperglycemia prompts fetal hyperinsulinemia, and this in turn stimulates excessive somatic growth. Except for the brain, most fetal organs are affected by the macrosomia that characterizes the fetus of diabetic women. Newborns are described as anthropometrically different from other large-for-gestational age (LGA) neonates (Catalano, 2003; Durnwald, 2004). Specifically, those whose mothers are diabetic have excessive fat deposition on the shoulders and trunk, which predisposes to shoulder dystocia or fetopelvic disproportion (Fig. 60-2).

The incidence of macrosomia rises significantly when mean maternal blood glucose concentrations chronically exceed 130 mg/dL (Hay, 2012). In addition, the overall birthweight distribution of neonates of diabetic mothers is skewed toward consistently heavier birthweights. In one sonographic study, the macrosomia rates for Nordic women with type 1, type 2, or gestational diabetes were 35, 28, and 24 percent, respectively (Hammoud, 2013). Moreover, the abdominal circumference grew disproportionately larger in the diabetic groups. Analysis of head circumference/abdominal circumference (HC/AC) ratios shows that this disproportionate growth occurs mainly in diabetic pregnancies that ultimately yield macrosomic newborns.

Unexplained Fetal Demise

The risk of fetal death is three to four times higher in women with pregestational diabetes (Gardosi, 2013; Patel, 2015). In the United Kingdom study of more than 17,000 pregnancies in women with pregestational diabetes, the stillbirth incidence was similar in those with type 1 or type 2 diabetes—10.4 versus 13.5 per 1000 live and stillbirths, respectively (Murphy, 2021). Stillbirth without an identifiable cause is a phenomenon relatively limited to pregnancies complicated by overt diabetes. These stillbirths are "unexplained" because common factors such as obvious placental insufficiency, placental abruption, fetal-growth restriction, or oligohydramnios are not identified. These fetuses are typically LGA and die before labor, usually later in the third trimester.

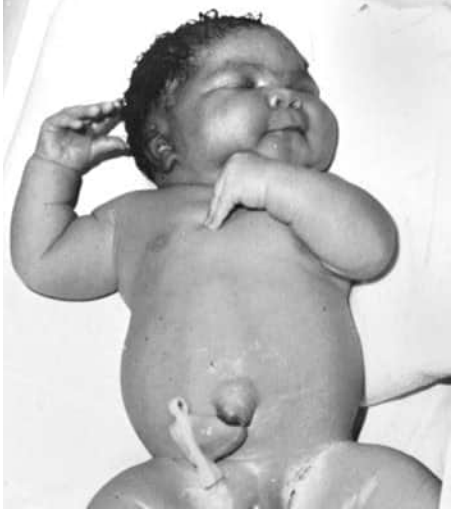

FIGURE 60-2 This 6050-g macrosomic neonate was born to a woman with gestational diabetes.

These unexplained stillbirths are usually associated with poor glycemic control. In one study, suboptimal glycemic control was identified in two thirds of unexplained stillbirths between 1990 and 2000 (Lauenborg, 2003). Fetuses of diabetic mothers also often have elevated lactic acid levels. Salvesen and colleagues (1992, 1993) analyzed fetal blood samples and reported that mean umbilical venous blood pH was lower in diabetic pregnancies and was significantly related to fetal insulin levels. These findings support a hypothesis that hyperglycemic-mediated chronic aberrations in oxygen and fetal metabolite transport may underlie these unexplained fetal deaths (Pedersen, 1977).

Maternal ketoacidosis also can cause fetal death (Bryant, 2017). Moreover, stillbirths from placental insufficiency occur with increased frequency in women with overt diabetes and are usually associated with severe preeclampsia. In the prior cited California study, the fetal death risk was sevenfold higher in women with hypertension and pregestational diabetes compared with the threefold increased risk associated with diabetes alone (Yanit, 2012). Stillbirth rates are also elevated in women with advanced diabetes and vascular complications.

Hydramnios

Diabetic pregnancies are often complicated by excess amnionic fluid. In one sonographic study, 18 percent of 314 pregnancies complicated by pregestational diabetes were found to have hydramnios in the third trimester, which was defined as an amnionic fluid index (AFI) >24 cm. Women with elevated HbA_{1c} values in the third trimester were more likely to have hydramnios (Idris, 2010). In a similar study, poor maternal glucose control was associated with macrosomia and hydramnios (Vink, 2006). A likely—albeit unproven—explanation is that fetal hyperglycemia causes fetal polyuria (Chap. 14, p. 256). In a study from Parkland Hospital, Dashe and coworkers (2000) found that the AFI parallels the amnionic fluid glucose level among women with diabetes.

Neonatal Effects

Before tests of fetal health and maturity became available, delivery before term was deliberately selected for women with diabetes to avoid unexplained stillbirth. Although this practice has been largely abandoned, a higher frequency of preterm delivery in women with diabetes persists. One analysis of early-term delivery ($37^{0/7}$ to $38^{6/7}$ weeks) showed a 13-percent reduction in such deliveries in women with diabetes between 2005 and 2011 (Little, 2015). Most indicated deliveries are prompted by advanced diabetes with superimposed preeclampsia.

Although modern neonatal care has reduced neonatal death rates due to immaturity, neonatal *morbidity* due to preterm birth continues to be a serious consequence. In one Neonatal Research Network study of 10,781 extremely preterm neonates, those born to diabetic women treated with insulin prior

to pregnancy were at greater risk for necrotizing enterocolitis and late-onset sepsis than similarly aged neonates of mothers without diabetes (Boghossian, 2016).

Respiratory Distress Syndrome

Gestational age rather than overt diabetes is likely the most significant factor associated with respiratory distress syndrome (Chap. 34, p. 615). Indeed, in one analysis of 19,399 very-low-birthweight neonates delivered between 24 and 33 weeks' gestation, rates of respiratory distress syndrome in newborns of diabetic mothers were not higher compared with rates in neonates of nondiabetic mothers (Bental, 2011). Diabetes does not appear to alter the beneficial effects of antenatal corticosteroids to hasten lung maturity (Battarbee, 2020a).

Hypoglycemia and Hypocalcemia

Newborns of a diabetic mother experience a rapid drop in plasma glucose concentration after delivery. This is attributed to the hyperplasia of fetal β-islet cells that is induced by chronic maternal hyperglycemia. Low glucose concentrations—defined as <45 mg/dL—are particularly common in newborns of women with unstable glucose concentrations during labor (van Kempen, 2020). Preliminary observations showed that early-term fetuses exposed to antenatal corticosteroids have a high rate of hypoglycemia (Gupta, 2020). Frequent blood glucose measurements in the newborn and active early feeding practices can mitigate this complication.

Hypocalcemia is defined as a total serum calcium concentration <8 mg/dL in term newborns. Early-onset hypocalcemia is one of the potential metabolic derangements in neonates of diabetic mothers. Its cause is unclear. Theories include altered magnesium–calcium economy, asphyxia, and preterm birth. In one randomized study, 137 pregnant women with type 1 diabetes were managed with strict versus customary glucose control (DeMarini, 1994). Almost a third of neonates in the customary control group developed hypocalcemia compared with only 18 percent of those in the strict-control group.

Hyperbilirubinemia and Polycythemia

The pathogenesis of hyperbilirubinemia in neonates of diabetic mothers is uncertain. A major contributing factor is newborn polycythemia, which raises the bilirubin load (Chap. 33, p. 606). Polycythemia is thought to be a fetal response to relative hypoxia. According to Hay (2012), the sources of this fetal hypoxia are hyperglycemia-mediated elevations in maternal affinity for oxygen and fetal oxygen consumption. Together with insulin-like growth factors, this hypoxia leads to elevated fetal erythropoietin levels and red cell production.

Cardiomyopathy

Newborns of pregestational and gestational diabetic pregnancies frequently have hypertrophic cardiomyopathy. This remodeling can be associated with cardiac dysfunction (Aguilera, 2020; Depla, 2021). Huang and coworkers (2013) propose that pathological ventricular hypertrophy in neonates born to women with diabetes is due to insulin excess. In severe cases, this cardiomyopathy may lead to obstructive cardiac failure. In one study, the fetuses of 26 women with pregestational diabetes underwent serial echocardiographic evaluation. In the first trimester, fetal diastolic dysfunction was already evident in some. In the third trimester, the fetal interventricular septum and right ventricular wall were thicker in fetuses of diabetic mothers (Russell, 2008). Others report similar observations (Aguilera, 2020). Most affected newborns are asymptomatic following birth, and hypertrophy usually resolves in the months after delivery. Any long-term adverse sequelae remain to be determined (Depla, 2021).

Long-term Cognitive Development

Intrauterine metabolic conditions are linked to neurodevelopment in offspring. In a study of more than 700,000 Swedish men, the intelligence quotient of those whose mothers had diabetes during pregnancy averaged 1 to 2 points lower (Fraser, 2014). DeBoer and associates (2005) demonstrated impaired memory performance at age 1 year in infants of diabetic mothers. Results from the Childhood Autism Risks from Genetics and the Environment (CHARGE) study indicated that autism spectrum disorders or developmental delay also were more common in children of diabetic women (Krakowiak, 2012). Adane and colleagues (2016) confirmed a consistent relationship between maternal diabetes and diminished cognitive and language development in studies of younger children but not older children. Because interpreting effects of the intrauterine environment on neurodevelopment is confounded by postnatal factors, the link between maternal diabetes, glycemic control, and long-term neurocognitive outcome remains unconfirmed.

Inheritance

The risk of developing type 1 diabetes if either parent is affected is 3 to 5 percent. Type 2 diabetes has a much stronger genetic component. If both parents have type 2 diabetes, the risk of their offspring developing it approaches 40 percent (Powers, 2018). Both types of diabetes develop after a complex interplay between genetic predisposition and environmental factors. Type 1 diabetes is prompted by environmental triggers such as infection, diet, or toxins and is heralded by the appearance of islet-cell autoantibodies in genetically vulnerable people (Pociot, 2016).

■ Maternal Effects

Diabetes and pregnancy can interact to an extent that maternal welfare can be jeopardized. With the possible exception of diabetic retinopathy, however, the long-term course of diabetes does not appear to be affected by pregnancy.

In one analysis of more than 800,000 pregnancies, the 1125 mothers with type 1 diabetes had greater risks for hypertension and respiratory complications than nondiabetic gravidas (Jovanovič, 2015). The 10,126 mothers with type 2 diabetes had an elevated risk for hypertension, infection, depression, and cardiac or respiratory complications compared with nondiabetic gravidas.

Maternal death is uncommon, but rates in women with diabetes are still higher than those in unaffected gravidas. In one analysis of 972 women with type 1 diabetes, the maternal mortality rate was 0.5 percent. Deaths stemmed from diabetic ketoacidosis, hypoglycemia, hypertension, and infection (Leinonen, 2001).

Preeclampsia

Pregnancy-associated hypertension is the complication that most often forces preterm delivery in diabetic women. The incidence of chronic and gestational hypertension—and especially preeclampsia—is remarkably increased (Chap. 40, p. 690). In one metaanalysis of 92 studies, women with pregestational diabetes had a nearly fourfold higher pooled relative risk for preeclampsia (Bartsch, 2016). In the prior cited California study, preeclampsia developed three to four times more often in women with overt diabetes. Moreover, those diabetics with coexistent chronic hypertension were almost 12 times more likely to develop preeclampsia (Yanit, 2012).

Women with type 1 diabetes in more advanced White classes typically exhibit preexisting vascular complications and nephropathy. These women are more likely to develop preeclampsia (Fig. 60-3). This rising risk may be related to oxidative stress, which plays a key role in the pathogenesis of diabetic complications and preeclampsia. With this in mind, the Diabetes and Preeclampsia Intervention Trial (DAPIT) randomly assigned 762 women with type 1 diabetes to antioxidant vitamin C and E supplementation or placebo in the first half of pregnancy (McCance, 2010). Preeclampsia rates were not improved except in the few with a low antioxidant status at baseline.

Preventively, low-dose aspirin prophylaxis is recommended in women at high risk of preeclampsia, which includes those with type 1 or type 2 diabetes (Chap. 40, p. 705). An 81-mg oral daily dose is initiated between 12 and 28 weeks' gestation and is continued until delivery (American College of Obstetricians and Gynecologists, 2020a).

Diabetic Nephropathy

Diabetes is the leading cause of end-stage renal disease in the United States (Chap. 56, p. 1003). Clinically detectable nephropathy begins with microalbuminuria, recognized as 30 to 300 mg of protein in a 24-hour urine collection specimen. This may manifest as early as 5 years after diabetes onset. Macroalbuminuria—more than 300 mg in a 24-hour collection specimen—develops in patients destined to have end-stage renal disease. Hypertension almost invariably develops during this period, and renal failure ensues typically in the next 5 to 10 years. The incidence of overt proteinuria is nearly 30 percent in individuals with type 1 diabetes and ranges from 4 to 20 percent in those with type 2 diabetes (Reutens, 2013). Regression is common, presumably from improved glucose control.

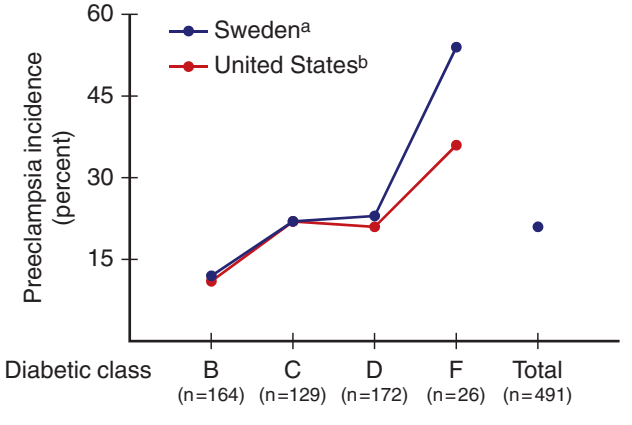

FIGURE 60-3 Incidence of preeclampsia in 491 women with type 1 diabetes stratefied by diabetic class in Sweden and the United States. (Data from Hanson[a], 1993; Sibai[b], 2000.)

Approximately 5 percent of gravidas with overt diabetes already have renal involvement (American College of Obstetricians and Gynecologists, 2020c). As many as 40 percent of these will develop preeclampsia (Vidaeff, 2008). In addition, Ambia and associates (2020) reported that the rates of preterm delivery, preeclampsia, and fetal-growth restriction were significantly higher in diabetic women with proteinuria >300 mg/d compared with rates in diabetic gravidas whose 24-hour protein excretion was <300 mg/d.

In general, pregnancy does not appear to worsen diabetic nephropathy. In one prospective study of 43 women with diabetes, diabetic nephropathy did not progress through 12 months after delivery (Young, 2012). Most of these women had only mild renal impairment. Conversely, pregnant women with moderate to severe renal impairment may have accelerated progression of their disease (Vidaeff, 2008). As in women with glomerulopathies, hypertension or substantial proteinuria before or during pregnancy is a major predictive factor for ultimate progression to renal failure in women with diabetic nephropathy.

Diabetic Retinopathy

Retinal vasculopathy is a highly specific complication of both type 1 and type 2 diabetes. In the United States, diabetic retinopathy is the most important cause of visual impairment in working-aged adults. The first and most common visible lesions are small microaneurysms followed by blot hemorrhages that form when erythrocytes escape from the aneurysms. These areas leak serous fluid that creates hard exudates. Such features are termed *background* or *nonproliferative retinopathy*.

With increasingly severe retinopathy, the abnormal vessels of background eye disease become occluded. This leads to retinal ischemia and infarctions that appear as *cotton wool exudates.* These are considered *preproliferative retinopathy.* In response to ischemia, neovascularization begins on the retinal surface and out into the vitreous cavity. Vision is obscured when these vessels bleed. Laser photocoagulation before hemorrhage reduces the rate of visual loss progression and blindness by half. The procedure may be performed during pregnancy when indicated.

In one study of nearly 500 pregnancies in women with type 1 diabetes, a third had prepregnancy retinopathy and 16 percent of these showed worsening (Bourry, 2021). Almost 25 percent of those without prepregnancy retinopathy developed disease during pregnancy. Fortunately, development of sight-threatening retinopathy was rare, and only 4 percent of patients followed postpartum had progression of disease.

Another group of investigators evaluated 80 women with type 2 diabetes and identified retinopathy, mostly mild, in 14 percent during early pregnancy (Rasmussen, 2010). Progression was identified in 14 percent.

Other risk factors that have been associated with progression of retinopathy include hypertension, higher levels of insulin-like growth factor 1, placental growth factor, and macular edema identified in early pregnancy (Huang, 2015; Vestgaard, 2010). The American Academy of Ophthalmology (2019)

recommends that pregnant women with overt diabetes should be offered retinal assessment after the first prenatal visit. Subsequent eye examinations depend on severity of retinopathy and level of glucose control. Currently, most agree that laser photocoagulation and good glycemic control during pregnancy minimize the potential for deleterious effects of pregnancy.

Ironically, "acute" rigorous metabolic control during pregnancy has been linked to acute worsening of retinopathy. In a study of 201 women with retinopathy, almost 30 percent suffered eye disease progression during pregnancy despite intensive glucose control (McElvy, 2001). That said, Wang and coworkers (1993) observed that although retinopathy worsened during the critical months of rigorous glucose control, long-term progression of eye disease actually slowed.

Diabetic Neuropathy

Peripheral, symmetrical sensorimotor diabetic neuropathy is uncommon in pregnant women. However, one form of this, *diabetic gastropathy*, can be troublesome during pregnancy. It causes nausea and vomiting, nutritional problems, and difficult glucose control. Affected women are advised that this complication is associated with a high risk of morbidity and poor perinatal outcome (Kitzmiller, 2008). Treatment with metoclopramide and dopamine D2 receptor antagonists is sometimes successful. Gastric neurostimulators have shown success during pregnancy (Fuglsang, 2015). Treatment of *hyperemesis gravidarum* can be challenging, and we routinely provide insulin initially by continuous infusion for diabetic women who are admitted with this condition (Chap. 57, p. 1015).

Diabetic Ketoacidosis

This serious complication develops in approximately 1 percent of diabetic pregnancies and is most often encountered in women with type 1 diabetes (Ehrmann, 2020). It is increasingly being reported in women with type 2 or even those with gestational diabetes (Bryant, 2017; Sibai, 2014). Diabetic ketoacidosis (DKA) may develop with hyperemesis gravidarum, infection, insulin noncompliance, insulin pump failures, β-mimetic drugs given for tocolysis, and corticosteroids given to induce fetal lung maturation. DKA results from an insulin deficiency combined with an excess in counter-regulatory hormones such as glucagon. This leads to gluconeogenesis and ketone body formation. The ketone body β-hydroxybutyrate is synthesized at a much greater rate than acetoacetate, which is preferentially detected by commonly used ketosis-detection methods. Thus, serum or plasma assays for β-hydroxybutyrate more accurately reflect true ketone body levels.

The maternal mortality rate with DKA is <1 percent, but perinatal mortality rates associated with a single episode of DKA may reach 35 percent (Bryant, 2017; Guntupalli, 2015). Noncompliance is a prominent factor, and this and DKA were historically considered prognostically bad signs in pregnancy (Pedersen, 1974). Importantly, pregnant women usually develop DKA at lower blood glucose thresholds than when nonpregnant. In a study from Parkland Hospital, the mean glucose level for pregnant women with DKA was 380 mg/dL, and the mean HbA_{1C} value was 10 percent (Bryant, 2017). Euglycemic ketoacidosis during pregnancy also is possible but is rare (Sibai, 2014; Smati, 2020).

One management protocol for diabetic ketoacidosis is shown in Table 60-7. An important cornerstone of management is

TABLE 60-7. Management of Diabetic Ketoacidosis During Pregnancy

Laboratory Assessment
Obtain arterial blood gases to document degree of acidosis present; measure glucose, creatinine, ketones, and electrolyte levels at 1- to 2-hour intervals
Insulin
Low-dose, intravenous Loading dose: 0.2–0.4 U/kg Maintenance: 2–10 U/hr
Fluids
Isotonic sodium chloride for 3L, then 0.45% saline Total replacement in first 12 hours of 4–6 L 1 L in first hour 500–1000 mL/hr for 2–4 hours 250 mL/hr until 80 percent replaced
Glucose
Begin 5-percent dextrose in 0.45% saline when glucose plasma level reaches 250 mg/dL (14 mmol/L)
Potassium
If initially normal or reduced, an infusion rate up to 15–20 mEq/hr may be required; if elevated, wait until levels decrease into the normal range, then add to intravenous solution in a concentration of 20–30 mEq/L
Bicarbonate
Add one ampule (44 mEq) to 1 L of 0.45 normal saline if serum pH is <7.1

Data from Bryant, 2017; Powers, 2018; Sibai, 2014.

vigorous rehydration with crystalloid solutions of normal saline or Ringer lactate.

Infections

The rates of many infections are higher in diabetic pregnant women. Common ones include candidal vulvovaginitis, bacterial urinary and respiratory tract infections, and puerperal pelvic sepsis. However, in one study of more than 1250 diabetic gravidas screened before 16 weeks' gestation, rates of bacterial vaginosis or vaginal colonization with *Candida* or *Trichomonas* species were not increased (Marschalek, 2016).

In one population-based study of almost 200,000 pregnancies, the risk of asymptomatic bacteriuria in women with diabetes was increased twofold (Sheiner, 2009). Another study found positive urine culture results in 25 percent of diabetic women (Alvarez, 2010). In a 2-year analysis of pyelonephritis in pregnant women at Parkland Hospital, 5 percent with diabetes developed pyelonephritis compared with 1.3 percent without diabetes (Hill, 2005). Rates of urinary tract infections can be minimized by screening and eradicating asymptomatic bacteriuria (Chap. 56, p. 995).

Last, Johnston and colleagues (2017) reported that 16.5 percent of women with pregestational diabetes had postoperative wound complications following cesarean delivery. Prevention options are described in Chapter 30 (p. 550).

Preconceptional Care

Because of the close relationship between pregnancy complications and maternal glycemic control, efforts to achieve glucose targets are typically more aggressive during pregnancy. Unfortunately, nearly half of pregnancies in the United States are unplanned, and diabetic women frequently begin pregnancy with suboptimal glucose control (Finer, 2016; Kim, 2005). Management preferably should begin before pregnancy and then include specific goals during each trimester.

To minimize early pregnancy loss and congenital malformations, the National Preconception Health and Healthcare Initiative Clinical Workgroup established values for optimal glycemic control before conception (Frayne, 2016). This was defined as a HbA_{1c} level <6.5 percent in women with pregestational diabetes. The American Diabetes Association (2017b) has also defined optimal preconceptional glucose control in those using insulin. Reflective values are self-monitored preprandial glucose levels of 70 to 100 mg/dL, peak 2-hour postprandial values of 100 to 120 mg/dL, and mean daily glucose concentrations <110 mg/dL.

In one prospective population-based study of 933 pregnant women with type 1 diabetes, the risk of congenital malformations was not demonstrably higher with HbA_{1c} levels <6.9 percent compared with the risk in more than 70,000 nondiabetic gravidas (Jensen, 2010). However, a substantial fourfold greater risk for malformations was found for HbA_{1c} levels >10 percent (see Fig. 60-1). Another study found fewer adverse outcomes with improved HbA_{1c} values from conception to midpregnancy (Davidson, 2020).

If indicated, evaluation and treatment for diabetic complications such as retinopathy or nephropathy should be instituted before pregnancy. Last, folate, 400 μg/d orally, is given periconceptionally and during early pregnancy to decrease the risk of neural-tube defects (Egan, 2020).

First-trimester Care

Careful monitoring of glucose control is essential. For this reason, we routinely hospitalize women with overt diabetes during early pregnancy to initiate an individualized glucose control program and provide education. This also affords an opportunity to assess the extent of diabetic vascular complications and precisely establish gestational age. The checklist provided by the Society for Maternal-Fetal Medicine (2020) is helpful. Some initial evaluations done at Parkland Hospital include assessment of 24-hour urine protein excretion and serum creatinine level, retinal examination, and echocardiogram if chronic hypertension is comorbid.

First-trimester screening for aneuploidy may include measurement of maternal serum pregnancy-associated plasma protein A (PAPP-A), β-human chorionic gonadotropin (hCG), and ultrasound measurement of fetal nuchal translucency (Chap. 17, p. 333). Noninvasive prenatal testing with cell-free DNA also is suitable. Although initially thought not to be different in women with pregestational diabetes, one analysis of more than 100 insulin-treated women identified reductions in median PAPP-A and β-hCG levels compared with gravidas without diabetes (Gurram, 2014). Not surprisingly, they detected no difference in nuchal translucency measurements. When calculating aneuploidy risks in women with diabetes, these differences should be considered.

Insulin Treatment

The gravida with overt diabetes is best treated with insulin. Although oral hypoglycemic agents have been used successfully for gestational diabetes (p. 1083), these agents are not currently recommended for overt diabetes, despite some controversy (American College of Obstetricians and Gynecologists, 2020c). In an international, placebo-controlled trial including 502 insulin-treated women with type 2 diabetes, adjunctive metformin therapy was associated with improved glycemic control, reduced maternal weight gain, lower cesarean delivery rate, and less neonatal adiposity (Feig, 2020). Importantly, the proportion of small-for-gestational age newborns was higher in the insulin plus metformin group, but the rate of composite serious neonatal outcomes was not increased compared with those receiving insulin plus placebo.

Maternal glycemic control can usually be achieved with multiple daily insulin injections and adjustment of dietary intake. Table 60-8 lists the action profiles of common short- and long-acting insulins (Powers, 2018). Subcutaneous insulin infusion by a calibrated pump does not yield better pregnancy outcomes compared with multiple daily injections. However, an infusion pump is a safe alternative in appropriately selected patients (Farrar, 2016). With the advent of sensor-augmented insulin pumps and closed-loop insulin delivery systems, improved glycemic control with either manual or computer-generated insulin adjustments based on continuous glucose monitoring is now possible (Bergenstal, 2021; Stewart, 2016). In one study of insulin pump use in women with type 1 diabetes, total daily insulin doses declined in the first trimester but later rose more than threefold. Postprandial glucose elevations prompted most of the required daily-dose increases (Roeder, 2012). If a

TABLE 60-8. Action Profiles of Commonly Used Insulins

Insulin Type	Onset	Peak (hr)	Duration (hr)
Short-acting (SC)			
Lispro	<15 min	0.5–1.5	2–4
Glulisine	<15 min	0.5–1.5	2–4
Aspart	<15 min	0.5–1.5	2–4
Regular (SC)	30–60 min	2–3	3–6
Regular inhaled	30–60 min	2–3	3
Long-acting (SC)			
Degludec	1–9 hr	—	<12
Detemir	1–4 hr	Minimal[a]	12–24
Glargine	1–4 hr	Minimal[a]	20–24
NPH	1–4 hr	4–10	10–16

[a]Minimal peak activity.
NPH = neutral protamine Hagedorn; SC = subcutaneous.

continuous-infusion insulin pump is elected, initiation prepregnancy may help avoid hypoglycemia and ketoacidosis risks associated with the device's learning curve (Sibai, 2014).

Monitoring

Self-monitoring of capillary glucose levels using a glucometer is recommended because this involves the woman in her own care (Dong, 2020). The American Diabetes Association (2017b) recommends fasting and postprandial glucose monitoring, and Table 60-9 lists glucose goals recommended in pregnancy. Currently not standard care, one study showed that longitudinal HbA_{1c} values could be used for risk stratification (Finneran, 2020). Advances in noninvasive glucose monitoring will undoubtedly render intermittent capillary glucose monitoring obsolete. Subcutaneous continuous glucose monitoring devices have shown that pregnant women with diabetes experience significant periods of daytime hyperglycemia and nocturnal hypoglycemia that are undetected by traditional monitoring (Combs, 2012). Such glucose monitoring systems, coupled with a continuous insulin pump, offer the potential of an "artificial pancreas" to avoid hypo- or hyperglycemia during pregnancy (Bergenstal, 2021).

Diet

Nutritional planning includes appropriate weight gain through carbohydrate and caloric modifications based on height, weight, and degree of glucose intolerance (American Diabetes Association, 2017b; Egan, 2020). The mix of carbohydrate, protein, and fat is adjusted to meet the metabolic goals and individual patient preferences. A minimum of 175 g/d of carbohydrates ideally is provided. In one analysis of more than 200 obese pregnant women with glucose intolerance, a lower carbohydrate intake, particularly late in pregnancy, was associated with lower fat mass in offspring at birth (Renault, 2015). Allotted carbohydrates are distributed throughout the day in three small- to moderate-sized meals and two to four snacks. Weight loss is not recommended, but modest caloric restriction may be appropriate for overweight or obese women. An ideal dietary composition is 55 percent carbohydrate, 20 percent protein, and 25 percent fat, of which <10 percent is saturated fat.

TABLE 60-9. Self-Monitored Capillary Blood Glucose Goals

Specimen	Level (mg/dL)
Fasting	≤95
Premeal	≤100
1-hr postprandial	≤140
2-hr postprandial	≤120
0200–0600	≥60
Mean (average)	100
Hemoglobin A_{1c}	≤6%

Hypoglycemia

Diabetic control can be unstable in the first half of pregnancy, and the incidence of hypoglycemia peaks during the first trimester. One study found hypoglycemic events—blood glucose values <40 mg/dL—in 37 of 60 women with type 1 diabetes. A fourth of these were considered severe because the women were unable to treat their own symptoms and required assistance from another person (Chen, 2007). *Caution is recommended when attempting to achieve euglycemia in women with recurrent episodes of hypoglycemia.*

From one Cochrane database review, loose glycemic control, defined as fasting glucose values >120 mg/dL, was associated with greater risks for preeclampsia, cesarean delivery, and birthweight >90th percentile compared with women with tight or moderate control (Middleton, 2016). With *very* tight control, defined by fasting values <90 mg/dL, no obvious benefits were gained, but the number of cases of hypoglycemia increased.

■ Second-trimester Care

Maternal serum alpha-fetoprotein determination at 16 to 20 weeks' gestation is used in association with targeted sonographic examination to detect neural-tube defects and other anomalies (Chap. 17, p. 338). These serum levels may be lower in diabetic pregnancies, and interpretation is altered accordingly. Because the incidence of congenital cardiac anomalies shown in Table 60-6 is increased fivefold in mothers with diabetes, fetal echocardiography is an important part of second-trimester sonographic evaluation (Society for Maternal-Fetal Medicine, 2020). Dashe and coworkers (2009) cautioned that detection of fetal anomalies in obese diabetic women is more difficult than in similarly sized women without diabetes.

Regarding second-trimester glucose control, normoglycemia with self-monitoring continues to be the goal. After the first trimester's glucose instability, a stable period ensues. This is then followed by higher insulin requirements. These stem from the enhanced peripheral resistance to insulin that is related to pregnancy and is described in Chapter 4 (p. 57).

Although most women with pregestational diabetes require a higher total daily insulin dose with advancing gestational age, a small proportion will experience a reduction in their daily dose later in pregnancy. The significance of this drop remains uncertain. One Australian study evaluated women with falling

insulin requirements (FIR), defined as a ≥15 percent drop in the peak total daily insulin dose after 20 weeks' gestation (Padmanabhan, 2017). In 158 women with type 1 and type 2 diabetes and FIR, the risk for a composite of adverse outcomes indicative of placental insufficiency was fourfold greater than in those without FIR. The composite primary outcome included preeclampsia, fetal-growth disorders, delivery before 30 weeks' gestation, placental abruption, and fetal death before 20 weeks. FIR was more common in women with type 1 diabetes.

Third-trimester Care and Delivery

During the past several decades, the threat of late-pregnancy stillbirth in women with diabetes prompted recommendations for various fetal surveillance programs beginning in the third trimester. Such protocols include fetal movement counting, periodic fetal heart rate monitoring, intermittent biophysical profile evaluation, and contraction stress testing (Chap. 20, p. 384). None of these techniques has been subjected to prospective randomized clinical trials, and their primary value seems related to their low false-negative rates. The American College of Obstetricians and Gynecologists (2020c, 2021) suggests initiating such testing at 32 to 34 weeks' gestation. With reassuring testing and no other complications, delivery is anticipated between $39^{0/7}$ and $39^{6/7}$ weeks.

At Parkland Hospital, women with diabetes are seen in a specialized Maternal–Fetal Medicine clinic every 2 weeks. During these visits, glycemic control records are evaluated, and insulin doses are adjusted. Women are routinely instructed to perform fetal kick counts beginning early in the third trimester. At 34 weeks' gestation, admission to our High-Risk Pregnancy Unit is offered to all insulin-treated women. Approximately half of these women choose admission. While in the hospital, they continue daily fetal movement counts and undergo fetal heart rate monitoring three times a week. With no other complications, delivery at Parkland is typically planned for 38 weeks.

At the University of Alabama at Birmingham, weekly antenatal testing is initiated no later than 34 weeks' gestation. Twice-weekly testing is reserved for those with poorly controlled diabetes or supervening medical or obstetrical complications. Delivery is planned for 39 weeks' gestation in those with good glycemic control and reassuring antenatal testing. Earlier delivery is planned for those with poor glycemic control or significant comorbidities.

For vaginal delivery, labor induction may be attempted when the fetus is not excessively large and the cervix is considered favorable (Chap. 26, p. 486). Cesarean delivery at or near term has frequently been used to avoid the traumatic birth of a large fetus in a woman with diabetes. In women with more advanced diabetes, especially those with vascular disease, the reduced likelihood of successful labor induction remote from term has also contributed to an increased cesarean delivery rate.

In an analysis of pregnancy outcomes of diabetic women from University of Alabama at Birmingham according to the White classification, the rates of cesarean delivery and preeclampsia escalated with White class (Bennett, 2015). In another study, a HbA_{1c} level >6.4 percent at delivery was independently associated with urgent cesarean delivery (Miailhe, 2013). This suggests that tighter glycemic control during the third trimester might reduce late fetal compromise and cesarean delivery for fetal indications. Many of these women have undergone prior cesarean delivery. Somewhat related to this, the cesarean delivery rate for women with overt diabetes has remained at approximately 80 percent for the past 40 years at Parkland Hospital.

Reducing or withholding the dose of long-acting insulin on the day of delivery is recommended. Regular insulin should be used to meet most or all of the insulin needs of the mother during this time, because insulin requirements typically drop markedly after delivery. During labor, continuous insulin infusion by calibrated intravenous pump is most satisfactory (Table 60-10). The woman should be adequately hydrated intravenously and given glucose in sufficient amounts to maintain euglycemia. Capillary or plasma glucose levels are checked hourly during active labor, and regular insulin is administered accordingly.

Puerperium

Often, many diabetic women may require virtually no insulin for the first 24 hours or more postpartum. Subsequently, insulin requirements may fluctuate markedly during the next few days. Infection must be promptly detected and treated. When appropriate, oral agents can be restarted. For type 2 diabetic women who will be transitioned to oral agents, this can be done on postoperative day 1.

Counseling in the puerperium should include a discussion of birth control. Effective contraception is especially important in women with overt diabetes to allow optimal glucose control before subsequent conception (Chap. 38, p. 664).

GESTATIONAL DIABETES

In the United States in 2016, almost 6 percent of pregnancies were complicated by gestational diabetes (Deputy, 2018). Worldwide, its prevalence differs according to race, ethnicity, age, and body composition and by screening and diagnostic criteria. As discussed in the following sections, several persisting controversies pertain to the diagnosis and treatment of gestational diabetes.

TABLE 60-10. Insulin Management for Labor Induction or Scheduled Cesarean Delivery

Give evening dose insulin.
Withhold morning dose.
Infuse intravenous normal saline at 100–125 mL/hr.
Regular insulin is infused at 1–1.25 units/hr if glucose levels >100 mg/dL.
Measure glucose levels hourly.
With active labor or if glucose levels are >70 mg/dL, change from intravenous saline to 5% dextrose given at 100–150 mL/hr with a target glucose level of ~100mg/dL.

The word *gestational* implies that diabetes is induced by pregnancy—ostensibly because of exaggerated physiological changes in glucose metabolism (Chap. 4, p. 57). Gestational diabetes is defined as carbohydrate intolerance of variable severity with its onset or first recognition during pregnancy (American College of Obstetricians and Gynecologists, 2019a). This definition applies whether or not insulin is used for treatment and undoubtedly includes some women with previously unrecognized overt diabetes.

The term *gestational diabetes* aims to communicate the need for enhanced surveillance during pregnancy and to stimulate further testing postpartum. The most important perinatal correlate is excessive fetal growth, which may result in both maternal and fetal birth trauma. The likelihood of fetal death with appropriately treated gestational diabetes is not different from that in the general population. More than half of women with gestational diabetes ultimately develop overt diabetes in the ensuing 20 years. Moreover, mounting evidence implicates long-range complications that include obesity and diabetes in their offspring.

Screening and Diagnosis

Despite almost 50 years of research, there is still no agreement on the optimal screening method for gestational diabetes. The difficulty in achieving consensus is underscored by the controversy following publication of the single-step approach shown in Table 60-11, which assesses the glucose values following a 75-g oral glucose load. This strategy is espoused by the International Association of Diabetes and Pregnancy Study Groups Consensus Panel (2010) and was greatly influenced by results of the Hypoglycemia and Pregnancy Outcomes (HAPO) study, described subsequently. Although the American Diabetes Association (2019) supports this new scheme, the American College of Obstetricians and Gynecologists (2019a) continues to recommend a two-step approach to screen and then diagnose gestational diabetes. Similarly, the National Institutes of Health (NIH) Consensus Development Conference in 2013 concluded that evidence is insufficient to adopt a one-step approach.

The recommended two-step approach begins with either universal or risk-based selective screening using a 50-g, 1-hour oral glucose challenge test. Participants in the Fifth International Workshop Conferences on Gestational Diabetes endorsed use of *selective screening* criteria shown in Table 60-12 (Metzger, 1998).

TABLE 60-11. Threshold Values for Diagnosis of Gestational Diabetes with 75-g OGTT

Plasma Glucose	Glucose Concentration Threshold[a]		Above Threshold (%)
	mmol/L	mg/dL	Cumulative
Fasting	5.1	92	8.3
1-hr OGTT	10.0	180	14.0
2-hr OGTT	8.5	153	16.1[b]

[a]One or more of these values from a 75-g OGTT must be equaled or exceeded for the diagnosis of gestational diabetes.
[b]In addition, 1.7% of participants in the initial cohort were unblinded because of fasting plasma glucose levels >5.8 mmol/L (105 mg/dL) or 2-hr OGTT values >11.1 mmol/L (200 mg/dL), bringing the total to 17.8%.
OGTT = oral glucose tolerance test.

TABLE 60-12. Risk-Based Recommended Screening Strategy for Detecting GDM[a]

GDM risk assessment: should be ascertained at the first prenatal visit

Low Risk: Blood glucose testing not routinely required if all the following are present:
- Member of an ethnic group with a low prevalence of GDM
- No known diabetes in first-degree relatives
- Age <25 years
- Weight normal before pregnancy
- Weight normal at birth
- No history of abnormal glucose metabolism
- No history of poor obstetrical outcome

Average Risk: Perform blood glucose testing at 24 to 28 weeks using either:
- Two-step procedure: 50-g oral glucose challenge test (GCT), followed by a diagnostic 100-g OGTT for those meeting the threshold value in the GCT
- One-step procedure: diagnostic 100-g OGTT performed on all subjects

High Risk: Perform blood glucose testing as soon as feasible, using the procedures described above, if one or more of these are present:
- Severe obesity
- Strong family history of type 2 diabetes
- Previous history of GDM, impaired glucose metabolism, or glucosuria
- If GDM is not diagnosed, blood glucose testing should be repeated at 24 to 28 weeks' gestation or at any time symptoms or signs suggest hyperglycemia

[a]Criteria of the Fifth International Workshop-Conference on Gestational Diabetes.
GDM = gestational diabetes mellitus; OGTT = oral glucose tolerance test.

Conversely, the American College of Obstetricians and Gynecologists (2019a) recommends *universal screening* of pregnant women with a protocol that provides a 50-g oral glucose load and that is followed in 1 hour by a laboratory-based blood glucose test. It is suggested that attempts to identify the minority of women who should *not* be screened would add unnecessary complexity. Screening should be performed between 24 and 28 weeks' gestation in those women not known to have glucose intolerance earlier in pregnancy. This *50-g screening test* is followed by a *diagnostic 100-g, 3-hour oral glucose tolerance test (OGTT)* if screening results meet or exceed a predetermined plasma glucose concentration.

For the 50-g screening test, the plasma glucose level is measured 1 hour after a 50-g oral glucose load without regard to the time of day or time of last meal. In an earlier review, the pooled sensitivity for a threshold of 140 mg/dL ranged from 74 to 83 percent depending on 100-g thresholds used for diagnosis (van Leeuwen, 2012). Sensitivity estimates for a 50-g screen threshold of 135 mg/dL improved only slightly to 78 to 85 percent, but specificity dropped from a range of 72 to 85 percent for 140 mg/dL to 65 to 81 percent. Using a threshold of 130 mg/dL marginally improves sensitivity with a further decline in specificity (Donovan, 2013). In the absence of clear evidence supporting one cutoff value over another, the American College of Obstetricians and Gynecologists (2019a) sanctions using any one of these three 50-g screen thresholds. At Parkland Hospital, we continue to use 140 mg/dL as the screening threshold to prompt the 100-g test. The threshold used at the University of Alabama at Birmingham is 135 mg/dL.

Justification for screening and treatment of women with gestational diabetes was strengthened by a randomized treatment trial in 1000 women (Crowther, 2005). Women diagnosed with gestational diabetes after a 75-g OGTT and assigned to receive dietary advice with blood glucose monitoring plus insulin therapy were compared with a cohort assigned to usual prenatal care. The former group had a significantly lower risk of a composite perinatal adverse outcome that included death, shoulder dystocia, bone fracture, and nerve palsy. Macrosomia defined by birthweight ≥4000 g complicated 10 percent of deliveries in the intervention group compared with 21 percent in the routine prenatal care group. Cesarean delivery rates were almost identical in the two study groups.

Slightly different results were reported by the Maternal–Fetal Medicine Units Network randomized trial of 958 women identified with mild gestational diabetes using a two-step screening and diagnosis approach (Landon, 2009). They reported no differences in rates of composite morbidity that included stillbirth, birth trauma, and neonatal hypoglycemia, hyperinsulinemia, and hyperbilirubinemia. Secondary analyses did demonstrate a 50-percent reduction in macrosomia, fewer cesarean deliveries, and a significant decrease in shoulder dystocia rate—1.5 versus 4 percent—in treated versus routine care groups.

Based largely on these two landmark studies, the U.S. Preventive Services Task Force (2021) recommends universal screening in low-risk women after 24 weeks' gestation. However, the Task Force concluded that evidence is insufficient to assess the balance of benefits versus harms of screening before 24 weeks. Earlier screening in obese women did not result in better outcomes (Harper, 2020).

TABLE 60-13. Diagnosis of Gestational Diabetes Mellitus Using Threshold Glucose Values from 100-g Oral Glucose Tolerance Test[a,b]

	NDDG[c]		Carpenter–Coustan[d]	
Time	(mg/dL)	(mmol/L)	(mg/dL)	(mmol/L)
Fasting	105	5.8	95	5.3
1-hr	190	10.6	180	10.0
2-hr	165	9.2	155	8.6
3-hr	145	8.0	140	7.8

[a]The test should be performed when the patient is fasting.
[b]Two or more of the venous plasma glucose concentrations listed are met or exceeded for a positive diagnosis.
[c]Serum glucose level.
[d]Serum or plasma glucose level.
NDDG = National Diabetes Data Group.
Data from American College of Obstetricians and Gynecologists, 2019a; American Diabetes Association, 2019; Ferrara, 2002.

The optimal OGTT to identify gestational diabetes also is debated. Proposed criteria for interpretation of the diagnostic 100-g OGTT are shown in Table 60-13. Criteria for the 75-g OGTT are shown in Table 60-11. A secondary analysis of the Maternal-Fetal Medicine Units Network treatment trial showed that women diagnosed with either the National Diabetes Data Group (NDDG) or the Carpenter-Coustan criteria benefited from treatment (Harper, 2016). However, the number needed to treat to prevent a shoulder dystocia was higher for the Carpenter-Coustan criteria. Others report similar observations (Ghaffari, 2020). At Parkland Hospital, we use the NDDG criteria for diagnosis, whereas Carpenter-Coustan criteria are preferred at the University of Alabama at Birmingham.

Controversies of Screening and Diagnosis

The HAPO study was a 7-year international epidemiological study of 23,325 pregnant women at 15 centers in nine countries analyzing the association of various levels of glucose intolerance during the third trimester with adverse perinatal outcomes (HAPO Study Cooperative Research Group, 2008). Blood glucose levels were stratified into seven categories (Fig. 60-4). These values were then correlated with rates for birthweight >90th percentile, primary cesarean delivery, neonatal hypoglycemia, and cord serum C-peptide levels >90th percentile. Cord serum C-peptide is secreted in equimolar concentrations with insulin and reflects fetal β-islet cell function. Findings generally supported the supposition that increasing plasma glucose levels were associated with increasing adverse outcomes.

The International Association of Diabetes and Pregnancy Study Group

This workshop conference in 2008 concerned the diagnosis and classification of gestational diabetes. After reviewing the results of the HAPO study, a panel developed recommendations for the diagnosis and classification of hyperglycemia during pregnancy.

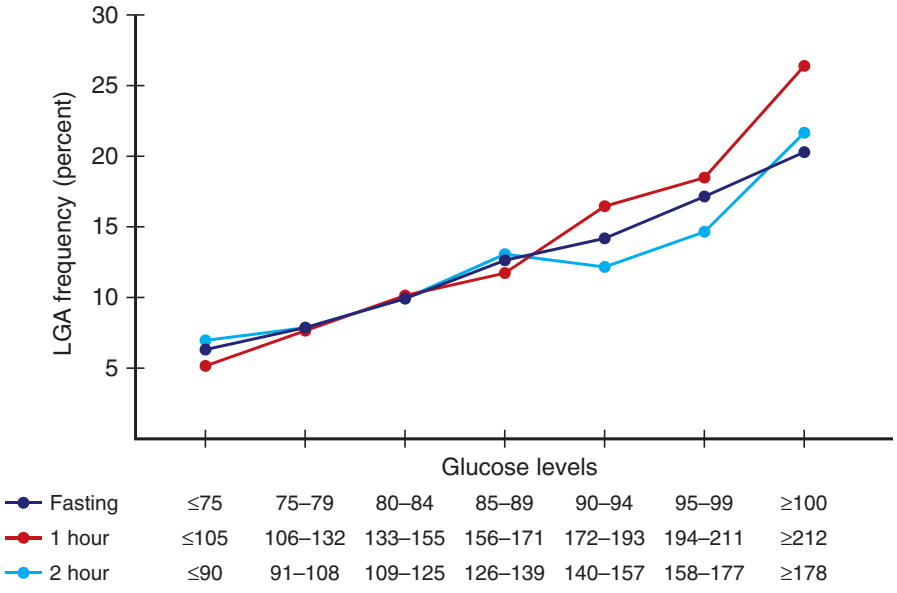

FIGURE 60-4 Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Study. The frequency of newborn birthweight ≥90th percentile for gestational age plotted against glucose levels fasting and at 1- and 2-hr intervals following a 75-g oral glucose load. LGA = large for gestational age. (Reproduced with permission from HAPO Study Cooperative Research Group, Metzger BE, Lowe LP, et al: Hyperglycemia and adverse pregnancy outcomes, N Engl J Med. 2008 May 8;358(19):1991–2002.)

This panel allowed for the diagnosis of overt diabetes during pregnancy as shown in Table 60-4. It also recommended a single-step approach to the diagnosis of gestational diabetes using the 75-g, 2-hour OGTT and thresholds derived using an arbitrary 1.75 odds ratio of outcomes such as LGA birthweight and cord serum C-peptide levels >90th percentile. Only one of these thresholds, shown in Table 60-11, would need to be met or exceeded to make the diagnosis of gestational diabetes.

During their deliberations, the IADPSG estimated that implementation of these recommendations would raise the prevalence of gestational diabetes in the United States to 17.8 percent! Said another way, using this approach, the number of women with mild gestational diabetes would increase almost threefold with no evidence of treatment benefit (Cundy, 2012). Feldman and coworkers (2016) evaluated the implementation of the IADPSG paradigm in a before-after analysis that included more than 6000 women. Compared with a two-step approach, the new strategy was associated with a significant rise in gestational diabetes diagnosis rates but not with reduced macrosomia rates. Remarkably, they identified a higher primary cesarean delivery rate associated with adoption of the IADPSG recommendations. The American Diabetes Association (2013, 2019) initially recommended adopting this new approach, based on benefits inferred from trials in women identified using a two-step approach described earlier. However, it now concludes that data also support a two-step strategy.

NIH Consensus Development Conference

Prompted by these disparate recommendations, the NIH Consensus Development Conference on Diagnosing Gestational Diabetes Mellitus (2013) was convened. The panel found insufficient evidence to adopt the one-step diagnostic process proposed by the IADPSG and recommended continuation of the two-step approach. The Consensus Conference panel did also suggest that further studies resolving the beneficial uncertainties associated with the one-step approach could warrant revision of their conclusions.

A recent trial compared the IADPSG single-step approach to the more traditional two-step approach in almost 24,000 women (Hillier, 2021). Consistent with the IADPSG prediction, the incidence of gestational diabetes was 16.5 percent in those who underwent single-step testing compared with 8.5 percent in women assigned to two-step testing. However, incidences of hypertensive disorders of pregnancy, primary cesarean delivery, LGA newborns, and/or a perinatal composite outcome including measures of birth trauma and perinatal death were not materially different between testing groups. Thus, this large and pragmatic trial does *not* show maternal or perinatal benefit and thus does not justify the increased patient and healthcare costs of broadening the diagnosis of gestational diabetes using the proposed single-step approach (Casey, 2021).

■ Maternal and Fetal Effects

Adverse consequences of gestational diabetes differ from those of pregestational diabetes (see Table 60-5). Similar to women with overt diabetes, adverse maternal effects associated with gestational diabetes include a higher frequency of hypertension and cesarean delivery.

Unlike women with overt diabetes, women with gestational diabetes do not appear to have fetuses with substantially higher rates of anomalies than the general obstetrical population (American College of Obstetricians and Gynecologists, 2019a; Sheffield, 2002). In a study of more than 1 million women from the Swedish Medical Birth Registry, major malformation rates were marginally elevated in fetuses of gestational diabetics compared with those of nondiabetic controls—2.3 versus 1.8 percent (Fadl, 2010).

From this Registry, the stillbirth rate was not higher. Additionally, the stillbirth rate was not increased in an analysis of more than 800,000 pregnancies from 2005 through 2011 (Jovanovič, 2015). That said, women with *elevated* fasting glucose levels have elevated rates of unexplained stillbirths similar to those of women with overt diabetes. This increasing risk with progressive maternal hyperglycemia emphasizes the importance of identifying women with evidence of preexisting diabetes early in pregnancy (see Table 60-4).

Fetal Macrosomia

The primary effect attributed to gestational diabetes is excessive fetal size that is variably defined and discussed in Chapter 47

(p. 832). The perinatal goal is to avoid difficult delivery from macrosomia and concomitant birth trauma associated with shoulder dystocia. In one analysis of more than 80,000 vaginal births in Chinese women, the calculated risk for shoulder dystocia in newborns weighing ≥4200 g was 76-fold greater than the risk in those weighing <3500 g (Cheng, 2013). However, the odds ratio for shoulder dystocia in women with diabetes was <2. Said another way, although gestational diabetes is certainly a risk factor, it accounts for only a small number of pregnancies complicated by shoulder dystocia.

One study identified shoulder dystocia in approximately 4 percent of women with mild gestational diabetes compared with <1 percent of women with a 50-g glucose screen result <120 mg/dL (Landon, 2011). The excessive shoulder and trunk fat that commonly characterizes the macrosomic newborn of a diabetic mother predisposes such neonates to shoulder dystocia or cesarean delivery (Durnwald, 2004; McFarland, 2000). However, one prospective study of fetal adipose measurements demonstrated no differences between measurements in 630 offspring of women with gestational diabetes and 142 without diabetes (Buhling, 2012). The authors attributed this negative finding to successful treatment of gestational diabetes.

Insulin-like growth factors also influence fetal growth. These proinsulin-like polypeptides are produced by virtually all fetal organs and are potent stimulators of cell differentiation and division. Although not a current clinical tool, one study found that maternal insulin-like growth factor 1 levels strongly correlated with birthweight (Luo, 2012). The HAPO Study Cooperative Research Group (2008) also found dramatic elevations in cord serum C-peptide levels associated with rising maternal glucose levels following a 75-g OGTT. C-peptide levels >90th percentile were found in almost a third of newborns in the highest glucose categories. Other factors implicated in macrosomia include epidermal growth factor, fibroblast growth factor, platelet-derived growth factor, leptin, and adiponectin (Grissa, 2010; Loukovaara, 2004; Mazaki-Tovi, 2005).

Maternal body mass index (BMI) is an independent and more substantial risk factor for fetal macrosomia than is glucose intolerance (Ehrenberg, 2004; Mission, 2013). In a secondary analysis of women with either untreated mild gestational diabetes or normal glucose tolerance testing results, higher BMI levels were associated with rising birthweight, regardless of glucose levels (Stuebe, 2012). Another analysis found that gestational diabetes, compared with obesity or gestational weight gain, contributed the least to the population-attributable fraction of LGA neonates (Kim, 2014). The highest fraction of LGA neonates was attributable to maternal obesity plus excessive gestational weight gain. Similarly, Egan and colleagues (2014) found that excessive gestational weight gain is common in women with gestational diabetes and confers an additive risk for fetal macrosomia.

Weight distribution also seems to play a role because the risk of gestational diabetes is greater with maternal truncal obesity. One cohort study found that increased maternal abdominal subcutaneous fat thickness at 18 to 22 weeks' gestation correlated with BMI and was a better predictor of gestational diabetes (Suresh, 2012).

Neonatal Hypoglycemia

Hyperinsulinemia may provoke severe neonatal hypoglycemia within minutes of birth, but only three fourths of these episodes occur in the first 6 hours (Harris, 2012). The definition of neonatal hypoglycemia is debated, and recommended clinical thresholds range from 35 to 45 mg/dL. One NIH workshop conference on the topic supported a threshold of 35 mg/dL in term newborns but cautioned that this practice is not strictly evidence based (Hay, 2009). Treating neonates with glucose levels <47 mg/dL did not improve outcomes compared with treating those with glucose levels <36 mg/dL (van Kempen, 2020).

Newborns described by the HAPO Study Cooperative Research Group (2008) had an incidence of clinical neonatal hypoglycemia that rose with increasing maternal OGTT result values defined in Figure 60-4. The frequency varied from 1 to 2 percent, but it was as high as 4.6 percent in women with fasting glucose levels ≥100 mg/dL. Similarly, an analysis of more than 3000 Korean women who underwent a 50-g OGTT found that neonates born to women with a screening result ≥200 mg/dL were 84 times more likely to have hypoglycemia than those born to women with a result <140 mg/dL (Cho, 2016). The risk of neonatal hypoglycemia correlates with umbilical cord C-peptide levels. The risk also rises with birthweight, independent of a maternal diabetes diagnosis (Mitanchez, 2014).

Management

Women with gestational diabetes can be divided into two functional classes using fasting glucose levels. Pharmacological methods are usually recommended if diet modification does not consistently maintain the fasting plasma glucose levels <95 mg/dL or the 2-hour postprandial plasma glucose <120 mg/dL (American College of Obstetricians and Gynecologists, 2019a). Whether pharmacological treatment should be used in women with lesser degrees of fasting hyperglycemia is unclear. No controlled trials have been done to identify ideal glucose targets for fetal risk prevention. On the other hand, the HAPO Study Cooperative Research Group (2008) did demonstrate increased fetal risk at glucose levels below the threshold used for diagnosis of diabetes. The Fifth International Workshop Conference recommended that fasting capillary glucose levels be kept ≤95 mg/dL (Metzger, 2007).

In their systematic review, Hartling and associates (2013) concluded that treating gestational diabetes resulted in significantly lower incidences of preeclampsia, shoulder dystocia, and macrosomia. For example, the calculated risk ratio was 0.50 for delivering a newborn >4000 g after treatment. These investigators caution that the attributed risk for these outcomes is low, especially when glucose values are only moderately elevated. They were unable to demonstrate an effect on neonatal hypoglycemia or on future metabolic outcomes in the offspring.

Diabetic Diet

Nutritional instructions generally include a carbohydrate-controlled diet sufficient to maintain normoglycemia and avoid ketosis. On average, this includes a caloric intake of 30 to 35 kcal/kg/d. In one study, 152 women with gestational diabetes were randomly assigned to a 40- or a 55-percent daily carbohydrate

diet, and no differences in insulin levels and pregnancy outcomes were found (Moreno-Castilla, 2013). The American College of Obstetricians and Gynecologists (2019a) suggests that carbohydrate intake be limited to 33 to 40 percent of the total daily calories. The remaining calories are apportioned to give 20 percent as protein and 40 percent as fat.

The most appropriate dietary approach for women with gestational diabetes has not been established. One metaanalysis of trials of low-glycemic-index diets found that diets higher in complex carbohydrates and dietary fiber reduced the risk of macrosomia and likelihood of insulin use in women with gestational diabetes (Wei, 2016). However, there clearly are limits to what can be accomplished with various dietary approaches alone. Most and Langer (2012) found that insulin was effective in reducing the risk of excessive birthweight in offspring of obese women with gestational diabetes. Casey and colleagues (2015b) also found that dietary treatment alone for morbidly obese women with mild gestational diabetes did not reduce neonatal fat mass or LGA birthweights.

Exercise

Few trials have evaluated exercise specifically for women with gestational diabetes. The American College of Obstetricians and Gynecologists (2020b) recommends regular physical activity that incorporates aerobic and strength-conditioning exercise during pregnancy and extends this to women with gestational diabetes. Two recent metaanalyses demonstrate that structured exercise programs during pregnancy diminish weight gain during pregnancy and even reduce the risk of developing gestational diabetes (Russo, 2015; Sanabria-Martinez, 2015). Exercise during pregnancy in women with gestational diabetes also lowers glucose levels (Jovanovic-Peterson, 1989).

Glucose Monitoring

Hawkins and associates (2008) compared outcomes in 315 women with diet-treated gestational diabetes who used personal glucose monitors against those of 615 gestational diabetics who were also diet-treated but who underwent intermittent fasting glucose evaluation during weekly obstetrical visits. Women using daily blood-glucose self-monitoring had significantly fewer macrosomic newborns. They also gained less weight after diagnosis than women evaluated during clinic visits only. These findings support the common practice of blood-glucose self-monitoring for women with diet-treated gestational diabetes.

Postprandial surveillance for gestational diabetes is superior to preprandial surveillance (DeVeciana, 1995). The American College of Obstetricians and Gynecologists (2019a) and the American Diabetes Association (2019) recommend glucose assessment four times daily. The first check is performed fasting, and the remainder are done 1 or 2 hours after each meal. At Parkland Hospital in women with diet-treated gestational diabetes, changing to postprandial monitoring significantly reduced weekly maternal weight gain (0.45 lb) compared with preprandial monitoring (0.63 lb).

Insulin Treatment

Historically, insulin has been considered standard therapy in women with gestational diabetes when target glucose levels cannot be consistently achieved through nutrition and exercise. Insulin does not cross the placenta, and tight glycemic control can usually be achieved. Insulin therapy is typically added if fasting levels persist above 95 mg/dL in women with gestational diabetes. The American College of Obstetricians and Gynecologists (2019a) also recommends that insulin be considered in women with 1-hour postprandial levels that persistently exceed 140 mg/dL or those with 2-hour levels >120 mg/dL. Importantly, all of these thresholds are extrapolated from recommendations for managing women with overt diabetes.

The starting insulin dose is typically 0.7 to 1.0 U/kg/d and is given in divided doses (American College of Obstetricians and Gynecologists, 2019a). A combination of intermediate-acting and short-acting insulin may be used, and dose adjustments are based on glucose levels at particular times of the day.

At Parkland Hospital, the starting daily dose is divided so that two thirds is given in the morning before breakfast and one third in the evening before dinner. In the morning dose, one third is regular insulin and two thirds are NPH (neutral protamine Hagedorn) insulin. For the evening dose, one half is regular insulin and the other half is NPH. Insulin instruction for these women is accomplished either in a specialized outpatient clinic or during a short hospital stay.

At the University of Alabama at Birmingham, a basal-bolus approach using insulin glargine with rapid-acting insulin at each meal is preferred. After calculating an initial insulin dose, half is given as long-acting glargine at bedtime, and the other half is administered as rapid-acting insulin split into three doses given before breakfast, lunch, and dinner. As shown in Table 60-8, when using insulin analogues such as insulin aspart and insulin lispro, the more rapid onset of action must be considered during postprandial glucose management.

Oral Hypoglycemic Agents

Insulin is the preferred first-line agent for persistent hyperglycemia in women with gestational diabetes (American College of Obstetricians and Gynecologists, 2019a; American Diabetes Association, 2017b). Both organizations acknowledge that several studies support the safety and efficacy of either metformin (Glucophage) or glyburide (Micronase), which is also called glibenclamide (Feig, 2020; Langer, 2000; Nicholson, 2009). Balsells and coworkers (2015) completed a metaanalyses of trials that compared both agents with insulin or with each other. In the seven trials comparing glyburide with insulin, glyburide was associated with higher birthweight, more macrosomia, and more frequent neonatal hypoglycemia. In the six trials comparing metformin with insulin, metformin was associated with less maternal weight gain, more preterm birth, and less severe neonatal hypoglycemia. Women requiring insulin initiation or insulin addition were considered to have failed treatment. On average, such failures occurred in 6 percent of women treated with glyburide and 34 percent of those treated with metformin. In the two studies directly comparing oral hypoglycemic agents, however, treatment failure rates of both agents were equivalent. Moreover, reminiscent of findings from the trial of adjunctive metformin therapy in women with type 2 diabetes previously described, metformin treatment was associated with less maternal weight gain, lower birthweight, and less macrosomia.

Conversely, in a randomized trial of glyburide treatment as an adjunct to diet therapy in 395 women with mild gestational diabetes, Casey and colleagues (2015a) did not identify any significant improvements in pregnancy outcomes in women treated with adjunctive glyburide.

Concerns have also emerged regarding potential adverse outcomes among women treated with glyburide. First, glyburide crosses the placenta and reaches concentrations in the fetus that are more than two thirds of maternal levels (Caritis, 2013). In a study of more than 9000 women with gestational diabetes treated with either insulin or glyburide, a significant rise in rates of neonatal intensive care unit admission, respiratory distress, and neonatal hypoglycemia was associated with glyburide use (Castillo, 2015).

Similarly, metformin reaches fetal serum concentrations nearly equal to maternal levels. However, in one study of 751 women with gestational diabetes who were randomly assigned to metformin or insulin treatment, short-term perinatal adverse events such as neonatal hypoglycemia, respiratory distress syndrome, phototherapy, or birth trauma did not differ between groups (Rowan, 2008; 2011). The fat distribution in children exposed to metformin showed a tendency toward a more favorable pattern. From a smaller randomized metformin trial, at 18 months, offspring exposed as fetuses to metformin were slightly heavier. However, markers of early motor or language development did not differ compared with those in offspring exposed as fetuses to insulin (Ijäs, 2015).

The Food and Drug Administration has not approved glyburide or metformin use for treatment of gestational diabetes. The American College of Obstetricians and Gynecologists (2019a) recognizes both as reasonable choices for second-line glycemic control in women with gestational diabetes. Because long-term outcomes have not been fully studied, the College recommends disclosure of the limitations in current safety data.

Obstetrical Management

In general, for women with gestational diabetes who do not require insulin, early delivery or other interventions are seldom required. There is no consensus regarding the value or timing of antepartum fetal testing. It is typically reserved for women with pregestational diabetes because of the greater stillbirth risk. The American College of Obstetricians and Gynecologists (2019a, 2020c) endorses fetal surveillance in women with gestational diabetes and poor glycemic control. At Parkland Hospital, women with gestational diabetes are routinely instructed to perform daily fetal kick counts in the third trimester. As previously discussed, insulin-treated women are offered inpatient admission after 34 weeks' gestation. Approximately half of these women accept admission, and antepartum fetal monitoring is performed three times each week.

Women with gestational diabetes and adequate glycemic control are managed expectantly. Elective labor induction to prevent shoulder dystocia compared with spontaneous labor remains controversial. In the truncated GINEXMAL randomized trial of 425 women with gestational diabetes, outcomes of labor induction between 38 and 39 weeks' were compared with expectant management until 41 weeks' gestation (Alberico, 2017). Although underpowered, this trial demonstrated no clinically meaningful difference in the cesarean delivery rate between the induction and expectantly managed groups—12.6 versus 11.8 percent. However, with early labor induction, neonatal hyperbilirubinemia rates were significantly higher, and there was a nonsignificant threefold greater shoulder dystocia rate. In a cohort study of 8392 women with gestational diabetes, routine delivery at 38 or 39 weeks' gestation was associated with a lower rate of cesarean delivery but with an elevated rate of neonatal intensive care unit admission (Melamed, 2016).

The American College of Obstetricians and Gynecologists (2019a) recommends that routine labor induction in women with diet-treated gestational diabetes should not occur before 39 weeks' gestation. As mentioned previously, at Parkland Hospital, those treated with insulin are delivered at 38 weeks' gestation. At the University of Alabama at Birmingham, delivery is carried out after 39 weeks.

Elective cesarean delivery to avoid brachial plexus injuries in overgrown fetuses is another issue. The American College of Obstetricians and Gynecologists (2019b) concludes that data are insufficient to determine whether women with *gestational* diabetes whose fetuses have a sonographically estimated weight ≥4500 g should undergo cesarean delivery to avoid risk of birth trauma. In one systematic review, Garabedian and associates (2010) estimated that as many as 588 cesarean deliveries in women with gestational diabetes and an estimated fetal weight of ≥4500 g would be necessary to avoid one case of permanent brachial plexus palsy. In one analysis of 903 women with gestational diabetes, sonographic estimates of fetal weight within 1 month of delivery typically overdiagnosed fetuses as being LGA. Only 22 percent of women estimated to have an LGA fetus actually delivered an overgrown newborn (Scifres, 2015). Still, the American College of Obstetricians and Gynecologists (2020b) acknowledges that prophylactic cesarean delivery may be considered in diabetic women with an estimated fetal weight ≥4500 g.

Postpartum Evaluation

Recommendations for postpartum evaluation are based on the 50- to 75-percent likelihood that women with gestational diabetes will develop overt diabetes within 15 to 25 years (American Diabetes Association, 2019). The Fifth International Workshop Conference on Gestational Diabetes recommended that women diagnosed with gestational diabetes undergo postpartum evaluation with a 75-g OGTT (Metzger, 2007). These recommendations and the classification scheme of the American Diabetes Association are shown in Table 60-14. However, one study of insurance claim data from 2000 to 2013 showed that only 24 percent of women with a pregnancy complicated by gestational diabetes underwent postpartum screening within a year. Less than half of those underwent a 75-g OGTT (Eggleston, 2016). The American College of Obstetricians and Gynecologists (2019a) recommends either a fasting glucose assessment or a 75-g, 2-hour OGTT at 4 to 12 weeks postpartum for the diagnosis of overt diabetes. The American Diabetes Association (2019) recommends testing every 1 to 3 years in women with a history of gestational diabetes but normal postpartum glucose screening.

Women with a history of gestational diabetes are also at risk for cardiovascular complications associated with dyslipidemia,

TABLE 60-14. Fifth International Workshop-Conference: Metabolic Assessments Recommended After Pregnancy with Gestational Diabetes

Time	Test	Purpose
Postdelivery (1–3 d)	Fasting or random plasma glucose	Detect persistent, overt diabetes
Early postpartum (6–12 wk)	75-g, 2-hr OGTT	Postpartum classification of glucose metabolism
1-yr postpartum	75-g, 2-hr OGTT	Assess glucose metabolism
Annually	Fasting plasma glucose	Assess glucose metabolism
Triennially	75-g, 2-hr OGTT	Assess glucose metabolism
Prepregnancy	75-g, 2-hr OGTT	Classify glucose metabolism
Classification of the American Diabetes Association (2013)		
Normal Values	**Impaired Fasting Glucose or Impaired Glucose Tolerance**	**Diabetes Mellitus**
Fasting <100 mg/dL	100–125 mg/dL	≥126 mg/dL
2 hr <140 mg/dL	2 hr ≥140–199 mg/dL	2 hr ≥200 mg/dL
Hemoglobin A_{1c} <5.7%	5.7–6.4%	≥6.5%

OGTT = oral glucose tolerance test.
Data from American Diabetes Association, 2013, 2017a; Metzger, 2007.

hypertension, and abdominal obesity—the *metabolic syndrome* (Chap. 51, p. 903). In a study of 47,909 parous women, the nearly 5000 women with prior gestational diabetes were 2.6 times more likely to be hospitalized for cardiovascular morbidity (Kessous, 2013). Another study evaluated 483 women between 5 and 10 years after being diagnosed with mild gestational diabetes (Varner, 2017). Investigators found no increased risk for developing metabolic syndrome associated with additional pregnancies. However, risk for subsequent diabetes rose almost fourfold if gestational diabetes complicated at least one subsequent pregnancy.

■ Recurrent Gestational Diabetes

In one large metaanalysis, the pooled gestational diabetes recurrence rate was 48 percent. The same investigative group identified elevated maternal BMI, insulin use, fetal macrosomia, and weight gain between pregnancies as additional risk factors for gestational diabetes recurrence (Schwartz, 2015, 2016).

Lifestyle behavioral changes that include weight control and exercise between pregnancies would seem likely to prevent gestational diabetes recurrence. However, women randomized to an exercise program that started before 14 weeks' gestation in a subsequent pregnancy did not have a lower recurrence rate (Guelfi, 2016). Conversely, Ehrlich and coworkers (2011) found that prepregnancy loss of at least two BMI units was associated with a lower subsequent risk of gestational diabetes in women who were overweight or obese in the first pregnancy.

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CHAPTER 61

Endocrine Disorders

Endocrinopathies are closely related to pregnancy for several reasons. One example is the gestational proclivity for prodigious hormone secretion, which is perhaps best illustrated by placental lactogen in diabetes. This is the most common endocrinopathy encountered in pregnancy and discussed in Chapter 57. Pregnancy is also interrelated with some endocrinopathies that are at least partially due to autoimmune dysregulation. Clinical manifestations result from complex interplay among genetic, environmental, and endogenous factors that activate the immune system against targeted cells within endocrine organs. In one extraordinary interaction, studies have implicated maternal organ engraftment by fetal cells transferred during pregnancy. These cells later provoke antibody production, tissue destruction, and autoimmune endocrinopathies.

THYROID DISORDERS

Taken in aggregate, these disorders are common in young women and thus frequently encountered in pregnancy. Maternal and fetal thyroid function are intimately related, and drugs that affect the maternal thyroid affect the fetal gland. Moreover, thyroid autoantibodies are associated with increased rates of early pregnancy wastage. Uncontrolled thyrotoxicosis and untreated hypothyroidism are both associated with adverse pregnancy outcomes. Last, evidence suggests that the severity of some autoimmune thyroid disorders may be ameliorated during pregnancy, only to be exacerbated postpartum.

Thyroid Physiology and Pregnancy

Maternal thyroid changes are substantial, and normally altered gland structure and function can sometimes be confused with thyroid abnormalities. These alterations are discussed in detail in Chapter 4 (p. 71), and normal serum hormone level values are found in the Appendix (p. 1230). First, maternal serum concentrations of thyroid binding globulin are increased concomitantly with total or bound thyroid hormone levels. Second, *thyrotropin*, also called *thyroid-stimulating hormone (TSH)*, plays a central role in screening and diagnosis of many thyroid disorders, but levels change throughout pregnancy. Notably, TSH receptors are cross stimulated, albeit weakly, by massive quantities of human chorionic gonadotropin (hCG) secreted by placental trophoblast. Because TSH does not cross the placenta, it has no direct fetal effects. During the first 12 weeks of gestation, when maternal hCG serum levels are maximal, thyroid hormone secretion is stimulated. The resulting greater serum free thyroxine (T_4) levels act to suppress hypothalamic *thyrotropin-releasing hormone (TRH)* and in turn limit pituitary TSH secretion (Fig. 61-1). Accordingly,

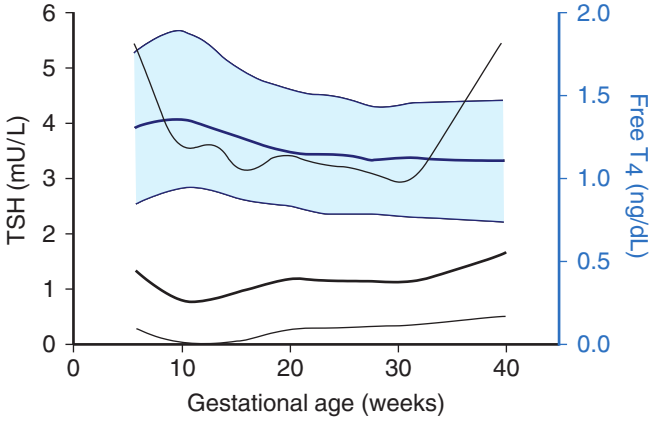

FIGURE 61-1 Gestational-age-specific values for serum thyroid-stimulating hormone (TSH) levels (*black lines*) and free thyroxine (T_4) levels (*blue lines*). Data were derived from 17,298 women tested during pregnancy. For each color, the dark solid lines represent the 50th percentile, whereas the upper and lower light lines represent the 2.5th and 97.5th percentiles, respectively. (Data from Casey, 2005; Dashe, 2005.)

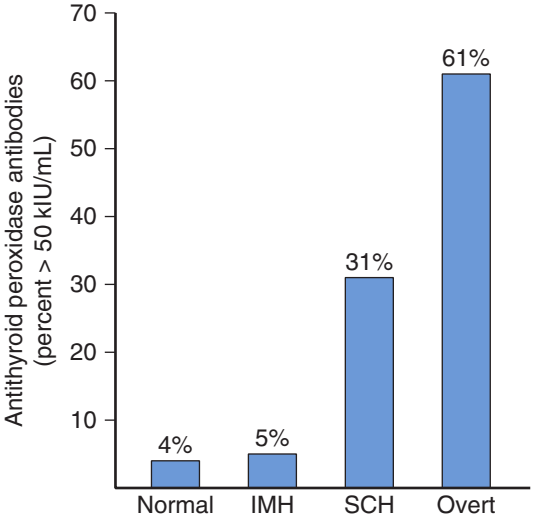

FIGURE 61-2 Incidence of antithyroid peroxidase antibodies in 16,407 women who are normal or euthyroid, in 233 with isolated maternal hypothyroxinemia (IMH), in 598 with subclinical hypothyroidism (SCH), and in 134 with overt hypothyroidism.

TRH is undetectable in maternal serum. Conversely, in fetal serum, beginning at midpregnancy, TRH becomes detectable, but levels are static and do not rise.

Throughout pregnancy, maternal thyroxine is transferred to the fetus (American College of Obstetricians and Gynecologists, 2020). Maternal thyroxine is important for normal fetal brain development, especially before the onset of fetal thyroid gland function (Bernal, 2007; Korevaar, 2016b). Both high and low maternal thyroid function in the first trimester are negatively associated with cortical gray matter volume in childhood (Jansen, 2019). Although the fetal gland begins concentrating iodine and synthesizing thyroid hormone after 12 weeks' gestation, maternal thyroxine contribution remains important. Maternal sources account for 30 percent of thyroxine in fetal serum at term (Thorpe-Beeston, 1991). Still, developmental risks associated with maternal hypothyroidism after midpregnancy remain poorly understood (Morreale de Escobar, 2004; Sarkhail, 2016).

Autoimmunity and Thyroid Disease

Most thyroid disorders are inextricably linked to autoantibodies against nearly 200 thyrocyte components. These antibodies variably stimulate thyroid function, block function, or cause thyroid inflammation that may lead to follicular cell destruction. Often, these effects overlap.

Thyroid-stimulating autoantibodies, also called *thyroid-stimulating immunoglobulins (TSIs)*, bind and activate the TSH receptor to cause thyroid hyperfunction and growth. Although these antibodies are identified in most patients with classic Graves disease, simultaneous production of *thyroid-stimulating blocking antibodies* may blunt this effect (Jameson, 2015).

Thyroid peroxidase (TPO) is a thyroid gland enzyme that normally functions to produce thyroid hormones. *Thyroid peroxidase antibodies* are directed against TPO and are identified in 5 to 15 percent of all gravidas (Fig. 61-2) (Abbassi-Ghanavati, 2010; Casey, 2007; Sarkhail, 2016). TPO antibodies have been associated in some studies with early pregnancy loss and preterm birth (Consortium on Thyroid and Pregnancy, 2019; Plowden, 2017; Thangaratinam, 2011). In another study with more than 1000 pregnant women with TPO antibodies, the risk for preterm birth was not elevated. The risk for placental abruption was greater (Abbassi-Ghanavati, 2010). These women are also at high risk for postpartum thyroid dysfunction and at lifelong risk for permanent thyroid failure (Andersen, 2016; Jameson, 2015).

Fetal Microchimerism

Autoimmune thyroid disease is more common in women than in men. One intriguing explanation for this disparity is fetal-to-maternal cell trafficking (Greer, 2011). Fetal cells are known to enter maternal circulation during pregnancy. When fetal lymphocytes enter maternal circulation, they can live for more than 20 years. Stem cell interchange can lead to engraftment in several maternal tissues and is termed *fetal microchimerism.* In some cases, this may involve the thyroid gland (Bianchi, 2003; Boddy, 2015). A high prevalence of Y chromosome–positive cells has been identified in the thyroid glands of women with Hashimoto thyroiditis—60 percent, or with Graves disease—40 percent (Renné, 2004). In another study of women giving birth to a male fetus, more circulating male mononuclear cells were found in those with Hashimoto thyroiditis (Lepez, 2011). Conversely, for some autoimmune thyroid disorders, fetal microchimerism may actually have a protective role (Cirello, 2015).

Hyperthyroidism

The incidence of thyrotoxicosis or hyperthyroidism in pregnancy varies and complicates between 0.4 and 1.7 percent of births when gestational-age-appropriate TSH threshold values are used (Table 61-1). Because normal pregnancy simulates some clinical findings similar to thyroxine excess, clinically mild thyrotoxicosis may be difficult to diagnose. Suggestive

TABLE 61-1. Incidence of Overt Hyperthyroidism in Pregnancy

Study	Country	Incidence
Wang (2011)[a]	China	1%
Vaidya (2007)[a]	United Kingdom	0.7%
Lazarus (2007)[b]	United Kingdom	1.7%
Casey (2006)[c]	United States	0.4%
Andersen (2016)[c,d]	Denmark	0.4–0.7%
Dong (2019)[e]	International	0.64–0.91%

[a]Screened in the first trimester.
[b]Screened at 9–15 weeks.
[c]Screened before 20 weeks.
[d]Diagnosed in early versus later pregnancy.
[e]Systematic review.

findings include tachycardia that exceeds that usually seen with normal pregnancy, thyromegaly, exophthalmos, and failure to gain weight despite adequate food intake. Laboratory testing is confirmatory. TSH levels are markedly depressed, while serum free T_4 (fT_4) levels are elevated. Rarely, hyperthyroidism is caused by abnormally high serum triiodothyronine (T_3) levels and called *T_3-toxicosis*.

Thyrotoxicosis and Pregnancy

The overwhelming cause of thyrotoxicosis in pregnancy is Graves disease, an organ-specific autoimmune process associated with thyroid-stimulating TSH-receptor antibodies (De Leo, 2016). These antibodies are specific for Graves hyperthyroidism, and targeted assays have been proposed for diagnosis, management, and prognosis in pregnancies complicated by hyperthyroidism (Alexander, 2017; Barbesino, 2013). With Graves disease, during the course of pregnancy, hyperthyroid symptoms may initially worsen because of hCG stimulation. Symptoms then diminish after a decline in receptor-antibody titers in the second half of pregnancy (Mestman, 2012; Sarkhail, 2016). Levels of blocking antibodies also decline during pregnancy (Amino, 2003).

Treatment

Thyrotoxicosis during pregnancy can nearly always be controlled by thionamide drugs. *Propylthiouracil (PTU)* has been historically preferred because it partially inhibits the conversion of T_4 to T_3 and crosses the placenta less readily than *methimazole*. The latter has also been associated with a rare methimazole embryopathy, characterized by *esophageal* or *choanal atresia* and *aplasia cutis*, a congenital skin defect. In one analysis of Japanese women with first-trimester hyperthyroidism, the risk of major fetal malformation in pregnancies exposed to methimazole was twofold higher than risks with either PTU or potassium iodide use (Yoshihara, 2012, 2015). Specifically, seven of nine cases with aplasia cutis and the only case of esophageal atresia were in the group of methimazole-exposed fetuses. A PTU-associated embryopathy also has been described (Andersen, 2014).

Treatment with PTU is associated with a higher risk for liver injury (Yu, 2020). In 2009, the U.S. Food and Drug Administration issued a safety alert on PTU-associated hepatotoxicity. This warning initially prompted the American Thyroid Association and the American Association of Clinical Endocrinologists (2011) to recommend PTU therapy during the first trimester followed by a switch to methimazole beginning in the second trimester. The obvious disadvantage is that this might lead to poorly controlled thyroid function. More recently, the American Thyroid Association recommends PTU therapy through 16 weeks' gestation but does not make a recommendation regarding switching to methimazole treatment because both agents are associated with adverse effects and the harm from poorer control during the switch is unknown (Alexander, 2017).

Transient leukopenia can be documented in up to 10 percent of women taking antithyroid drugs, but this does not require therapy cessation (American College of Obstetricians and Gynecologists, 2020). In approximately 0.3 percent, however, *agranulocytosis* develops suddenly and mandates drug discontinuance (Thomas, 2013). It is not dose related, and because of its acute onset, routine serial leukocyte counts during therapy are not helpful. *Instead, if fever or sore throat develops, women are instructed to discontinue medication immediately and report for a complete blood count.*

Therapy may have other side effects. First, as noted, hepatotoxicity develops in approximately 0.1 percent of treated women. Serial measurement of hepatic enzyme levels does not prevent fulminant PTU-related hepatotoxicity. Second, an allergic rash may develop in 3 to 5 percent of women taking thionamide drugs (Alexander, 2017). In addition, although approximately 20 percent of patients treated with PTU develop *antineutrophil cytoplasmic antibodies (ANCA)*, only a small percentage of these subsequently develops serious vasculitis (Kimura, 2013). Last, thionamides have the potential to cause fetal complications, but these are uncommon. In some cases, thionamides may even be therapeutic for the fetus. This is because TSH-receptor antibodies cross the placenta and can stimulate the fetal thyroid gland to cause thyrotoxicosis and goiter.

The initial thionamide dose is empirical. For nonpregnant patients, the American Thyroid Association recommends that methimazole be used at an initial higher daily dose of 10 to 20 mg orally followed by a lower maintenance dose of 5 to 10 mg. If PTU is selected, a dose of 50 to 150 mg orally three times daily may be initiated depending on clinical severity. At Parkland Hospital, we usually initially give 300 or 450 mg of PTU daily in three divided doses for pregnant women. Occasionally, daily doses of 600 mg or higher are necessary. We routinely transition women to methimazole after the first trimester. If a switch is deemed appropriate, a dose ratio of 20:1—PTU to methimazole—is recommended (Alexander, 2017). The goal is treatment with the lowest possible thionamide dose to maintain thyroid hormone levels slightly above or in the high normal range, while TSH levels remains suppressed. Serum free T_4 concentrations are measured every 4 to 6 weeks.

Subtotal thyroidectomy can be performed after thyrotoxicosis is medically controlled. This seldom is done during pregnancy but may be appropriate for the very few women who cannot adhere to medical treatment or in whom drug therapy proves toxic (Pearce, 2019; Stagnaro-Green, 2012a). Surgery is best accomplished in the second trimester. Potential drawbacks of thyroidectomy include inadvertent resection of parathyroid glands and injury to the recurrent laryngeal nerve.

Thyroid ablation with therapeutic radioactive iodine is contraindicated in pregnancy (Lee, 2021). These doses may also cause fetal thyroid gland destruction. Thus, when radioactive iodine is given unintentionally, some clinicians recommend abortion. Any exposed fetus must be carefully evaluated, and the incidence of fetal hypothyroidism depends on gestational age and radioiodine dose (Berlin, 2001). Importantly, several cases of inadvertent periconceptional exposure to radioactive iodine have been reported with no obvious ill effects for the offspring (Radacic-Aumiler, 2016; Sadakata, 2014). The International Commission on Radiological Protection recommends that women avoid pregnancy for 6 months after radioablative therapy (Brent, 2008). Moreover, during lactation, the breast also concentrates a substantial amount of iodine. This may pose a neonatal risk due to ^{131}I-containing milk ingestion and maternal risk from significant breast irradiation. To limit the latter, a delay of 3 months after breastfeeding cessation will more reliably ensure complete breast involution.

Pregnancy Outcome

Women with thyrotoxicosis have pregnancy outcomes that largely depend on whether metabolic control is achieved. For example, excess thyroxine may cause miscarriage or preterm birth (Andersen, 2014; Moleti, 2019; Sheehan, 2015). In untreated women or in those who remain hyperthyroid despite therapy, incidences of preeclampsia, heart failure, and adverse perinatal outcomes are higher (Table 61-2). One case-cohort study in the Danish National Birth Cohort found that maternal hyperthyroidism was also a risk for epilepsy and autism spectrum disorders in children (Andersen, 2018).

Fetal and Neonatal Effects

In most cases, the perinate is euthyroid. In some, however, hyper- or hypothyroidism can develop with or without a goiter (Fig. 61-3). Clinical hyperthyroidism develops in up to 1 percent of neonates born to women with Graves disease (Barbesino, 2013; Fitzpatrick, 2010). If fetal thyroid disease is suspected, nomograms exist for sonographically measured thyroid volume (Gietka-Czernel, 2012).

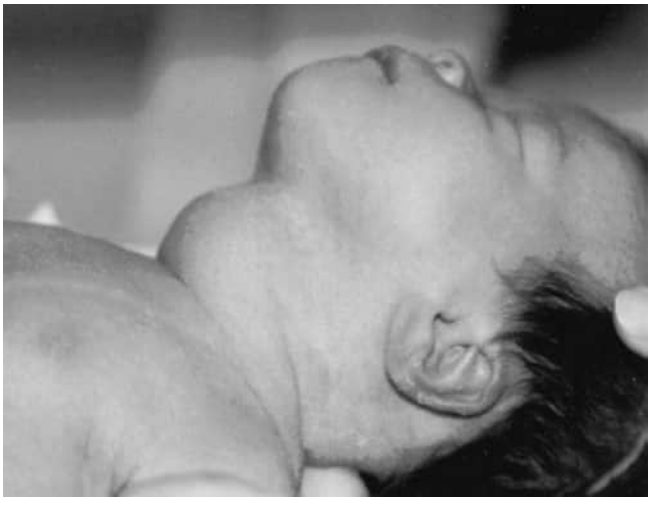

FIGURE 61-3 Term hypothyroid neonate delivered of a woman with a 3-year history of thyrotoxicosis that recurred at 26 weeks' gestation. The mother was given methimazole, 30 mg orally daily, and was euthyroid at delivery.

The fetus or neonate who was exposed to excessive maternal thyroxine may have any of several clinical presentations. First, *goitrous thyrotoxicosis* stems from placental transfer of thyroid-stimulating immunoglobulins. Nonimmune hydrops and fetal demise can complicate fetal thyrotoxicosis (Nachum, 2003; Stulberg, 2000). The best predictor of perinatal thyrotoxicosis is the presence of thyroid-stimulating TSH-receptor antibodies in women with Graves disease (Moleti, 2019; Nathan, 2014). This is especially true if their levels are more than threefold higher than the upper normal limit (Barbesino, 2013). In one study of 72 pregnant women with Graves disease, none of the fetuses in 31 low-risk mothers had a goiter, and all were euthyroid at delivery (Luton, 2005). Low risk was defined as no requirement for antithyroid medications during the third trimester or an absence of antithyroid antibodies. Conversely, in a group of 41 women who either were taking antithyroid medication at delivery or had thyroid-receptor antibodies, 11 fetuses—27 percent—had sonographic evidence of a goiter at 32 weeks' gestation. Seven of these 11 fetuses were determined to be hypothyroid, and the remaining fetuses were hyperthyroid.

Because of these findings, the American Thyroid Association recommends routine evaluation of TSH-receptor antibodies (TRAb) in early pregnancy in women treated with antithyroid medication (Alexander, 2017). In those who have elevated TRAb levels or who continue therapy, repeat testing is recommended between 18 and 22 weeks' gestation. The American College of Obstetricians and Gynecologists (2020), however, does not recommend such testing. If the fetus is thyrotoxic, maternal thionamide drugs are increased even though maternal thyroid function may be within targeted range (Mestman, 2012). If secondary maternal hypothyroidism develops, the fetus can be treated by a reduced maternal antithyroid medication dose and injections of intraamnionic thyroxine if

TABLE 61-2. Pregnancy Outcomes in Women with Overt Thyrotoxicosis

	Treated and Euthyroid[a] (n = 380)	Uncontrolled Thyrotoxicosis[a] (n = 90)
Maternal Outcome		
Preeclampsia	40 (10%)	15 (17%)
Heart failure	1	7 (8%)
Death	0	1
Perinatal Outcome		
Preterm delivery	51 (16%)	29 (32%)
Growth restriction	37 (11%)	15 (17%)
Stillbirth	0/59	6/33 (18%)
Thyrotoxicosis	1	2
Hypothyroidism	4	0
Goiter	2	0

[a]Data presented as n (%).
From Davis, 1989; Kriplani, 1994; Luewan, 2011; Medici, 2014; Millar, 1994.

necessary. Although usually short-lived, neonatal thyrotoxicosis may require a short course of antithyroid drug treatment (Levy-Shraga, 2014; Nathan, 2014).

A second fetal presentation is *goitrous hypothyroidism* caused by fetal exposure to maternally administered thionamides (see Fig. 61-3). Despite theoretical neurological implications, reports of adverse fetal effects seem to have been exaggerated. For example, in at least 239 treated thyrotoxic women shown in Table 61-2, evidence of hypothyroidism was found in only four newborns. Furthermore, at least four long-term studies report no abnormal intellectual or physical development of these children (Mestman, 1998). As long as the maternal free thyroxine level remains in the upper therapeutic to mildly thyrotoxic range, the likelihood of fetal hypothyroidism is remote (Moleti, 2019).

A third presentation, *nongoitrous hypothyroidism,* may develop from transplacental passage of maternal TSH-receptor blocking antibodies (Fitzpatrick, 2010). And last, *fetal thyrotoxicosis* after maternal thyroid gland ablation, usually with ^{131}I radioiodine, may result from transplacental thyroid-stimulating antibodies. In one report of early fetal exposure to radioiodine, neonatal thyroid studies indicated transient hyperthyroidism from maternal transfer of stimulating antibodies (Tran, 2010).

Fetal Diagnosis

Evaluation of fetal thyroid function remains controversial. Although the fetal thyroid volume can be measured sonographically in women taking thionamide drugs or in those with thyroid-stimulating antibodies, most investigators do not currently recommend this routinely (Cohen, 2003; Luton, 2005). Fetal hyper- or hypothyroidism may cause hydrops, growth restriction, goiter, or tachycardia, and fetal blood sampling may be appropriate (Brand, 2005). The American Thyroid Association guidelines for management of thyroid disease during pregnancy recommend that umbilical cord blood sampling only be considered when a fetal goiter is detected and the thyroid status of the fetus is unclear (Alexander, 2017). Diagnosis and treatment are considered further in Chapter 19 (p. 370).

Thyroid Storm and Thyrotoxic Heart Failure

Both of these are acute and life-threatening in pregnancy. Thyroid storm is a hypermetabolic state and is rare in pregnancy. In contrast, pulmonary hypertension and heart failure from cardiomyopathy caused by the profound myocardial effects of thyroxine are common in pregnant women (Sheffield, 2004). As shown in Table 61-2, heart failure developed in 8 percent of 90 women with uncontrolled thyrotoxicosis. In a registry of almost 70,000 pregnancies from one province in China, six of 155 (4 percent) women diagnosed with thyrotoxicosis were found to have hyperthyroid heart disease (Shan, 2019).

The pregnant woman with thyrotoxicosis has minimal cardiac reserve, and decompensation is usually precipitated by preeclampsia, anemia, sepsis, or a combination. Fortunately, thyroxine-induced cardiomyopathy and pulmonary hypertension are frequently reversible (Shan, 2019; Sheffield, 2004).

Management

Treatment is similar for thyroid storm and heart failure and should be carried out in an intensive care area that may include special-care units within labor and delivery (American College of Obstetricians and Gynecologists, 2020). Shown in **Figure 61-4** is our stepwise approach to medical management of thyroid storm or thyrotoxic heart failure. An hour or two after initial thionamide administration, iodide is given to inhibit thyroidal release of T_3 and T_4. It can be given intravenously (IV) as sodium iodide or orally as either saturated solution of potassium iodide (SSKI) or Lugol solution. With a history of iodine-induced anaphylaxis, lithium carbonate, 300 mg every 6 hours, is given instead. Most authorities recommend dexamethasone, 2 mg IV every 6 hours for four doses, to further block peripheral conversion of T_4 to T_3. If a β-blocking drug is given to control tachycardia, its effect on heart failure must be considered. Propranolol, labetalol, and esmolol are options. Coexisting severe preeclampsia, infection, or anemia are aggressively managed before delivery is considered.

Hyperemesis Gravidarum

Transient biochemical features of hyperthyroidism may be observed in 2 to 15 percent of women in early pregnancy (Fitzpatrick, 2010). Many women with hyperemesis gravidarum have abnormally high serum T_4 levels and low TSH levels (Chap. 57, p. 1014). This results from TSH-receptor stimulation from hCG. This transient condition is also termed *gestational transient thyrotoxicosis.* Even if associated with hyperemesis, antithyroid drugs are not warranted (American College of Obstetricians and Gynecologists, 2020). The hCG levels do not correlate with T_4 and TSH values, which trend to normal by midpregnancy (Nathan, 2014; Yoshihara, 2015).

Gestational Trophoblastic Disease

The prevalence of T_4 level elevation in women with a molar pregnancy ranges between 25 and 65 percent (Hershman, 2004). As discussed, abnormally high hCG levels lead to overstimulation of the TSH receptor. Because these tumors are now usually diagnosed early, clinically apparent hyperthyroidism is less common. With molar evacuation, serum free T_4 levels usually drop to normal levels rapidly in parallel with declining hCG concentrations.

Subclinical Hyperthyroidism

Third-generation TSH assays with an analytical sensitivity of 0.002 mU/mL permit identification of subclinical thyroid disorders. These biochemically defined extremes usually represent normal biological variations but may herald the earliest stages of thyroid dysfunction. *Subclinical hyperthyroidism* is characterized by an abnormally low serum TSH concentration in concert with normal T_4 hormone levels. Long-term effects of persistent subclinical thyrotoxicosis include osteoporosis, cardiovascular morbidity, and progression to overt thyrotoxicosis or thyroid failure. In one recent metaanalysis of 20 studies, the prevalence of subclinical hyperthyroidism was 1.77 percent in pregnant women (Dong, 2019). Importantly, subclinical hyperthyroidism has not been associated with adverse pregnancy outcomes (Casey, 2006). In separate retrospective analyses of almost 25,000 women who underwent thyroid screening throughout pregnancy, investigators also found no relationship between

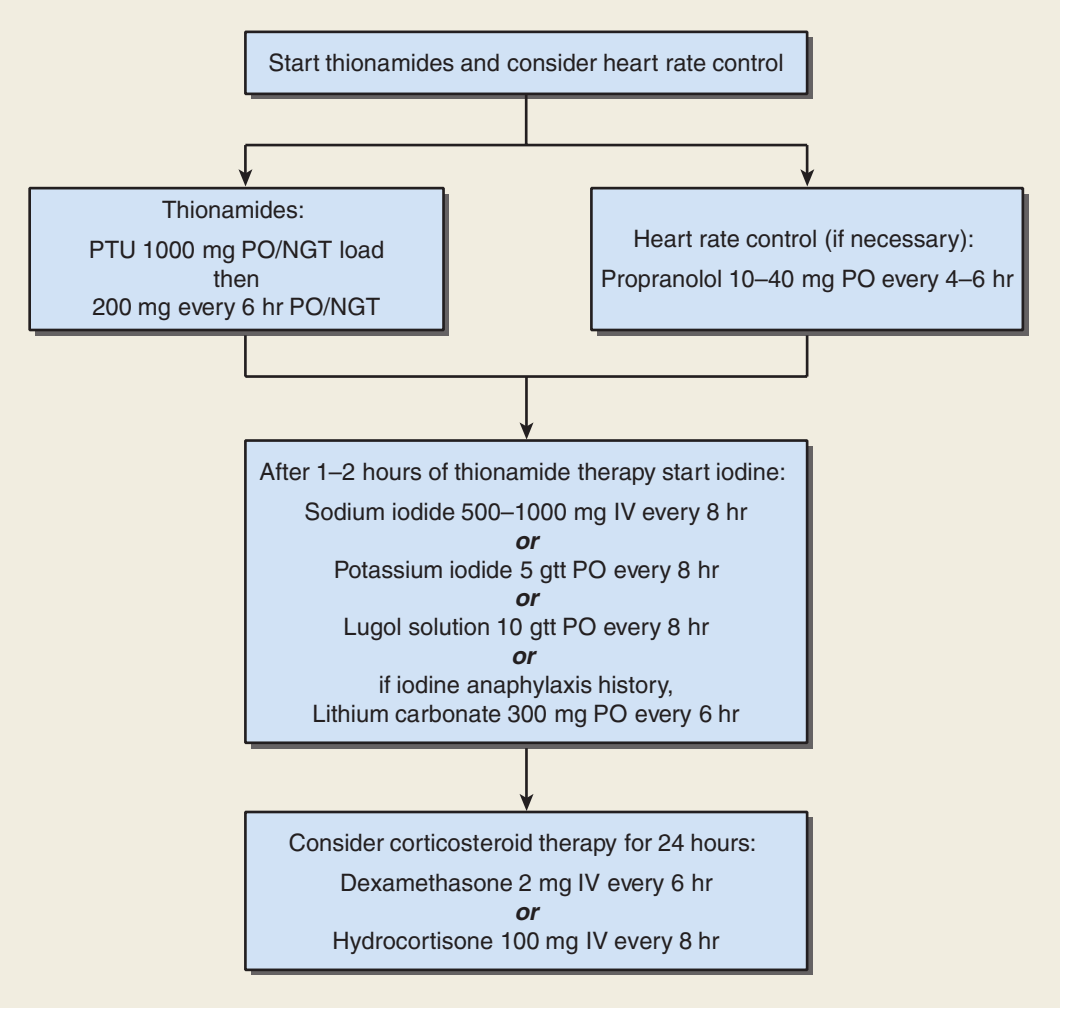

FIGURE 61-4 Parkland Hospital management for thyroid storm or thyrotoxic heart failure. gtt = drops; IV = intravenous; NGT = nasogastric tube; PO = orally; PTU = propylthiouracil.

subclinical hyperthyroidism and preeclampsia or gestational diabetes (Wilson, 2012; Tudela, 2012).

Treatment of subclinical hyperthyroidism is unwarranted in pregnancy because antithyroid drugs may affect the fetus. These women may benefit from periodic surveillance, and approximately half eventually have normal TSH concentrations.

Hypothyroidism

Overt or symptomatic hypothyroidism complicates between 0.2 and 1.2 percent of pregnancies (Andersen, 2016; Casey, 2017). Its insidious, nonspecific clinical findings include fatigue, constipation, cold intolerance, muscle cramps, and weight gain. A pathologically enlarged thyroid gland depends on the etiology of hypothyroidism and is more likely in women in areas of endemic iodine deficiency or those with Hashimoto thyroiditis. Other findings are edema, dry skin, hair loss, and a prolonged relaxation phase of deep tendon reflexes. *Clinical* or *overt hypothyroidism* is confirmed by an abnormally high serum TSH level and an abnormally low T_4 level. *Subclinical hypothyroidism,* discussed later, is defined by an elevated serum TSH level but *normal* serum T_4 concentration (Jameson, 2015). Asymptomatic individuals with high levels of anti-TPO or antithyroglobulin antibodies often are included in the spectrum of subclinical thyroid disease and will also be discussed.

Overt Hypothyroidism and Pregnancy

The most common cause of hypothyroidism in pregnancy is Hashimoto thyroiditis, characterized by glandular destruction from autoantibodies, particularly anti-TPO antibodies. Another cause is postablative Graves disease. Clinical identification of hypothyroidism is especially difficult during pregnancy because many of the signs or symptoms are also common pregnancy itself. Thyroid analyte testing should be performed on symptomatic women, those with a personal or family history of thyroid disease, or those with type 1 diabetes (American College of Obstetricians and Gynecologists, 2020). *Severe hypothyroidism* during pregnancy is uncommon, probably because it is often associated with infertility and higher miscarriage rates (De Groot, 2012).

Treatment

The American College of Obstetricians and Gynecologists (2020) recommends oral replacement therapy for overt hypothyroidism beginning with levothyroxine in doses of 1 to 2 μg/kg/d or approximately 100 μg daily. Women who are athyreotic

after thyroidectomy or radioiodine therapy may require higher doses. Surveillance is with TSH levels measured at 4-week intervals in the first half of pregnancy and at least once in the third trimester. The levothyroxine dose is adjusted by 25- to 50-μg increments until TSH values approximate 2.5 mU/L. Pregnancy is associated with an increased dose requirement in approximately a third of supplemented women (Abalovich, 2010; Alexander, 2004). The greater demand in pregnancy is believed to be related to augmented estrogen production (Arafah, 2001).

Higher dose requirements begin as early as 5 weeks' gestation. Significant hypothyroidism may develop early in women without thyroid reserve, such as those with a previous thyroidectomy, those with prior radioiodine ablation, or those undergoing assisted reproductive techniques (Alexander, 2004; Loh, 2009). Theoretically, an anticipatory 25-percent increase in the levothyroxine dose at pregnancy confirmation will reduce this likelihood. However, one randomized trial compared empiric increases in dose against dose adjustments based on TSH levels and found both equally effective (Sullivan, 2017). Those in the empiric-dosing group had a higher risk of TSH suppression. At Parkland Hospital, all women with hypothyroidism undergo TSH testing at initiation of prenatal care and subsequent indicated dose adjustments. TSH determinations are repeated in each trimester.

Pregnancy Outcome with Overt Hypothyroidism

Observational studies, although limited, indicate that excessive adverse perinatal outcomes are associated with overt T_4 deficiency (Table 61-3). Preterm birth rates also are higher (Sheehan, 2015). With appropriate replacement therapy, however, rates of adverse effects are not increased in most reports (Bryant, 2015; Matalon, 2006; Tan, 2006). In one dissenting study, risks for some pregnancy complications were greater even in women taking replacement therapy (Wikner, 2008). Most experts agree that adequate hormone replacement during pregnancy minimizes the risk of adverse outcomes and most complications.

TABLE 61-3. Pregnancy Complications in 440 Women with Hypothyroidism

Complications	Hypothyroidism (%)	
	Overt (n = 112)	Subclinical (n = 328)
Preeclampsia	32	8
Placental abruption	8	1
Cardiac dysfunction	3	2
Birthweight <2000 g[a,b]	33	32
Stillbirths[c]	9	3[c]

[a]Preterm or term deliveries were the only outcomes reported by Abalovich, 2002.
[b]Low birthweight and stillbirth were outcomes reported by Su, 2011.
[c]One infant died from syphilis.
Data from Abalovich, 2002; Davis, 1988; Leung, 1993; Männistö, 2009; Su, 2011.

Fetal and Neonatal Effects

Undoubtedly, maternal and fetal thyroid abnormalities are related. In both, thyroid function is dependent on adequate iodine intake, and its deficiency early in pregnancy can cause both maternal and fetal hypothyroidism. In one analysis of 4273 mother-child pairs, an association between maternal thyroid function during pregnancy and both neonatal and childhood thyroid function was confirmed (Korevaar, 2016a). As discussed, maternal TSH-receptor-blocking antibodies can cross the placenta and cause fetal thyroid dysfunction. Rovelli and colleagues (2010) evaluated 129 neonates born to women with autoimmune thyroiditis. They found that 28 percent had an elevated TSH level on the third or fourth day of life, and 47 percent of these had TPO antibodies on day 15. Still, autoantibodies were undetectable at age 6 months. In their analysis, Korevaar and coworkers (2016a) concluded that maternal TPO antibodies have no clinically relevant effects on the thyroid function of offspring. Indeed, prevalence of fetal hypothyroidism in women with Hashimoto thyroiditis is estimated to be only 1 case in 180,000 newborns (Brown, 1996).

■ Subclinical Hypothyroidism

Although common in women, the incidence of subclinical hypothyroidism varies depending on age, race, dietary iodine intake, and serum TSH thresholds used (Jameson, 2015). In two large studies totaling more than 25,000 pregnant women screened in the first half of pregnancy, subclinical hypothyroidism was identified in 2.3 percent (Casey, 2005; Cleary-Goldman, 2008). The rate of progression to overt thyroid failure is affected by TSH level, age, other disorders such as diabetes, and presence and concentration of antithyroid antibodies.

Diez and Iglesias (2004) prospectively followed 93 nonpregnant women with subclinical hypothyroidism for 5 years and reported that in a third, TSH values became normal. In the other two thirds, those women whose TSH levels were 10 to 15 mU/L developed overt disease at a rate of 19 cases per 100 patient-years. Those women whose TSH levels were <10 mU/L developed overt hypothyroidism at a rate of 2 cases per 100 patient-years.

Regarding screening for subclinical hypothyroidism in nonpregnant individuals, the U.S. Preventive Services Task Force also reports that nearly all patients who develop overt hypothyroidism within 5 years have an initial TSH level >10 mU/L (Helfand, 2004; Karmisholt, 2008). From one metaanalysis of data from nonpregnant adults with subclinical hypothyroidism, thyroid hormone therapy was not associated with improved general quality of life, thyroid-related symptoms, depression, blood pressure, or other cardiovascular outcomes (Feller, 2018).

In a 20-year follow-up study of 5805 women who were screened in early pregnancy, only 3 percent developed thyroid disease. Of the 224 women identified with subclinical hypothyroidism during pregnancy, 17 percent developed thyroid disease in the next 20 years, and most of these had either TPO or thyroglobulin antibodies during pregnancy (Männistö, 2010). Thus, the likelihood of progression to overt hypothyroidism *during* pregnancy in otherwise healthy women with subclinical hypothyroidism seems remote.

Subclinical Hypothyroidism and Pregnancy

Interest in this subject was heightened 20 years ago by two studies reporting that undiagnosed maternal thyroid hypofunction may impair fetal neuropsychological development (Haddow, 1999; Pop, 1999). Notably, in the Haddow study, many women had both elevated TSH and abnormally low serum free T_4 levels and thus had *overt* hypothyroidism. To evaluate any adverse pregnancy effects, Casey and colleagues (2005) identified subclinical hypothyroidism in 2.3 percent of 17,298 women screened at Parkland Hospital before midpregnancy. These women had small but significantly higher incidences of preterm birth, placental abruption, and neonates admitted to the intensive care nursery compared with euthyroid women. In another study of 10,990 similar women, however, Cleary-Goldman and associates (2008) did not find such associations.

Other studies subsequently confirmed a link between subclinical thyroid function and adverse outcomes (Chen, 2017; Maraka, 2016). One included 24,883 women screened throughout pregnancy and showed an almost twofold greater risk of severe preeclampsia (Wilson, 2012). In an analysis of the latter cohort, a consistent relationship was shown between rising TSH levels and the risk for gestational diabetes (Tudela, 2012). Last, Nelson and associates (2014) found an elevated risk for diabetes and stillbirth.

Lazarus and coworkers (2012) reported the findings of the international multicenter Controlled Antenatal Thyroid Screening (CATS) study. They evaluated prenatal thyroid screening with randomized treatment of both subclinical hypothyroidism and isolated maternal hypothyroxinemia. They found that offspring IQ scores at age 3 years were not superior in the treated cohort. Later evaluation of these offspring through age 9 confirmed that maternal treatment offered no benefit (Hales, 2018). Last, the Maternal-Fetal Medicine Units (MFMU) Network screened more than 97,000 pregnant women for thyroid disorders and reported that 3.3 percent had subclinical hypothyroidism. These 677 women were randomly assigned to thyroxine replacement therapy or placebo. As reported by Casey and colleagues (2017) and shown in Table 61-4, adverse pregnancy outcomes or cognitive development in the offspring at 5 years did not differ between groups. Annual developmental testing scores and behavioral and attention-deficit hyperactivity disorder results also did not differ.

Because of earlier study findings, some professional organizations began to recommend routine prenatal screening and treatment of subclinical hypothyroidism. However, after the CATS and MFMU Network studies, more recent clinical practice guidelines from the Endocrine Society, the American Thyroid Association, and the American Association of Clinical Endocrinologists now uniformly recommended screening only those at greater risk during pregnancy (Alexander, 2017; De Groot, 2012; Garber, 2012). This has been and still is the recommendation of the American College of Obstetricians and Gynecologists (2020).

Isolated Maternal Hypothyroxinemia

Women with low serum free T_4 values but a normal-range TSH level are considered to have *isolated maternal hypothyroxinemia*. Its incidence in two large trials was 1.3 to 2.1 percent (Casey, 2007; Cleary-Goldman, 2008). As shown in Figure 61-2, unlike in subclinical hypothyroidism, these women have a low prevalence of antithyroid antibodies.

Initial studies reported that offspring of women with isolated hypothyroxinemia had neurodevelopmental difficulties (Levie, 2018; Li, 2010; Pop, 1999, 2003). Casey and colleagues

TABLE 61-4. Maternal-Fetal Medicine Unites Network: Pregnancy Outcomes According to Diagnosis and Treatment of Thyroid Disorders[a]

	Subclinical Hypothyroidism		Isolated Hypothyroxinemia	
Outcome	**Thyroxine**	**Placebo**	**Thyroxine**	**Placebo**
Maternal				
EGA at delivery (weeks)	39.1 ± 2.5	38.9 ± 3.1	39.0 ± 2.4	38.8 ± 3.1
Preterm birth <34 weeks	9.1%	10.9%	3.8%	2.7%
Placental abruption	0.3%	1.5%	1.1%	0.8%
Preeclampsia	6.5%	5.9%	3.4%	4.2%
Diabetes	7.4%	6.5%	8.0%	9.2%
Perinatal and Childhood				
Stillbirth	12/1000	21/1000	8/1000	19/1000
Neonatal death	0	3/1000	4/1000	4/1000
NICU admission	8.6%	6.2%	11.8%	11.9%
Birthweight <10th centile	9.8%	8.1%	8.8%	7.8%
IQ median (25th, 75th percentile)	97 (85,105)	94 (85,107)	94 (83,101)	91 (82,101)

[a]For all comparisons, $p > 0.05$.
EGA = estimated gestational age; IQ = intelligence quotient; NICU = neonatal intensive care unit.

(2007), however, found no higher risks in these women for other adverse perinatal outcomes compared with those of euthyroid women. In contrast, a recent individual patient data systematic analysis including 47,045 pregnant women identified a higher risk of preterm birth associated with isolated hypothyroxinemia (Consortium on Thyroid and Pregnancy, 2019).

The aforementioned CATS study, including follow-up of offspring through age 9 years, did not find improved neurodevelopmental outcomes in women with isolated hypothyroxinemia who were then treated with thyroxine (Hales, 2018; Lazarus, 2012). The randomized trial conducted by the MFMU Network also demonstrated no improvement in neurocognitive development with thyroxine treatment during pregnancy (Casey, 2017). This large randomized study also found no higher rates of adverse pregnancy outcomes between groups and found that early thyroxine treatment offered no benefits (see Table 61-4). The American Thyroid Association currently recommends against routine treatment of isolated hypothyroxinemia in pregnancy (Alexander, 2017).

Euthyroid Autoimmune Thyroid Disease

Autoantibodies to TPO and thyroglobulin have been identified in 2 to 17 percent of pregnant women worldwide (Alexander, 2017). Most who test positive for such antibodies, however, are euthyroid. That said, such women carry a two- to fivefold increased risk for early pregnancy loss (Stagnaro-Green, 2004; Thangaratinam, 2011). The presence of thyroid antibodies has also been associated with preterm birth (He, 2012). In a randomized treatment trial of 115 euthyroid women with TPO antibodies, levothyroxine astoundingly reduced the preterm birth rate from 22 to 7 percent (Negro, 2006). In a follow-up trial restricted to women with a TSH <2.5 mU/L, however, levothyroxine treatment had no effect on this risk (Negro, 2016).

In another study, Abbassi-Ghanavati and associates (2010) evaluated pregnancy outcomes in more than 1000 untreated women with TPO antibodies and did not find a higher risk for preterm birth compared with the risk in 16,000 euthyroid women without antibodies. These investigators, however, did find a threefold greater risk of placental abruption in these women. More recently, the Consortium on Thyroid and Pregnancy-Study Group on Preterm Birth (2019) estimated a marginal 1.3-fold increased risk for preterm birth in their meta-analysis of women with TPO antibodies.

As with nonpregnant subjects with TPO antibodies, pregnant women are also at increased risk in later life for progression of thyroid disease and postpartum thyroiditis (Jameson, 2015; Stagnaro-Green, 2012a). Currently, universal screening for the thyroid autoantibodies is not recommended by any professional organization (Alexander, 2017; American College of Obstetricians and Gynecologists, 2020; De Groot, 2012).

Iodine Deficiency

Decreasing iodide fortification of table salt and bread products in the United States during the past 25 years has led to occasional iodide deficiency (Caldwell, 2005; Hollowell, 1998). Importantly, the most recent National Health and Nutrition Examination Survey indicated that, overall, the United States population remains iodine sufficient (Herrick, 2018). However, experts agree that iodine nutrition in vulnerable populations, such as pregnant women, requires continued monitoring. In 2014, the Office of Dietary Supplements of the National Institutes of Health sponsored three workshops to identify information gaps and develop an iodine research agenda. Participants emphasized the gradual decline in median urinary iodine levels in pregnant women and the serious potential effects on developing fetuses (Pearce, 2016).

Dietary iodine requirements are higher during pregnancy due to augmented thyroid hormone production, increased renal losses, and fetal iodine requirements. Adequate iodine is requisite for fetal neurological development beginning soon after conception, and abnormalities vary by the degree of deficiency. For example, Levie and colleagues (2019) demonstrated a positive correlation between maternal urinary iodine/creatinine ratio in the first trimester and offspring nonverbal IQ scores. UNICEF (2018) estimates that nearly 19 million babies born globally every year are at risk of permanent yet preventable brain damage or of reduced cognitive function from iodine deficiency.

Although it is doubtful that *mild deficiency* causes intellectual impairment, supplementation does prevent fetal goiter (Stagnaro-Green, 2012b). In one randomized trial with more than 800 women who had mild deficiency, daily iodine supplementation had no effect on child neurodevelopment at age 5 to 6 years (Gowachirapant, 2017). Supplementation studies conducted in regions with *moderate deficiency* have reported inconsistent findings with regard to psychomotor development (Bell, 2016). Berbel and associates (2009) began daily supplementation in more than 300 pregnant women with moderate deficiency at three time periods. They found improved neurobehavioral development scores in offspring of women supplemented with 200 μg of potassium iodide very early in pregnancy. Similarly, Velasco and coworkers (2009) found improved Bayley Psychomotor Development scores in offspring of women supplemented with 300 μg of iodine daily in the first trimester. In contrast, Murcia and colleagues (2011) identified lower psychomotor scores in 1-year-old infants whose mothers reported daily supplementation of more than 150 μg. *Severe deficiency* is frequently associated with damage typically encountered with *endemic cretinism*, and benefits of universal salt iodization or supplementation have been confirmed (Alexander, 2017).

Regarding daily iodine intake, the Institute of Medicine (2001) recommends 220 μg/d during pregnancy and 290 μg/d during lactation (Chap. 10, p. 185). The American Thyroid Association recommends an average iodine intake of 250 μg/d in all pregnant women and has recommended that 150 μg of iodine be added to prenatal vitamins to achieve this average daily oral intake (Alexander, 2017; Kerver, 2021). In an older study, Leung and coworkers (2011) reported that only half of the prenatal multivitamins in the United States contained iodine. Without evidence of benefit, however, it is hard to justify the cost of iodine supplementation of large numbers of pregnant women in areas with mild iodine deficiency (Pearce, 2016).

Importantly, experts caution against oversupplementation since excessive iodine exposure can lead to subclinical thyroid dysfunction and is associated with increased prevalence of thyroid autoimmunity (Pearce 2016; Shi, 2015). The American Thyroid Association advises against exceeding twice the daily recommended intake of iodine, which is 500 μg/d (Alexander, 2017).

Congenital Hypothyroidism

Universal newborn screening for neonatal hypothyroidism was introduced in 1974 and is now required by law in all states (Chap. 32, p. 594). This develops in approximately 1 in 2000 newborns. The reported incidence has increased during the past few decades and is thought to stem from greater preterm neonate survival rates and methodological shifts in newborn screening (McGrath, 2019). Variation in TSH percentiles according to gestational age at delivery have led some to propose age-adjusted cutoffs to avoid overdiagnosis (Kaluarachchi, 2019). Developmental disorders of the thyroid gland such as agenesis and hypoplasia account for 80 to 90 percent of cases. The remainder may be caused by hereditary defects in thyroid hormone production, but it is estimated that up to 15 percent may have a transient form of the disease (McGrath, 2018; Oron, 2018).

Early and aggressive thyroxine replacement is critical for affected newborns (van Trotsenburg, 2021). In one study of 76 children with congenital hypothyroidism, IQ scores at age 18 years did not differ from those in 40 siblings, provided the initial thyroxine dose was sufficiently high (Aleksander, 2018).

Postpartum Thyroiditis

Transient autoimmune thyroiditis is consistently found in approximately 5 to 10 percent of women during the first year after childbirth (Nathan, 2014; Nguyen, 2019). With an onset within 12 months, postpartum thyroid dysfunction includes hyperthyroidism, hypothyroidism, or both. The propensity for thyroiditis antedates pregnancy and is directly related to increasing serum levels of thyroid autoantibodies. Up to 50 percent of women who have thyroid antibodies in the first trimester will develop postpartum thyroiditis (Stagnaro-Green, 2012a). As mentioned previously, routine thyroid autoantibody testing during pregnancy is currently not recommended (American College of Obstetricians and Gynecologists, 2020).

In clinical practice, postpartum thyroiditis is diagnosed infrequently because it typically develops months after delivery and causes vague symptoms (Nguyen, 2019). The presentation varies, and classically two clinical phases that may develop in succession are recognized. The first and earliest is *destruction-induced thyrotoxicosis* with symptoms from excessive release of hormone from glandular disruption. The onset is abrupt, and a small, painless goiter is common. From many possible symptoms, only fatigue and palpitations are more frequent in thyrotoxic women compared with normal controls. This thyrotoxic phase usually lasts only a few months. Thionamides are ineffective, and if symptoms are severe, a β-blocking agent may be given. The second and usually later phase between 4 and 8 months postpartum is *hypothyroidism* from thyroiditis. Thyromegaly and other symptoms are common and more prominent than during the thyrotoxic phase. Levothyroxine replacement at doses of 25 to 75 μg/d is typically given for 6 to 12 months.

Stagnaro-Green and associates (2011) reported postpartum surveillance results in 4562 Italian gravidas who had been screened for thyroid disease in pregnancy. Serum TSH and anti-TPO antibody levels were measured again at 6 and 12 months. Overall, 169 women (3.9 percent) developed postpartum thyroiditis, and two thirds of these were identified to have hypothyroidism only. The other third were diagnosed with hyperthyroidism. Only 14 percent of all women demonstrated the classic biphasic progression. These findings are consistent with data compiled from 20 other studies between 1982 and 2008 (Stagnaro-Green, 2012a).

Importantly, women who experience either type of postpartum thyroiditis have a 20- to 30-percent risk of eventually developing permanent hypothyroidism, and the annual progression rate is 3.6 percent (Nathan, 2014). Women at greater risk for developing hypothyroidism are those with higher titers of thyroid antibodies and higher TSH levels during the initial hypothyroid phase. Others may develop subclinical disease, but half of those with thyroiditis who are positive for TPO antibodies develop permanent hypothyroidism by 6 to 7 years (Stagnaro-Green, 2012a).

An association between postpartum thyroiditis and postpartum depression has been proposed but remains unresolved (Alexander, 2017). Similarly unsettled is the link between depression and thyroid antibodies. Kuijpens and associates (2001) reported that TPO antibodies were a marker for postpartum depression in euthyroid women. In a randomized trial, however, Harris and coworkers (2002) reported no difference in postpartum depression in 342 women with TPO antibodies who were given either levothyroxine or placebo. Somewhat related, in the MFMU Network randomized trial, women with subclinical hypothyroidism allocated to thyroxine treatment during pregnancy did not experience improvement in their depression (Costantine, 2020).

Nodular Thyroid Disease

Palpable thyroid nodules can be found in up to 5 percent of reproductive-aged women (Angell, 2019). Management of a palpable thyroid nodule during pregnancy depends on gestational age and mass size. Small nodules detected by sensitive sonographic methods are more common during pregnancy in some populations. Kung and associates (2002) used high-resolution sonography and found that 15 percent of Chinese women had nodules larger than 2 mm in diameter. Almost half of cases had multiple masses. The nodules usually enlarged modestly across pregnancy and did not regress postpartum. Biopsy of those measuring >5 mm^3 that persisted at 3 months usually showed nodular hyperplasia, and none was malignant. In most studies, 90 to 95 percent of solitary nodules are benign (Burch, 2016).

Evaluation of thyroid nodules during pregnancy should be similar to that for nonpregnant patients. As discussed in Chapter 49 (p. 875), *radioiodine scanning* in pregnancy is usually not recommended (American College of Obstetricians and Gynecologists, 2020). *Sonographic* examination reliably detects

nodules >5 mm, and their solid or cystic structure also is determined. According to the American Association of Clinical Endocrinologists, sonographic characteristics associated with malignancy include hypoechogenic pattern, irregular margins, and microcalcifications (Gharib, 2016). *Fine-needle aspiration (FNA)* under ultrasound guidance is an excellent assessment method because cytological diagnostic criteria are not substantially influenced by pregnancy (Gharib, 2016). If the FNA biopsy shows a follicular lesion, surgery may be deferred until postpartum.

Evaluation of thyroid cancer involves a multidisciplinary approach (Fagin, 2016). Most thyroid carcinomas are well differentiated and indolent. Messuti and coworkers (2014) provided evidence that persistence or recurrence of these tumors may be more common in pregnant women. For thyroid malignancy diagnosed in the first or second trimester, thyroidectomy may be performed before the third trimester. In women without evidence of an aggressive thyroid cancer or in those diagnosed in the third trimester, surgical treatment can be deferred until the early puerperium (Gharib, 2016) (Chap. 66, p. 1174).

PARATHYROID DISEASE

Parathyroid hormone (PTH) maintains extracellular fluid calcium concentration. This 84-amino-acid hormone acts directly on bone and kidney and indirectly on small intestine to increase serum calcium (Potts, 2015). PTH secretion is regulated by serum ionized calcium concentration through a negative feedback system. *Calcitonin* is a potent parathyroid hormone that acts as a physiological PTH antagonist. The relationships between these hormones, calcium metabolism, and *PTH-related protein (PTH-rP)* produced by fetal tissue are discussed in Chapter 4 (p. 73).

Of fetal demands, calcium requirements reach 300 mg/d in late pregnancy and 30 g for the entire gestation. These needs and greater renal calcium loss from augmented maternal glomerular filtration substantively raise maternal calcium demands. Total serum calcium levels decline with serum albumin concentrations, but ionized calcium levels remain unchanged. Pregnancy is also associated with a twofold rise in serum concentrations of 1,25-dihydroxyvitamin D, which increases gastrointestinal calcium absorption. The effectuating hormone is probably of placental and decidual origin since maternal PTH levels are low normal or decreased during pregnancy (Cooper, 2011). Calcium is actively transported across the placenta and deposited in the developing fetal skeletal system. Fetal calcium homeostasis is maintained through a complex interplay between PTH-rP, PTH, and receptors in the placenta, fetal kidney, and fetal skeleton (Hirai, 2015).

Hyperparathyroidism

Hypercalcemia is caused by hyperparathyroidism or cancer in 90 percent of cases (Potts, 2015). Because many automated laboratory systems include serum calcium measurement, hyperparathyroidism has changed from being a condition defined by symptoms to one that is discovered on routine screening (Pallan, 2012). Hypercalcemia has a reported prevalence of 2 to 3 cases per 1000 women, but some estimate the rate to reach 14 cases per 1000 if asymptomatic women are included. Almost 80 percent are caused by a solitary adenoma, and another 15 percent by hyperfunctioning of all four glands. In the remainder, an associated malignancy is usually obvious. Of note, PTH produced by tumors is not identical to the natural hormone and may not be detected by routine assays.

In most patients with hyperparathyroidism, the serum calcium level is elevated to within only 1 to 1.5 mg/dL above the upper normal limit. This may help to explain why only 20 percent of those who have abnormally elevated levels are symptomatic (Bilezikian, 2004). In a fourth, however, symptoms become apparent when the serum calcium level continues to rise. *Hypercalcemic crisis* manifests as stupor, nausea, vomiting, weakness, fatigue, and dehydration.

Women with symptomatic hyperparathyroidism should be surgically treated (Davis, 2020; Potts, 2015). Indications for parathyroidectomy include a serum calcium level 1.0 mg/dL above the upper normal range, a calculated creatinine clearance <60 mL/min, reduced bone density, or age >50 years (Bilezikian, 2009). Those not meeting these criteria should undergo annual serum calcium and creatinine level measurement and bone density assessment every 1 to 2 years (Pallan, 2012).

Hyperparathyroidism in Pregnancy

In their review, Schnatz and Thaxton (2005) found fewer than 200 reported cases of hyperparathyroidism complicating pregnancy. As in nonpregnant patients, parathyroid adenoma is the most common etiology. Ectopic parathyroid hormone production and rare cases of parathyroid carcinoma have been reported in pregnancy (Montoro, 2000; Saad, 2014). Symptoms of hyperparathyroidism during pregnancy include hyperemesis, generalized weakness, renal calculi, and psychiatric disorders. Occasionally, pancreatitis is the presenting disorder (Hirsch, 2015).

Pregnancy theoretically improves hyperparathyroidism by significantly shunting calcium to the fetus and by augmented renal excretion. When these effects are withdrawn, however, postpartum hypercalcemic crisis is a danger. This life-threatening complication can be seen with serum calcium levels >14 mg/dL, and nausea, vomiting, tremors, dehydration, and mental status changes are symptoms (Malekar-Raikar, 2011).

Early reports described excessive stillbirths and preterm deliveries in pregnancies complicated by hyperparathyroidism. More recent reports, however, describe lower rates of stillbirth, neonatal death, and neonatal tetany (Kovacs, 2011). Other fetal complications include miscarriage, fetal-growth restriction, and low birthweight (Chamarthi, 2011).) One group reported a 30-percent incidence of preeclampsia (Rigg, 2019).

Management in Pregnancy

Surgical removal of a symptomatic parathyroid adenoma is preferable. This should prevent fetal and neonatal morbidities and postpartum parathyroid crises (Kovacs, 2011). In one case series from an Australian referral hospital, 22 pregnancies were managed medically, and six women underwent parathyroidectomy. Preterm delivery was reported in 66 percent of pregnancies managed without surgery, whereas all surgically treated women delivered at term (Rigg, 2019). Elective neck

exploration during pregnancy is usually well tolerated, even in the third trimester (Hirsch, 2015; Stringer, 2017). In at least two cases, a mediastinal adenoma was removed at midpregnancy (Rooney, 1998; Saad, 2014).

Medical management may however be appropriate in asymptomatic pregnant women with mild hypercalcemia (Hirsch, 2015). If so, patients are carefully monitored in the puerperium for hypercalcemic crisis. Initial medical management might include *calcitonin* to decrease skeletal calcium release, or oral phosphate, 1 to 1.5 g daily in divided doses, to bind excess calcium. For women with dangerously elevated serum calcium levels or those who are mentally obtunded with *hypercalcemic crisis*, emergency treatment is instituted. Diuresis with IV normal saline is begun so that urine flow exceeds 150 mL/hr. *Furosemide* is given in conventional doses to block tubular calcium reabsorption. Importantly, hypokalemia and hypomagnesemia should be prevented. Adjunctive therapy includes *mithramycin*, which inhibits bone resorption.

Neonatal Effects

Normally, cord blood calcium levels are higher than maternal levels (Chap. 7, p. 136). With maternal hyperparathyroidism, abnormally elevated maternal and thus fetal levels further suppress fetal parathyroid function. Because of this, newborn calcium levels rapidly drop after birth, and 15 to 25 percent of these neonates develop severe hypocalcemia with or without tetany (Molitch, 2000). Neonatal hypoparathyroidism caused by maternal hyperparathyroidism is usually transient and is treated with calcium and 1,25-dihydroxyvitamin D_3 (calcitriol). The latter will not be effective in preterm infants, however, because the intestinal vitamin D receptor is insufficiently expressed (Kovacs, 2011). Neonatal tetany or seizures should stimulate an evaluation for maternal hyperparathyroidism (Beattie, 2000; Ip, 2003).

■ Hypoparathyroidism

The most common cause of hypocalcemia is hypoparathyroidism that usually follows parathyroid or thyroid surgery. It is estimated that almost 80 percent of cases are attributable to complications of anterior neck surgery (Gafni, 2019). Hypoparathyroidism is characterized by facial muscle spasms, muscle cramps, and paresthesias of the lips, tongue, fingers, and feet. This can progress to tetany and seizures (Potts, 2015). Chronically, hypocalcemic pregnant women may also have a fetus with skeletal demineralization resulting in multiple bone fractures in the neonatal period (Alikasifoglu, 2005).

Maternal treatment includes calcitriol, dihydrotachysterol, or large vitamin D doses of 50,000 to 150,000 U/d; calcium gluconate or calcium lactate in doses of 3 to 5 g/d; and a low-phosphate diet. Fetal risks from large doses of vitamin D have not been established. During treatment, the therapeutic challenge in women with known hypoparathyroidism is management of blood calcium levels. It is possible that the greater calcium absorption typical of pregnancy will result in lower calcium requirements or that the fetal demand for calcium will result in greater need. The goal during pregnancy is to maintain a corrected calcium level in the low normal range.

■ Pregnancy and Lactation-associated Osteoporosis

In most gravidas, even with their remarkably increased calcium requirements, it is uncertain whether pregnancy causes osteopenia. In one study of 200 women, bone density declined during pregnancy (Kraemer, 2011). Women who breastfed, carried twin pregnancies, or had a low body mass index were at higher risk of bone loss. Thomas and Weisman (2006) in their review cite a 3- to 4-percent average reduction in bone mineral density during pregnancy. Lactation also represents a period of negative calcium balance that may be corrected through maternal skeletal resorption. However, data from the Women's Health Initiative found that parity, number of pregnancies, age at first pregnancy, breastfeeding, and duration of breastfeeding were not associated with postmenopausal hip fracture risk or bone density losses (Crandall, 2017).

The most common symptom of this rare disorder of pregnancy-associated osteoporosis is back pain in late pregnancy or postpartum. Other symptoms are hip pain, either unilateral or bilateral, and difficulty in weight bearing until the woman is nearly immobilized (Maliha, 2012). In more than half of women, no apparent reason for osteopenia is found. Some known causes are heparin (unfractionated only), bed rest, and corticosteroid therapy (Cunningham, 2005; Galambosi, 2016). In a few cases, overt hyperparathyroidism or thyrotoxicosis eventually develops.

Treatment is problematic and includes calcium and vitamin D supplementation and pain management. Long-term surveillance of osteopenia indicates that although bone density improves, these women and their offspring may have chronic osteopenia (Carbone, 1995). Related, prenatal supplementation of normal women with cholecalciferol, 1000 IU/d, did not increase offspring bone mineral content, although it did ensure maternal vitamin D repletion (Cooper, 2016). In lactating women with osteoporosis, some advocate cessation of breastfeeding (Zhang, 2017).

ADRENAL GLAND DISORDERS

■ Pheochromocytoma

Pregnancy has profound effects on adrenal cortical secretion. These interrelationships were reviewed by Lekarev and New (2011) and are discussed in detail in Chapter 4 (p. 73). Several adrenal disorders may be encountered in pregnancy.

Of these, pheochromocytomas are chromaffin tumors that secrete catecholamines and usually are located in the adrenal medulla, although 10 percent are located in sympathetic ganglia. They are called the *10-percent tumor* because approximately 10 percent are bilateral, 10 percent are extra adrenal, and 10 percent are malignant. These tumors can be associated with medullary thyroid carcinoma and hyperparathyroidism in some of the autosomally dominant or recessive *multiple endocrine neoplasia syndromes*, as well as in neurofibromatosis and von Hippel-Lindau disease (Neumann, 2018).

Pheochromocytomas complicate approximately 1 per 50,000 pregnancies (Quartermaine, 2018). Notably, they are found in 0.2 to 0.6 percent of hypertensive patients (Lenders, 2019). Symptoms are usually paroxysmal and manifest as hypertensive crisis, seizures, or anxiety attacks. Others are headaches,

sweating, palpitations, chest pain, nausea, vomiting, and pallor or flushing. Hypertension is sustained in 60 percent of patients, but half of these also have paroxysmal crises.

Standard screening is quantification of metanephrines and catecholamine metabolites in a 24-hour urine specimen (Neumann, 2018). Diagnosis is established by measurement of a 24-hour urine collection with at least two of three assays for free catecholamines, metanephrines, or vanillylmandelic acid (VMA). Determination of plasma catecholamine metabolite levels is the most sensitive test, and a pheochromocytoma diagnosis is excluded if they are within normal range (Eisenhofer, 2018). In nonpregnant patients, adrenal localization is usually successful with either computed tomography (CT) or magnetic resonance (MR) imaging. For most cases, preferred treatment is laparoscopic adrenalectomy (Neumann, 2018).

In pregnancy, these tumors are rare but result in dangerous complications. Geelhoed (1983) provided an earlier review of 89 cases in which 43 mothers died. Maternal death was much more common if the tumor was not diagnosed antepartum—58 versus 18 percent. As seen in Table 61-5, maternal mortality rates are now lower but still formidable. In one review of 77 cases, antepartum diagnosis was the most important determinant of maternal mortality risk (Biggar, 2013). However, Salazar-Vega and colleagues (2014) described good outcomes in women diagnosed after delivery.

Diagnosis of pheochromocytoma in pregnancy is similar to that for nonpregnant patients. MR imaging is the preferred technique to locate adrenal and extra-adrenal pheochromocytomas (Fig. 61-5). Importantly, differentiating preeclampsia from the hypertensive crisis caused by pheochromocytoma is essential.

Immediate control of hypertension and symptoms is attained with an α-adrenergic blocking agent such as *phenoxybenzamine*. The dose is 10 to 30 mg, two to four times daily. After α-blockade is achieved, β-blocking drugs such as propranolol may be given for tachycardia. In many cases, surgical exploration and tumor removal are performed during pregnancy, preferably during the second trimester (Biggar, 2013; Dong, 2014). Successful laparoscopic removal of adrenal tumors has become the norm (Miller, 2012; Zuluaga-Gómez, 2012). Donatini and colleagues (2018) described three cases of women with bilateral tumors who had laparoscopic unilateral adrenalectomy of the largest tumor during pregnancy and subsequent contralateral adrenalectomy after delivery to avoid the maternal and fetal effects of adrenal insufficiency. If diagnosed later in pregnancy, either planned cesarean delivery with tumor excision or postpartum resection is appropriate.

Recurrent tumors are troublesome, and even with good blood pressure control, dangerous peripartum hypertension may develop. We have cared for three women in whom recurrent pheochromocytoma was identified during pregnancy. Hypertension was managed with phenoxybenzamine in all three. Two newborns were healthy, but a third was stillborn in a mother with a massive tumor burden who was receiving phenoxybenzamine, 100 mg daily. In all three women, the tumor was resected postpartum.

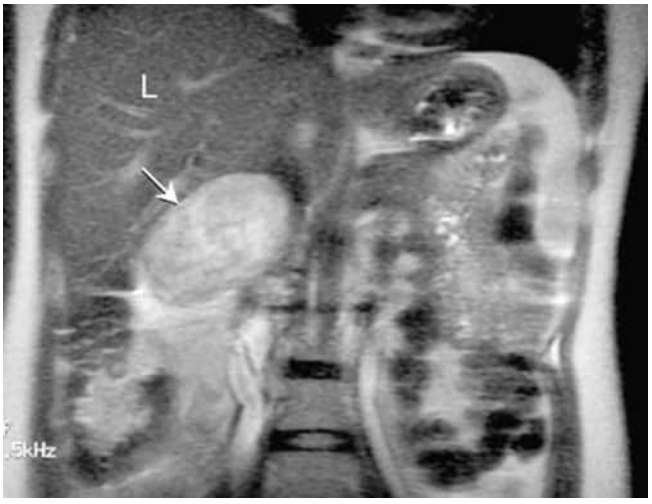

FIGURE 61-5 Coronal magnetic resonance image taken in a 32-week pregnant woman shows a right-sided pheochromocytoma (*arrow*) and its position relative to the liver (*L*) above it.

TABLE 61-5. Outcomes of Pregnancies Complicated by Pheochromocytoma and Reported in Four Contiguous Epochs

	Incidence (%)			
Factor	1980–87 Harper (1989) n = 48	1988–97 Ahlawat (1999) n = 42	1998–2008 Sarathi (2010) n = 60	2000–2001 Biggar (2013) n = 78
Diagnosis				
Antepartum	51	83	70	73
Postpartum	36	14	23	28
Autopsy	12	2	7	
Maternal death	16	4	12	8
Fetal wastage	26	11	17	17

■ Cushing Syndrome

This syndrome is rare and the female:male ratio is 3:1 (Arit, 2018). Most cases of *Cushing syndrome* are iatrogenic from long-term corticosteroid treatment. Excessive glucocorticoids can also be the result of a pituitary adenoma, adrenal tumor, or bilateral adrenal hyperplasia (Melmed, 2020). *Cushing disease* refers to bilateral adrenal hyperplasia stimulated by corticotropin-producing pituitary adenomas. Corticotropin is also called adrenocorticotropic hormone (ACTH). Most adenomas are microadenomas measuring <1 cm, and half measure <5 mm. Rarely, abnormal secretion of hypothalamic corticotropin-releasing factor may cause corticotropic hyperplasia. Such hyperplasia may also be caused by nonendocrine tumors that produce polypeptides similar to either corticotropin-releasing factor or corticotropin. Less than a fourth of cases of Cushing syndrome are corticotropin independent, and most of these are caused by an adrenal adenoma (Machado, 2018). Tumors are usually bilateral, and half are malignant. Occasionally, associated androgen excess may lead to severe virilization.

The typical cushingoid body habitus is caused by adipose tissue deposition creating *moon facies*, a *buffalo hump*, and *truncal*

obesity. Fatigability and weakness, hypertension, hirsutism, and amenorrhea are each encountered in 75 to 85 percent of nonpregnant patients (Hatipoglu, 2012; Melmed, 2020). Personality changes, easy bruising, and cutaneous striae are common. Up to 60 percent may have impaired glucose tolerance. Diagnosis can be difficult and is suggested by elevated plasma cortisol levels that cannot be suppressed by dexamethasone or by elevated 24-hour urinary free cortisol excretion in three collections (Arit, 2018; Loriaux, 2017). Neither test is totally accurate, and each is more difficult to interpret in obese patients. Serum corticotropin levels and CT and MR imaging are used to localize pituitary and adrenal tumors or hyperplasia.

In pregnancy, diagnosis can be difficult because of pregnancy-induced increases in plasma cortisol, corticotropin, and corticotropin-releasing factor levels. Measurement of urinary free cortisol excretion in a 24-hour collection sample is recommended. With interpretation of results, the normal elevation seen in pregnancy is factored. Because most women have corticotropin-dependent Cushing syndrome, associated androgen excess may cause anovulation, and pregnancy is rare. Caimari and coworkers (2017) identified 263 pregnancies in 220 women with Cushing syndrome in their systematic review. These differ compared with nonpregnant women in that more than half are caused by corticotropin-independent adrenal adenomas (Kamoun, 2014; Lacroix, 2015; Machado, 2018). Approximately 30 percent of cases are from a pituitary adenoma, and 10 percent from adrenal carcinomas. Pregnancy outcomes reviewed by Caimari and associates (2017) in women with Cushing syndrome are listed in Table 61-6.

Long-term medical therapy for Cushing syndrome usually is ineffective, and definitive therapy is resection of the pituitary or adrenal adenoma or bilateral adrenalectomy for hyperplasia (Lacroix, 2015; Machado, 2018). During pregnancy, management of hypertension in mild cases may suffice until delivery. In their review, Lindsay and associates (2005) described primary medical therapy in 20 women with Cushing syndrome. Most were successfully treated with *metyrapone* as an interim treatment until definitive surgery after delivery. A few cases were treated with oral *ketoconazole*. However, because this drug also blocks testicular steroidogenesis, treatment during pregnancy with a male fetus is worrisome. *Mifepristone,* the norethindrone derivative used for abortion and labor induction, has shown promise for treating Cushing disease but should not be used in pregnancy for obvious reasons. Transsphenoidal resection of a pituitary mass or laparoscopic adrenalectomy are considered first-line treatment options in the second trimester (Brue, 2018; Manoharan, 2020). Unilateral adrenalectomy has been safely performed in the early third trimester and can also be curative (Abdelmannan, 2011).

TABLE 61-6. Complications in Pregnancies of Women with Active and Cured Cushing Syndrome

Complication	Incidence (%)	
	Active Disease (n = 214)	Cured (n = 49)
Maternal		
Diabetes	37	2
Gestational hypertension	40	2
Preeclampsia	26	2
Cesarean delivery	52	22
Mortality	1	0
Perinatal		
Preterm birth	66	3
Fetal-growth restriction	15	5
Spontaneous abortion	11	6
Stillbirth	6	2
Neonatal death	5	0

Adrenal Insufficiency—Addison Disease

Primary adrenocortical insufficiency is rare because more than 90 percent of total gland volume must be destroyed for symptoms to develop. *Autoimmune adrenalitis* is the most common cause in the developed world, but tuberculosis is a more frequent etiology in resource-poor countries (Arit, 2018; Betterle, 2019; Kamoun, 2014). In the United States, the prevalence in 7.7 million births was 1 case per 10,000 to 20,000 (Schneiderman, 2017). There is an increased incidence of concurrent Hashimoto thyroiditis, primary ovarian insufficiency, type 1 diabetes, and Graves disease. These *polyglandular autoimmune syndromes* also include pernicious anemia, vitiligo, alopecia, nontropical sprue, and myasthenia gravis.

Untreated adrenal hypofunction frequently causes infertility, but with replacement therapy, ovulation is restored. If untreated, women often note weakness, nausea, vomiting, and weight loss. Low levels of plasma cortisol and elevated ACTH levels are generally considered diagnostic (Betterle, 2019). Because serum cortisol levels rise during pregnancy, a short ACTH-stimulation test documenting less than a twofold increase in plasma cortisol in response to infused corticotropin confirms the diagnosis (Manoharan, 2020).

In a large cohort study, 1188 women with Addison disease were compared with more than 11,000 age-matched controls who delivered between 1973 and 2006 (Björnsdottir, 2010). Women diagnosed with adrenal insufficiency within 3 years of delivery were significantly more likely to deliver preterm, to deliver a low-birthweight newborn, and to undergo cesarean delivery. Others have reported similar adverse outcomes (Quartermaine, 2018). Most pregnant women with Addison disease are already taking glucocorticoid and mineralocorticoid replacement drugs. These should be continued, and women are observed for evidence of either inadequate or excessive corticosteroid replacement. A 20- to 40-percent dose increase is usually expected after midpregnancy to mimic the physiological cortisol elevation in pregnancy (Oliveira, 2018). During labor, delivery, and postpartum, or after a surgical procedure, corticosteroid replacement must be increased appreciably to approximate the normal adrenal response. This augmented dose is called a *stress dose*, and one option is hydrocortisone, 100 mg, given IV every 8 hours for 48 hours. Importantly, shock from causes other than adrenocortical insufficiency—for example, hemorrhage or sepsis—must be recognized and treated promptly.

Primary Aldosteronism

Hyperaldosteronism is caused by an adrenal adenoma—Conn syndrome—in approximately 75 percent of cases. Idiopathic bilateral adrenal hyperplasia makes up the remainder, except for rare cases of adrenal carcinoma (Eschler, 2015; Yang, 2020). Findings include hypertension, hypokalemia, and muscle weakness. High serum or urine levels of aldosterone confirm the diagnosis.

In normal pregnancy, as discussed in Chapter 4 (p. 74), progesterone blocks aldosterone action, and this results in very high aldosterone levels (Appendix, p. 1230). Accordingly, the diagnosis of hyperaldosteronism during pregnancy can be difficult. Because renin levels are suppressed in pregnant women with hyperaldosteronism, a plasma aldosterone-to-renin activity ratio may be helpful for diagnosis (Morton, 2015). Hypertension worsens as pregnancy progresses, and medical management includes potassium supplementation and antihypertensive therapy. In many cases, hypertension responds to *spironolactone.* However, β-blocking or calcium channel–blocking drugs may be preferred because of the potential fetal antiandrogenic effects of spironolactone. Mascetti and coworkers (2011) reported successful use of *amiloride* in a pregnant woman. Use of *eplerenone*, a selective aldosterone-receptor antagonist, also has been described (Manoharan, 2020). Laparoscopic tumor resection is considered curative, but the optimal management during pregnancy, either surgical or medical, remains unclear (Eschler, 2015; Morton, 2015).

PITUITARY DISORDERS

Prolactinomas

The pituitary enlarges impressively during pregnancy, predominantly from lactotrophic cellular hyperplasia induced by estrogen (Chap. 4, p. 70). Several pituitary disorders also can complicate pregnancy.

Of these, prolactinomas are tumors that constitute 75 percent of pituitary adenomas in women (Melmed, 2020). They are often found in nonpregnant women since the advent of widely available serum prolactin assays. Serum levels <25 pg/mL are considered normal in nonpregnant women. Adenoma symptoms and findings include amenorrhea, galactorrhea, and hyperprolactinemia. Tumors are classified arbitrarily by their size measured by CT or MR imaging. A microadenoma is ≤10 mm, and a macroadenoma is >10 mm. Treatment for microadenomas is usually with bromocriptine, a dopamine agonist and powerful prolactin inhibitor, which frequently restores ovulation. For suprasellar macroadenomas, most recommend surgical resection before pregnancy is attempted (Araujo, 2015; Melmed, 2020).

In a pooled analysis of more than 750 pregnant women with prolactinomas, only 2.4 percent with *microadenomas* developed symptomatic enlargement during pregnancy (Molitch, 2015). Symptomatic enlargement of *macroadenomas*, however, is more frequent and was found in 21 percent of 238 pregnant women. In another study of 46 women with a macroprolactinoma, 20 percent had tumor growth–related symptoms (Barraud, 2020). Nonfunctioning adenomas can also cause symptoms of pituitary expansion in pregnancy (Lambert, 2017).

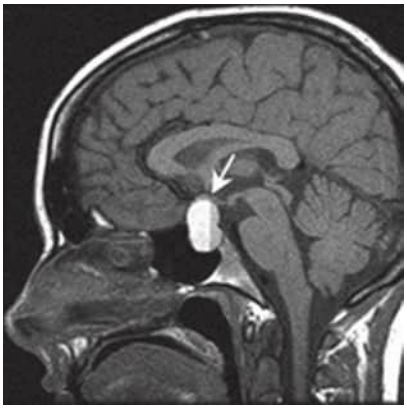

FIGURE 61-6 Magnetic resonance imaging of a pituitary adenoma. This sagittal T1-weighed image demonstrates a fluid-fluid level, consistent with intratumoral hemorrhage (*arrow*). (Reproduced with permission from Dr. Toral Patel.)

Pregnant women with microadenomas should be queried regularly for headaches and visual symptoms. Those with macroadenomas are followed more closely and have visual field testing each trimester. CT or MR imaging is recommended only if symptoms develop (Fig. 61-6). Serial serum prolactin levels serve little use because of normal rises during pregnancy (Appendix, p. 1231). Symptomatic tumor enlargement should be treated immediately with a dopamine antagonist. The safety of bromocriptine in pregnancy is well established. The safety profile is less well known for cabergoline. This drug is increasingly used in nonpregnant women because it is better tolerated and more effective. Cabergoline is generally considered safe for use in pregnancy (Huang, 2019; O'Sullivan, 2020). Surgery is recommended for women with no response, including those with pituitary apoplexy (Barraud, 2020).

Acromegaly

This is caused by excessive growth hormone, usually from an acidophilic or a chromophobic pituitary adenoma. In normal pregnancy, pituitary growth hormone levels decline as placental epitopes are secreted. Diagnosis is suggested by elevated insulin growth factor 1 (IGF-1) serum levels. Levels are more indicative in the first half of pregnancy because IGF-1 concentrations rise in normal pregnancy after midpregnancy (Abucham, 2017; Melmed, 2020). Definitive diagnosis may best be postponed until after delivery. Fewer than 100 cases of acromegaly have been reported during pregnancy (Cheng, 2012; Dias, 2013). Pregnancy is rare in women with acromegaly because half are hyperprolactinemic and anovulatory. During pregnancy, affected women are at marginally greater risk for gestational diabetes and hypertension (Dias, 2013; Jallad, 2018).

Management is similar to that for prolactinomas, and women are monitored for symptoms of tumor enlargement. Dopamine agonist therapy is less effective than for prolactinomas. Transsphenoidal resection, generally considered first-line treatment outside of pregnancy, may be necessary for symptomatic tumor enlargement during pregnancy (Motivala, 2011). Guven and associates (2006) reported a case of pituitary apoplexy necessitating emergent transsphenoidal adenoma resection and

cesarean delivery at 34 weeks' gestation. Successful treatment of pregnant women with the somatostatin-receptor ligand *octreotide* and with the growth hormone analogue *pegvisomant* has been reported (Dias, 2013; Fleseriu, 2015).

Diabetes Insipidus

Vasopressin deficiency evident in diabetes insipidus (DI) is most commonly due to neurohypophysis agenesis or destruction. True DI rarely complicates pregnancy. Instead, other types of DI encountered during pregnancy include primary polydipsia, gestational DI, and nephrogenic DI. These show suppressed secretion of, increased degradation of, and renal insensitivity to vasopressin, respectively (Robertson, 2016). In our experiences, transient secondary DI is more likely encountered with acute fatty liver of pregnancy (Nelson, 2013). This probably stems from altered vasopressinase clearance because of hepatic dysfunction (Chap. 58, p. 1035).

DI therapy is intranasal administration of a synthetic analogue of vasopressin, *desmopressin*, which is 1-deamino-8-D-arginine vasopressin (DDAVP). Available data on the safety of DDAVP during pregnancy is reassuring (Chanson, 2019). Most women require higher doses during pregnancy because of an increased metabolic clearance rate stimulated by placental vasopressinase (Lindheimer, 1994). The prevalence of placental vasopressinase-induced DI is estimated at 2 to 4 cases per 100,000 pregnancies (Wallia, 2013).

Sheehan Syndrome

Sheehan (1937) reported that pituitary ischemia and necrosis associated with obstetrical blood loss could result in hypopituitarism. With modern methods of hemorrhagic shock treatment, Sheehan syndrome rates have gradually declined (Matsuzaki, 2017; Pappachan, 2015). Affected women may have persistent hypotension, tachycardia, hypoglycemia, and lactation failure. Because deficiencies of some or all pituitary-responsive hormones may develop after the initial insult, Sheehan syndrome can be heterogenous and may not be identified for years (Chanson, 2019). In one cohort study of 60 women with Sheehan syndrome, the average time to diagnosis was 13 years (Gei-Guardia, 2011). Because adrenal insufficiency is the most life-threatening complication, adrenal function should be immediately assessed. After glucocorticoid replacement, subsequent analyses and replacement of thyroid, gonadal, and growth hormones is considered. Women with Sheehan syndrome who become pregnant likely have a livebirth (Vila, 2020).

Lymphocytic Hypophysitis

This rare autoimmune pituitary disorder is characterized by massive infiltration by lymphocytes and plasma cells with parenchymal destruction of the gland. Many cases are temporally linked to pregnancy, and more than half of reported cases in women are identified during pregnancy or puerperium (Gubbi, 2018). However, more recent reports describe fewer cases associated with pregnancy (Chanson, 2019). The degrees of hypopituitarism or mass effect symptoms, including headaches and visual field defects, vary. A sellar mass is seen with CT or MR imaging. A mass accompanied by a modestly elevated serum prolactin level—usually <100 pg/mL—suggests lymphocytic hypophysitis. In contrast, levels >200 pg/mL are encountered with prolactinoma. The etiology is unknown, but nearly 30 percent have a history of coexisting autoimmune diseases including Hashimoto thyroiditis, Addison disease, type 1 diabetes, or pernicious anemia (Chanson, 2019). Treatment is with glucocorticoids and pituitary hormone replacement. The disease may be self-limited, and a careful withdrawal of hormone replacement is attempted after inflammation subsides (Foyouzi, 2011; Melmed, 2020). More than two thirds of women who require treatment for lymphocytic hypophysitis, however, will require long-term hormone replacement (Gubbi, 2018).

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CHAPTER 62

Connective Tissue Disorders

Connective tissue disorders, also termed collagen vascular disorders, have two basic underlying causes. First are the *immune-complex diseases*, in which deposition of immune complexes causes connective tissue damage. Because these manifest by sterile inflammation—predominantly of the skin, joints, blood vessels, and kidneys—they are referred to as rheumatic diseases. Many of these immune-complex diseases are more prevalent in women, and systemic lupus erythematosus (SLE) and rheumatoid arthritis are examples. Second are the *inherited disorders* that involve bone, skin, cartilage, blood vessels, and basement membranes. These include Marfan syndrome, osteogenesis imperfecta, and Ehlers-Danlos syndrome.

IMMUNE-MEDIATED CONNECTIVE TISSUE DISEASES

These disorders can be separated into those associated with and those without autoantibody formation. The *rheumatoid factor* is an autoantibody found in many autoimmune inflammatory conditions such as SLE, rheumatoid arthritis, systemic sclerosis (scleroderma), mixed connective tissue disease, dermatomyositis, polymyositis, and various vasculitis syndromes. Instead, the *RF-seronegative spondyloarthropathies* are strongly associated with expression of the antigen termed human leukocyte antigen B27 (HLA-B27). These include ankylosing spondylitis, psoriatic arthritis, Reiter disease, and other arthritis syndromes.

The normal immunosuppression of pregnancy that allows and is essential for successful engraftment of fetal and placental tissues may mitigate activity in some of these syndromes. First, estrogens upregulate and androgens downregulate T-cell response, and progesterone is immunosuppressive (Abdul Hussain, 2020; Robinson, 2012). Second, pregnancy induces a predominance of T2 helper cells compared with cytokine-producing T1 helper cells (Petri, 2019). These changes are discussed in detail in Chapter 4 (p. 61).

However, active immune-mediated disease may contribute to obstetrical complications (Kither, 2020). One longitudinal cohort study found that unrecognized autoimmune systemic rheumatic disorders are associated with significant risk for preeclampsia and fetal-growth restriction (Spinillo, 2016). In this study, the prevalence of unrecognized systemic rheumatic diseases approximated 0.3 percent, and preeclampsia or fetal-growth restriction complicated 25 percent of these pregnancies.

Last, some immune-mediated diseases may be either caused or activated as a result of prior pregnancies. To explain, fetal cells and cell-free DNA are detectable in maternal blood beginning early in pregnancy (Simpson, 2013; Waldorf, 2008). *Fetal cell microchimerism* is the persistence of fetal cells in the maternal circulation and in organs following pregnancy. These fetal cells may become engrafted in maternal tissues and stimulate production of autoantibodies. Evidence for this includes fetal stem cells engrafted in tissues in women with autoimmune thyroiditis and systemic sclerosis (Jimenez, 2005; Srivatsa, 2001). Such microchimerism has also been described in women with SLE

TABLE 62-1. Some Autoantibodies Produced in Patients with Systemic Lupus Erythematosus

Antibody	Prevalence (%)	Clinical Associations
Antinuclear (ANA)	84–98	Best screening test, multiple antibodies; a second negative test makes SLE unlikely
Anti-dsDNA	62–70	High titers SLE-specific; may correlate with disease activity, nephritis, and vasculitis
Anti-Sm (Smith)	25–38	Specific for SLE
Anti-SS-A (Ro)	30–49	Not SLE-specific; associated with sicca syndrome, predisposes to cutaneous lupus, neonatal lupus with heart block, reduced risk of nephritis
Anti-SS-B (La)	10–35	Associated with anti-Ro
Antiphospholipid	21–50	Lupus anticoagulant and anticardiolipin antibodies associated with thrombosis, fetal loss, thrombocytopenia, valvular heart disease; false-positive test for syphilis
Anti-RNP	33–40	Not SLE-specific, high titers associated with rheumatic syndromes
Antihistone	70	Common in drug-induced lupus
Antierythrocyte	60	Direct Coombs test, may develop hemolysis
Antiplatelet	30	Thrombocytopenia in 15%; poor clinical test

ANA = antinuclear antibody; dsDNA = double-stranded DNA; RNP = ribonucleoprotein; SLE = systemic lupus erythematosus.
Data from Arbuckle, 2003; Hahn, 2018; Petri, 2020a,b.

and those with rheumatoid arthritis–associated HLA alleles (da Silva, 2016; Lee, 2010). Conversely, engrafted maternal cells may provoke autoimmune conditions in a woman's offspring (Stevens, 2016; Ye, 2012).

SYSTEMIC LUPUS ERYTHEMATOSUS

This autoimmune disease has an intricate pathogenesis that results from interactions between susceptibility genes and environmental factors (Hahn, 2018). Tissue-binding autoantibodies and immune complexes that are directed at one or more nuclear components lead to cellular and organ damage (Tsokos, 2011). In addition to this B-cell antibody production, immunosuppression is impaired, including regulatory T-cell function (Tower, 2013). Some autoantibodies produced in patients with SLE are shown in Table 62-1. Most patients have autoantibodies for many years before clinical disease manifests.

Genetic influences are implicated, and the concordance is higher with monozygotic compared with dizygotic twins—25 versus 2 percent, respectively. Moreover, the frequency in patients with one affected family member is 10 percent. The relative risk of disease rises if the "autoimmunity gene" on chromosome 16 that predisposes to SLE, rheumatoid arthritis, Crohn disease, and psoriasis is inherited. However, susceptibility genes such as *HLA-DR3*, *STAT4*, *APOL1*, *FCGR3A*, and *DNAse1* explain only a portion of the genetic heritability (Hahn, 2018; Yang, 2013).

Interestingly, maternal exposure to fetal genes elevates susceptibility to SLE development. A case-control study found that a child's *HLA-DRB1* genotype raises the risk of SLE in the mother (Cruz, 2016). In contrast, neonatal lupus has been reported in an infant conceived via oocyte donor to a mother with autoimmune disease with circulating anti-Ro and anti-La antibodies (Chiou, 2016).

Clinical Manifestations and Diagnosis

Almost 90 percent of SLE cases develop in women, and it more commonly affects African-American women compared with other populations (Izmirly, 2017; Stojan, 2018). Its prevalence in those of childbearing age approximates 1 case in 500 (Pons-Estel, 2010). Accordingly, the disease is encountered relatively frequently during pregnancy.

SLE notoriously varies in its presentation, course, and outcome (Table 62-2) (Hahn, 2018). Findings may be confined initially to one organ system, and others become involved later. Instead, the disease may first be multisystem. Frequent findings are malaise, fever, arthritis, rash, pleuropericarditis, photosensitivity, anemia, and cognitive dysfunction. At least half of patients have renal involvement. SLE is also associated with declines in attention, memory, and reasoning (Hahn, 2018; Kozora, 2008).

Identification of antinuclear antibodies (ANA) is the best screening test, however, a positive result is not specific for SLE. Low titers can be found in normal individuals, other autoimmune diseases, acute viral infections, and chronic inflammatory processes. Several drugs also can cause a positive reaction. Antibodies to double-stranded DNA (dsDNA) and to Smith (Sm) antigens are relatively specific for SLE, whereas other antibodies are not (see Table 62-1). Although hundreds of autoantibodies have been described in SLE, only a few have been shown to participate in tissue injury (Tsokos, 2011). Microarray profiles are being developed for more accurate diagnosis (Putterman, 2016).

Chronic anemia develops frequently, and there may be leukopenia and thrombocytopenia. Proteinuria and casts are found in the half of patients with glomerular lesions. Lupus nephritis can also cause renal insufficiency, which is more common if there are antiphospholipid antibodies (Riancho-Zarrabeitia, 2020). Other laboratory findings include false-positive syphilis serology, prolonged partial thromboplastin time, and higher rheumatoid factor levels. Increased serum D-dimer concentrations often follow a flare or infection, but unexplained persistent elevations are associated with a high risk for thrombosis (Wu, 2008).

The diagnostic criteria for SLE are listed in Table 62-3. If any four or more of the 11 clinical criteria are present, serially or simultaneously, the diagnosis is made. Importantly, numerous

TABLE 62-2. Some Clinical Manifestations of Systemic Lupus Erythematosus

Organ System	Clinical Manifestations	Percentage
Systemic	Fatigue, malaise, fever, weight loss	~95
Musculoskeletal	Arthralgias, myalgias, polyarthritis, myopathy	~95
Hematological	Anemia, hemolysis, leukopenia, thrombocytopenia, lupus anticoagulant, splenomegaly	70–85
Cutaneous	Malar (butterfly) rash, discoid rash, photosensitivity, oral ulcers, alopecia, skin rashes	50–80
Neurological	Cognitive dysfunction, mood disorder, headache, seizures, stroke	40–60
Cardiopulmonary	Pleuritis, pericarditis, myocarditis, endocarditis, pneumonitis, pulmonary hypertension	30–60
Renal	Proteinuria, nephrotic syndrome, renal failure	30–50
Gastrointestinal	Nausea, pain, diarrhea, abnormal liver enzyme levels	30–40
Vascular	Thrombosis: venous (10%), arterial (5%)	10–15
Ocular	Conjunctivitis, sicca syndrome	10–15

drugs can induce a lupus-like syndrome. These include proton-pump inhibitors, thiazide diuretics, antifungals, antihypertensives, chemotherapeutics, statins, and antiepileptics. Drug-induced lupus is rarely associated with glomerulonephritis and usually regresses when the medication is discontinued (Laurinaviciene, 2017).

Lupus and Pregnancy

In a metaanalysis of nearly 9 million pregnancies, the incidence of lupus approximated 1 case in 900 births (He, 2020). During pregnancy, lupus improves in a third of women, remains unchanged in a third, and worsens in the remaining third. Thus, in any pregnancy, the clinical condition can worsen or *flare* without warning (Hahn, 2018).

In a cohort of 13,555 pregnant women with SLE, the maternal mortality rate was 325 per 100,000 (Clowse, 2008). Maternal deaths invariably occur in those with active disease (Ritchie, 2012). Women with SLE are at greater risk for thrombotic complications, infection, postpartum hemorrhage, and blood transfusion. He and Wei (2020) reported increased risks of adverse pregnancy outcomes in women with SLE compared with unaffected women (Table 62-4).

During the past several decades, pregnancy outcomes in women with SLE have improved remarkably. For most women with inactive or mild/moderate disease activity, pregnancy outcomes are relatively favorable (Buyon, 2015). Women who have confined cutaneous lupus do not usually have adverse outcomes (Hamed, 2013). However, newly diagnosed SLE during pregnancy tends to be severe (Zhao, 2013). In general, pregnancy outcome is best in women for whom: (1) lupus activity has been quiescent for at least 6 months before conception; (2) lupus nephritis manifest by proteinuria or renal dysfunction

TABLE 62-3. Clinical Criteria for Classification of Systemic Lupus Erythematosus

Clinical Manifestations
Skin
Oral ulcers
Alopecia
Synovitis
Serositis
Renal: proteinuria, casts, biopsy
Neurological: seizures, psychosis, myelitis, neuropathies, confusional state
Hemolytic anemia
Leukopenia
Lymphopenia
Thrombocytopenia
Immunological Manifestations
ANA
Anti-dsDNA
Anti-Sm
Antiphospholipid
Hypocomplementemia
Direct Coombs

ANA = antinuclear antibodies; dsDNA = double-stranded DNA; Sm = Smith.
Data from Hahn, 2018; Petri, 2020a,b.

TABLE 62-4. Risk of Adverse Pregnancy Outcomes in Women with Systemic Lupus Erythematosus

Outcome	Relative Risk (CI)
Preeclampsia/Eclampsia	3.4 (3.2–3.6)
Cesarean delivery	1.4 (1.1–1.7)
Stillbirth	16.5 (2.9–92.1)
Fetal loss	7.6 (4.8–11.9)
Preterm birth	2.3 (1.8–3.1)
SGA infants	2.5 (1.4–4.5)
LBW infants	4.8 (3.7–6.3)
NICU admission	2.8 (2.3–3.4)

CI = confidence interval; LBW = low birth weight; NICU = neonatal intensive care unit; SGA = small for gestational age.

is absent; (3) neither antiphospholipid syndrome nor lupus anticoagulant are detected; and (4) superimposed preeclampsia does not develop (Peart, 2014; Petri, 2020a; Stojan, 2012).

Lupus Nephritis

Active nephritis is associated with adverse pregnancy outcomes, although these have improved substantially and especially if disease remains in remission (Stojan, 2012; Wagner, 2009). Of complications, women with renal disease have a high incidence of gestational hypertension and preeclampsia. Of 137 women with SLE reported by Rodrigues and colleagues (2019), 27 percent of gravidas with preexisting renal disease developed preeclampsia compared with only 16 percent of those without underlying renal disease. In a review of 309 pregnancies complicated by lupus nephritis, 30 percent suffered a flare, and 40 percent of these had associated renal insufficiency (Moroni, 2005). The maternal mortality rate was 1.3 percent. These findings were corroborated in a subsequent prospective study (Moroni, 2016). In addition, a third of the 113 pregnancies were delivered preterm. Compared with women without nephritis or with inactive nephritis, those with active nephritis have a significantly increased incidence of maternal and fetal complications (Rodrigues, 2019; Wagner, 2009). The higher the histological class, the greater the risk.

Most recommend continuation of immunosuppressive therapy for nephritis during pregnancy. Hydroxychloroquine, cyclosporine, azathioprine, and tacrolimus are permissible in pregnancy (American College of Obstetricians and Gynecologists, 2019b; Parikh, 2020). New-onset nephritis or severe renal flare is treated aggressively with tacrolimus, and consideration is given to adding intravenous corticosteroids, immunosuppressive drugs, or intravenous immunoglobulin (IVIG) therapy (Maynard, 2019; Parikh, 2020).

Lupus Versus Preeclampsia-Eclampsia

Chronic hypertension complicates up to 30 percent of pregnancies in women with SLE (Egerman, 2005). Preeclampsia is common, and in those with nephritis or antiphospholipid antibodies, superimposed preeclampsia is encountered even more often and earlier (Bertsias, 2008; Dong, 2020). Preeclampsia and SLE flares share features of hypertension, proteinuria, edema, and renal function deterioration. However, the management is distinct. Lupus nephritis is treated with immunosuppression, and severe preeclampsia/eclampsia requires delivery. It may be difficult, if not impossible, to discriminate a lupus flare with nephropathy from severe preeclampsia if the kidney is the only involved organ (Petri, 2020b). Serum uric acid and complement levels and dsDNA titers may aid in differentiating the two. Last, central nervous system involvement with SLE may culminate in convulsions similar to those of eclampsia.

Management During Pregnancy

Care consists primarily of monitoring maternal clinical and laboratory status and fetal well-being. Establishment of baseline renal disease and hematological values is important because pregnancy-induced laboratory changes later in gestation can resemble SLE disease activity. A 24-hour urine collection to assess proteinuria and serum creatinine level measurement determine initial renal function. A complete blood count (CBC) identifies preexisting anemia, leukopenia, and thrombocytopenia. Continued assessment of renal function and hematological parameters is undertaken each trimester unless symptoms develop. In this event, measures are monthly (Baer, 2011).

For monitoring of SLE activity, various laboratory techniques have been recommended. As just discussed, establishing baseline values will assist comparisons later in pregnancy. Serum complement levels (C_3 and C_4) and dsDNA titers are drawn at the first prenatal care visit and when symptoms develop. Serum complement levels are normally increased in pregnancy (Appendix, p. 1231). Although falling or low C_3 and C_4 levels are more likely to be associated with active disease, higher levels provide no assurance against disease flare. If symptoms develop, the combination of declining complement levels and rising dsDNA titers does indicate a lupus flare (Baer, 2011). Women with SLE are also screened for antiphospholipid antibodies at the beginning of pregnancy. Last, screening for anti-SS-A (anti-Ro) and anti-SS-B (anti-La) antibodies is recommended because of associated fetal complications described later.

The combination of serial hematological, rheumatological, and renal studies may detect changes in disease activity. SLE-associated hemolysis is characterized by a positive Coombs test, anemia, reticulocytosis, and unconjugated hyperbilirubinemia. Thrombocytopenia, leukopenia, or both may develop. Chronic thrombocytopenia in early pregnancy may be due to antiphospholipid antibodies (Lockshin, 1995). Later, thrombocytopenia may indicate preeclampsia.

The fetus also is closely observed for adverse effects such as growth restriction and oligohydramnios. Sonographic evaluations are performed every 4 weeks beginning at 24 weeks' gestation to assess for both. Antepartum testing for fetal well-being is initiated in the third trimester and described in Chapter 20 (p. 392) (American College of Obstetricians and Gynecologists, 2021a,b). Unless evidence of maternal or fetal compromise develops, pregnancy is allowed to progress to term.

Pharmacological Treatment

There is no cure for SLE, and complete remissions are rare. Approximately a fourth of pregnant women have mild disease, which is not life threatening but may be disabling because of pain and fatigue. Arthralgia and serositis can be managed by nonsteroidal antiinflammatory drugs (NSAIDs). However, during pregnancy, chronic or large intermittent dosing is avoided due to related oligohydramnios or ductus arteriosus closure (Chap. 8, p. 151).

Antimalarials reduce dermatitis, arthritis, and fatigue (Hahn, 2018). Although these agents cross the placenta, hydroxychloroquine (Plaquenil) does not appear to cause congenital malformations (Briggs, 2022). Most recommend continuation during pregnancy because therapy interruption can precipitate a flare (Marder, 2019; Petri, 2019). For those not previously using hydroxychloroquine, others favor initiation in the first trimester because its use is associated with an 85-percent reduction in the risk of having a small-for-gestational-age neonate (Parikh,

2020). Also, it lowers the risk of fetal congenital heart block by 50 percent in women with anti-SS-A antibodies. Low-dose aspirin can be used throughout gestation.

Severe disease is managed with corticosteroids such as prednisone, 1 to 2 mg/kg/d orally or methylprednisolone, 1000 mg given intravenously over 90 minutes daily for 3 days (Petri, 2007). After the disease is controlled, this dose is tapered to a daily morning dose of 10 to 15 mg. Corticosteroid therapy can lead to gestational diabetes. During labor, delivery, and postpartum, corticosteroids in "stress doses" are given to women who take these drugs chronically or who have done so recently. This augmented dose reflects a normal adrenal response, and one option on admission for delivery is hydrocortisone, 100 mg, given IV every 8 hours for 48 hours.

Tacrolimus, rituximab, and IVIG therapy also have been used to treat lupus flares (Petri, 2019). These are usually reserved for lupus nephritis or disease that is corticosteroid resistant. Azathioprine has a good safety record during pregnancy (Hahn, 2018; Petri, 2019). Its recommended daily oral dose is 2 mg/kg. Teratogenic medications to be avoided include mycophenolate mofetil, methotrexate, and cyclophosphamide (Briggs, 2022; Hahn, 2018). However, cyclophosphamide can be considered in the second or third trimester for severe disease (Lazzaroni, 2016).

In nonpregnant subjects, antihypertensive therapy often includes an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin-receptor blocker. For pregnancy, these should be changed to safer fetal options such as calcium-channel blockers, alpha methyldopa, or labetalol (Cabiddu, 2016).

Perinatal Mortality and Morbidity

Adverse perinatal outcome rates are significantly elevated in pregnancies complicated by SLE. Among these are preterm delivery, fetal-growth restriction, stillbirth, and neonatal lupus syndrome (see Table 62-4) (He, 2020; Phansenee, 2018). Perinatal outcome rates worsen in women with active disease, significant proteinuria, or renal impairment and in those with chronic hypertension, preeclampsia, or both (Lazzaroni, 2016). Adverse outcomes are also more common in women with neuropsychiatric lupus (de Jesus, 2017). Reasons at least partially responsible for adverse fetal consequences include decidual vasculopathy with placental infarction and decreased perfusion (Hanly, 1988).

Neonatal Lupus Syndrome

This is characterized by newborn skin lesions—*lupus dermatitis*; various hematological and systemic derangements; and occasionally congenital heart block (Hahn, 2018). Cutaneous manifestations can be present in 30 to 40 percent of infants and appear at 4 to 6 weeks of age (Silverman, 2010). These are usually associated with anti-SS-A and SS-B antibodies, and up to 50 percent of women with SLE are positive for these (see Table 62-1). Thrombocytopenia and hepatic involvement are seen in 5 to 10 percent of affected infants.

In a review of outcomes in 128 infants born to women with lupus, 16 percent developed cutaneous lupus and 26 percent showed hematological abnormalities and elevated transaminase levels (Cimaz, 2003). Cutaneous lupus, thrombocytopenia, and autoimmune hemolysis are transient and clear within a few months (Zuppa, 2017). In subsequent offspring, the recurrence risk for neonatal lupus may approach 25 percent (Bramham, 2012). The only maternal treatment that lowers the risk of neonatal lupus is hydroxychloroquine (Izmirly, 2020; Petri, 2019).

Congenital Heart Block

Fetal and neonatal heart block results from diffuse myocarditis and fibrosis in the region between the atrioventricular (AV) node and bundle of His. Natural killer cells have been detected in fetal myocytes (Ivanchenko, 2021). Congenital heart block develops almost exclusively in fetuses of women with antibodies to the SS-A or SS-B antigens (Buyon, 1993). Even in the presence of such antibodies, the incidence of fetal myocarditis is only 2 to 3 percent (Bramham, 2012; Lateef, 2017). However, it rises to 20 percent with a prior affected child. The cardiac lesion is permanent, and a pacemaker is generally necessary. Long-term prognosis is poor. Of 325 infants with cardiac neonatal lupus, nearly 20 percent died, and of these, a third were stillborn (Izmirly, 2011). Another autoimmune disease, Sjögren syndrome, also is associated with fetal heart block (Brito-Zerón, 2020).

Maternal administration of corticosteroids, plasma exchange, or IVIG therapy does not reduce the risk of congenital heart block. For women with anti-SS-B and anti-SS-A antibodies, fetal cardiac monitoring is performed between 18 and 26 weeks' gestation. Maternal corticosteroid administration for treatment of fetal congenital heart block is controversial and discussed further in Chapter 19 (p. 369). This therapy to treat fetal heart block has not been studied in randomized trials. However, some evidence derives from fetuses exposed to their mother's corticosteroid treatment for SLE and shows that exposure may mitigate fetal myocarditis. Specifically, Shinohara and coworkers (1999) reported no cases of heart block in 26 neonates whose mothers received corticosteroids before 16 weeks' gestation as part of SLE maintenance therapy. By contrast, 15 of 61 neonates with heart block were born to women in whom corticosteroid therapy was begun after 16 weeks for an SLE exacerbation. Maternal hydroxychloroquine therapy is associated with a lower incidence of fetal heart block, especially in those with a prior affected child (Izmirly, 2010, 2020).

Long-term Prognosis and Contraception

The survival rate for women with SLE is 95 percent at 5 years, 90 percent at 10 years, and 78 percent at 20 years (Hahn, 2018). Infection, lupus flares, end-organ failure, hypertension, stroke, and cardiovascular disease account for most deaths. In general, women with SLE and chronic vascular or renal disease may limit family size because of morbidity associated with the disease and greater risks for adverse perinatal outcomes. For contraception, combination oral contraceptives did not increase the incidence of lupus flares in two large multicenter trials (Petri, 2005; Sánchez-Guerrero, 2005). Notably, comorbid antiphospholipid antibodies are a contraindication to estrogen-containing methods

(Chap. 38, p. 672). Progestin-only implants and injections provide effective contraception with no known effects on lupus flare rates (Sammaritano, 2020). Data do not support the concern that intrauterine device use and immunosuppressive therapy lead to higher infection rates in these patients. Tubal sterilization may be advantageous and is performed with greatest safety postpartum or whenever SLE is quiescent (Chap. 39, p. 681).

ANTIPHOSPHOLIPID SYNDROME

This is an autoantibody-mediated acquired thrombophilia that predisposes to recurrent thrombosis or pregnancy morbidity (Moutsopoulos, 2018). Specifically, antiphospholipid syndrome (APS) is diagnosed in women with persistently positive serum tests for antiphospholipid antibodies (APAs) *plus* arterial and/or venous thromboses or obstetrical morbidity. APAs include lupus anticoagulant, anticardiolipin antibody, and anti-β2 glycoprotein-I antibody.

Phospholipids are the main lipid constituents of cell and organelle membranes. Certain proteins in plasma associate noncovalently with these phospholipids. APAs are directed against these phospholipids or these phospholipid-binding proteins (Garcia, 2018; Giannakopoulos, 2013). This antibody group may be of immunoglobulin G (IgG), IgM, and IgA classes, alone or in combination. APAs are most common with SLE, other connective tissue disorders, and APS. That said, a small proportion of normal women and men have low levels of these antibodies.

The stimulus for autoantibody production is unclear, but it possibly is due to a preceding infection or another event that causes endothelial disruption. The resulting pathophysiology is mediated by one or more of the following: (1) activation of various procoagulants, (2) inactivation of natural anticoagulants, (3) complement activation, and (4) inhibition of syncytiotrophoblast differentiation (Garcia, 2018). Clinically, these actions lead to vascular thromboses or to pregnancy morbidity. Virtually every organ system may be affected.

Central nervous system involvement is one of the most prominent clinical manifestations. In addition to cerebrovascular arterial or venous thrombotic events, psychiatric features and even multiple sclerosis can be present (Binder, 2010). Renovascular involvement may lead to renal failure that can be difficult to differentiate from lupus nephritis (D'Cruz, 2009). Peripheral and visceral thromboses also are features. In one case, a puerpera developed a mesenteric vessel infarction and subsequent spontaneous cecal perforation (Ahmed, 2009). Obstetrical complications encompass recurrent pregnancy loss and placental dysfunction reflected by fetal-growth restriction, stillbirth, early-onset preeclampsia, and preterm birth. Treatment using aspirin, heparin, and close monitoring has increased live-birth rates to more than 70 percent in these women (Hamulyák, 2020; Schreiber, 2016).

A small proportion of these patients develop the *catastrophic antiphospholipid antibody syndrome (CAPS)* or *Asherson syndrome*. This is defined as a rapidly progressive thromboembolic disorder simultaneously affecting three or more organ systems or tissues (Garcia, 2018; Schreiber, 2016). It has a high mortality rate from activation of a cytokine storm. In half of cases, a triggering event is identified.

Specific Antiphospholipid Antibodies

As mentioned, several antibodies in APS are directed against a specific phospholipid or a phospholipid-binding protein:

1. *β2 glycoprotein-I*, also known as apolipoprotein H, is a phospholipid-binding plasma protein that inhibits prothrombinase activity within platelets and prevents platelet aggregation (Giannakopoulos, 2013). Thus, its normal action is to limit procoagulant binding and thereby prevent coagulation cascade activation. Logically, antibodies directed against this glycoprotein would reverse its anticoagulant activity and promote thrombosis. This is important from an obstetrical viewpoint because β2 glycoprotein-I is expressed in high concentrations on the syncytiotrophoblast surface. Complement activation may contribute to its pathogenesis (Avalos, 2009; Tsokos, 2011). Teleologically, this seems appropriate because the decidua intuitively should be a critical area to prevent coagulation that might lead to intervillous space thrombosis.
2. *Lupus anticoagulant (LAC)* is a heterogeneous group of antibodies directed against phospholipid-binding proteins. This antibody group induces prolongation in vitro of the prothrombin, partial thromboplastin, and Russell viper venom times. Thus, paradoxically, this so-called anticoagulant is actually powerfully thrombotic in vivo. This is the only APA that has been consistently associated with adverse pregnancy outcomes (Petri, 2020a).
3. *Anticardiolipin antibodies (ACAs)* are directed against one of the many phospholipid cardiolipins found in mitochondrial membranes and platelets.

Antibodies Against Natural Anticoagulants

Some APAs are also directed against the natural anticoagulant proteins C and S. Another is directed against the anticoagulant protein annexin V, which is expressed in high concentrations by syncytiotrophoblast (Giannakopoulos, 2013). Testing for these other antibodies is not recommended (American College of Obstetricians and Gynecologists, 2019a). However, some studies have evaluated these nonconventional antiphospholipid antibodies in women who clinically meet APS criteria but do not have the classic antibody profile. In one study, treatment of women who had these nonconventional antibodies offered some benefits, such as a lower pregnancy loss rate (Mekinian, 2016).

Clinical features shown in Table 62-5 provide indications for testing. By international consensus, APS is diagnosed based on laboratory and clinical criteria (Table 11-4, p. 205). First, one of two clinical criteria—which are vascular thrombosis or certain pregnancy morbidity—must be present. With laboratory criteria, high IgG or IgM titers of ACA or anti-β2 glycoprotein-I or LAC positivity should be confirmed on two occasions 12 weeks apart. The diagnosis can be further stratified based on the number of these tests that are positive.

Tests for LAC are nonspecific coagulation tests. The *partial thromboplastin time* is generally prolonged because the anticoagulant interferes with conversion of prothrombin to thrombin in vitro. The *dilute Russell viper venom test* is considered more specific.

TABLE 62-5. Some Clinical Features of Antiphospholipid Syndrome

Venous thrombosis: thromboembolism, thrombophlebitis, livedo reticularis
Arterial thrombosis: stroke, transient ischemic attack, Libman-Sacks cardiac vegetations, myocardial ischemia, distal extremity and visceral thrombosis and gangrene
Hematological: thrombocytopenia, autoimmune hemolytic anemia
Renal: thrombotic microangiopathy, glomerular thrombosis
Other: neurological manifestations, migraine headaches, epilepsy; renal artery or vein thrombosis; arthritis and arthralgia
Pregnancy: preeclampsia and HELLP syndrome, recurrent miscarriage, preterm delivery, fetal-growth restriction, fetal death

HELLP = hemolysis, elevated liver enzyme levels, low platelet count.
Data from Garcia, 2018; Giannakopoulos, 2013; Moutsopoulos, 2018.

Branch and Khamashta (2003) recommend conservative interpretation of results that are based on repeated tests from a reliable laboratory and that are consistent with each clinical case. Only approximately 20 percent of patients with APS have a positive LAC assay alone. Thus, ACA enzyme-linked immunosorbent assay (ELISA) testing also should be performed. Efforts have been made to standardize ACA assays, however, these remain without international standards (Garcia, 2018). For each APS test, interlaboratory variation can be large, and agreement between commercial kits is poor.

■ Pregnancy and Antiphospholipid Antibodies

As many as 30 percent of patients with SLE have APAs. In women without autoimmune diseases who have pregnancy complications, the prevalence of positive results with APA testing is 7 percent (Garcia, 2018).

In women with elevated APA levels, and especially when LAC is identified, risks for decidual vasculopathy, placental infarction, fetal-growth restriction, early-onset preeclampsia, and recurrent fetal death are increased (Saccone, 2017). Some of these women, like those with SLE, also have a high incidence of venous and arterial thromboses, cerebral thrombosis, hemolytic anemia, thrombocytopenia, and pulmonary hypertension (American College of Obstetricians and Gynecologists, 2019a; Clowse, 2008). In 191 LAC-negative women with APS, those with ACAs and β2-glycoprotein-I had significantly greater miscarriage rates than if either one alone was positive (Liu, 2013). Women with higher titers tend to have more adverse outcomes (Alijotas-Reig, 2020; Gabbay-Benziv, 2018).

■ Pregnancy Pathophysiology

It is not precisely known how APAs cause damage, but it is likely that their actions are multifactorial. Platelets may be damaged directly by APAs or indirectly by binding β2-glycoprotein-I, which causes platelets to be susceptible to aggregation (Giannakopoulos, 2013). One theory proposes that phospholipid-containing endothelial cell or syncytiotrophoblast membranes may be damaged directly by the APA or indirectly by antibody binding to either β2 glycoprotein-I or annexin V (Rand, 1997, 1998). This prevents the cell membranes from protecting the syncytiotrophoblast and endothelium. This exposes the basement membrane, to which damaged platelets can adhere and form a thrombus.

Pierro and colleagues (1999) reported that APAs decreased decidual production of the vasodilating prostaglandin E_2. Diminished protein C or S activity and greater prothrombin activation also may be contributory (Zangari, 1997). Evidence supports that thrombosis with APS stems from activation of the tissue factor pathway (Amengual, 2003). Last, uncontrolled placental complement activation by APAs is implicated in fetal loss and growth restriction (Holers, 2002).

Complications in APS cannot be completely explained by thrombosis alone. Animal models suggest that effects stem from inflammation rather than thrombosis (Cohen, 2011). Some investigators hypothesize that APS-associated clotting is triggered as a "second hit" from innate inflammatory immune responses. These investigators recommend treatment with anti-inflammatory agents (Meroni, 2011).

■ Adverse Pregnancy Outcomes

Overall, APAs are associated with higher rates of fetal wastage (Chap. 11, p. 204). In most early reports that describe these outcomes, however, women were included *because* they had repeated adverse outcomes. Both antibody prevalence and miscarriage are common—recall that the incidence of APAs in the general obstetrical population is about 5 percent and early miscarriage approximates 20 percent of call conceptions. Accordingly, current data are too limited to conclude the exact risks for adverse effects of these antibodies on pregnancy outcomes. Fetal deaths, however, are more characteristic with APS than are first-trimester miscarriages (Garcia, 2018; Roque, 2004).

When otherwise unexplained fetal deaths are examined, the data are mixed. One study measured ACA levels in 309 pregnancies with fetal death and found no differences in their frequency compared with levels in 618 normal pregnancies (Haddow, 1991). In another study of women with recurrent pregnancy loss, those with APAs had an increased rate of preterm delivery (Clark, 2007). In a case-control study of 582 stillbirths and 1547 live births, a three- to fivefold higher risk for stillbirth was found in women with elevated ACA and anti-β2 glycoprotein-I levels (Silver, 2013). In women with APAs, adverse outcomes are more common in the presence of: (1) all three classic APA types, (2) comorbid SLE or systemic autoimmune diseases, and (3) prior thrombosis and pregnancy morbidity. Logistic regression found the probability of pregnancy failure was 93 percent with two or more APA types but was 63 percent for those with only one (Ruffatti, 2011).

Thrombosis Prevention in Pregnancy

Because of study heterogeneity, current treatment recommendations for women with APAs can be confusing. Therapy is directed at thrombosis prevention. As discussed, APAs are immunoglobulins that may be of G, M, or A classes. Those directed against the phospholipids (PL) are termed GPL, MPL, and APL, respectively. During testing, these are reported as semiquantified phospholipid binding-unit levels and expressed as negative, low-positive, medium-positive, or high-positive (American College of Obstetricians and Gynecologists, 2019a).

As discussed in Chapter 55 (p. 979), women with prior thromboembolic events who have APAs are at risk for recurrence in subsequent pregnancies. For these women, prophylactic anticoagulation with heparin throughout pregnancy and for 6 weeks postpartum is recommended (American College of Obstetricians and Gynecologists, 2019a). For those without prior thromboembolic events, recommendations for management vary and are listed in Table 55-5 (p. 984). Some acceptable schemes include close antepartum maternal observation with or without prophylactic or intermediate-dose heparin, and then some form of postpartum anticoagulation for 6 weeks. Sciascia and coworkers (2016) have presented preliminary salutary results with hydroxychloroquine treatment. This currently is considered investigational (Garcia, 2018; Latino, 2020).

Several researchers have questioned the need for heparin for women with APAs but no history of thrombosis (Branch, 2010). Although this is less clear, some recommend that women be treated if they have medium- or high-positive ACA titers or LAC activity and a prior second- or third-trimester fetal death not attributable to other causes (Dizon-Townson, 1998; Lockshin, 1995). Others report that women with recurrent early pregnancy loss and medium- or high-positive titers of antibodies may benefit from therapy (Robertson, 2006).

Due to the risk of fetal-growth abnormalities and stillbirth, serial sonographic assessment of fetal growth and antepartum testing in the third trimester is recommended (American College of Obstetricians and Gynecologists, 2019a, 2021a,b).

Specific Therapy in Pregnancy

Other agents are used to treat gravidas that have APS but no prior thromboembolic event. *Aspirin*, in doses of 60 to 80 mg orally daily, blocks conversion of arachidonic acid to thromboxane A_2 while sparing prostacyclin production. Thromboxane A_2 usually causes platelet aggregation and vasoconstriction, and prostacyclin has the opposite effect. The only major side effect from low-dose aspirin is a slight risk of small-vessel bleeding during surgical procedures. Low-dose aspirin does not reduce adverse pregnancy outcomes in women who have APAs but who lack the complete APS syndrome (Amengual, 2015). Thus, its use is recommended for women with SLE or APS (American College of Obstetricians and Gynecologists, 2020b; Rahman, 2020).

Unfractionated heparin is given subcutaneously in dosages of 5000 to 10,000 units every 12 hours. Some prefer low-molecular-weight heparin, such as 40 mg enoxaparin (Lovenox) once daily (Kwak-Kim, 2013). With therapeutic dosing, measurement of heparin levels may be useful because clotting tests can be altered by LAC. The rationale for heparin therapy is to prevent venous and arterial thrombotic episodes. Heparin therapy also prevents thrombosis in the microcirculation, including the decidual-trophoblastic interface (Toglia, 1996). As discussed, heparin binds to β2-glycoprotein-I, which coats the syncytiotrophoblast. This prevents binding of ACAs and anti-β2 glycoprotein-I antibodies to their surfaces, which likely prevents cellular damage (Tsokos, 2011). Heparin also binds to APAs in vitro and likely in vivo.

Aspirin plus heparin therapy is the most effective regimen (de Jesus, 2014; Hamulyák, 2020). However, despite treatment, 30 percent of women with APS do not achieve a successful outcome (Arslan, 2020). Heparin therapy is associated with several complications that include bleeding, thrombocytopenia, osteopenia, and osteoporosis. A description of various heparins and their adverse effects is found in Chapter 55 (p. 983).

Corticosteroids generally should not be used with *primary APS*—that is, without an associated connective tissue disorder. For women with SLE or those being treated for APS who develop SLE, corticosteroid therapy is indicated. In such cases of *secondary APS* seen with SLE, the dose of prednisone should be maintained at the lowest effective level to prevent flares.

IVIG therapy is controversial and has usually been reserved for women with overt disease—including catastrophic antiphospholipid syndrome or heparin-induced thrombocytopenia or both (Rahman, 2020). It is used when other first-line therapies have failed, especially in the setting of preeclampsia and fetal-growth restriction. IVIG is administered by some in doses of 0.4 g/kg/d for 5 days—total dose of 2 g/kg. This is repeated monthly, or it is given as a single dose of 1 g/kg each month. Treatment is expensive, as one course costs more than $10,000. Tenti and colleagues (2016) found no benefits from adding IVIG to low-dose aspirin and low-molecular-weight heparin. One Cochrane review found no improvement in the live-birth rate for IVIG therapy given to women with recurrent pregnancy loss (Wong, 2014). Trials are needed before application of this expensive and cumbersome therapy is recommended.

Immunosuppression with hydroxychloroquine is commonly used with low-dose aspirin in the treatment of women with SLE. This regimen may be beneficial by reducing the risk of thrombosis and improving pregnancy outcomes in women who also have APS (Mekinian, 2015; Sciascia, 2016).

Statins have been examined due to their protective effects on endothelium. In a small trial in 21 women with APS who developed fetal-growth restriction or preeclampsia, the addition of pravastatin to low-dose aspirin and low-molecular-weight heparin improved placental blood flow, preeclampsia features, and pregnancy outcomes (Lefkou, 2016). Larger trials are needed before this therapy is recommended.

Described earlier (p. 1114), catastrophic antiphospholipid syndrome is treated aggressively with full anticoagulation, high-dose corticosteroids, plasma exchange, and/or IVIG therapy (Garcia, 2018; Rahman, 2020).

Treatment Efficacy

Fetal loss is common in women with untreated APS, and especially in those with LAC positivity. Even with treatment,

TABLE 62-6. Pregnancy Outcomes (%) in 750 Women Treated for Antiphospholipid Syndrome—the PREGNANTS Study

Outcome	Triple-Positive (n = 20)	Double-Positive LAC Negative (n = 90)	LAC Alone (n = 54)	ACA Alone (n = 458)	Anti-β2 Glycoprotein-I (n = 128)
Livebirth	30	43	80	56	48
Stillbirth	45	34	7	21	30
Preeclampsia[a]	55	54	11	34	48

[a]Nonsevere only.
ACA = anticardiolipin antibodies; LAC = lupus anticoagulant.

recurrent fetal loss rates remain at 20 to 30 percent (Arslan, 2020; Empson, 2005; Ernest, 2011). Shown in Table 62-6 are pregnancy outcomes from 750 treated women with primary APS (Saccone, 2017). Participants were treated with low-dose aspirin and prophylactic low-molecular-weight heparin starting in the first trimester. Importantly, some women with SLE and APAs have normal pregnancy outcomes without treatment. It is also emphasized that women with LAC and prior poor pregnancy outcomes have had liveborn neonates without treatment.

In a manner similar to neonatal lupus syndrome (p. 1113), up to 30 percent of newborns demonstrate passively acquired APAs (Nalli, 2017). One group found higher rates of learning disabilities in these children (Tincani, 2009). Another reported a fourfold greater risk for perinatal strokes (Simchen, 2009). Of 141 newborns followed in a European registry, the rate of preterm birth was 16 percent; low birthweight occurred in 17 percent; and later behavioral abnormalities developed in 4 percent of the children. There were no cases of neonatal thrombosis (Motta, 2012). A 7-year study of 36 pregnancies in 26 women who had APS reported three cases of autism spectrum disorder. All were associated with persistent neonatal anti-β2 glycoprotein-I IgG antibodies (Abisror, 2013).

RHEUMATOID ARTHRITIS

This chronic inflammatory disease stems from immunological dysfunction, and infiltrating T cells secrete cytokines to cause inflammation, polyarthritis, and systemic symptoms. The cardinal feature is inflammatory synovitis that usually involves the peripheral joints. The disease has a propensity for cartilage destruction, bony erosions, and joint deformities. Pain, aggravated by movement, is accompanied by swelling and tenderness. Extraarticular manifestations include rheumatoid nodules, vasculitis, and pleuropulmonary symptoms. Other complaints are fatigue, anorexia, and depression. The American College of Rheumatology has published diagnostic criteria (Shah, 2018).

The worldwide prevalence of rheumatoid arthritis is 0.5 to 1 percent, women are affected three times more often than men, and peak onset is from 25 to 55 years (Shah, 2018). There is a genetic predisposition, and heritability is estimated at 15 to 30 percent (McInnes, 2011). Genome-wide associated studies have identified more than 30 loci involved in rheumatoid arthritis pathogenesis (Kurkó, 2013). Class II major histocompatibility complex molecule HLA-DR4 and HLA-DRB1 alleles also show an association (McInnes, 2011; Shah, 2018). Pregnancy provides a protection against rheumatoid arthritis development, and this may be related to HLA-disparate fetal microchimerism (Förger, 2020; Guthrie, 2010).

Management

Treatment is directed at pain relief, inflammation reduction, protection of articular structures, and preservation of function. Physical and occupational therapy and self-care instructions are essential.

Aspirin and other NSAIDs nonspecifically inhibit both cyclooxygenase 1 (COX-1), which is an enzyme critical to normal platelet function, and COX-2, which mediates inflammatory response mechanisms. However, in one systematic review, a small increased rate of cardiac malformations was found in newborns exposed to NSAIDs in the first trimester (Briggs, 2022). In addition, NSAIDs are associated with early spontaneous abortions, ductus arteriosus constriction, and neonatal pulmonary hypertension (Briggs, 2022). Another potential side effect of chronic NSAID therapy is gastritis with acute bleeding. Thus, risks versus benefits of these medications must be considered. Glucocorticoid therapy in low to moderate doses is given to achieve more rapid symptom control. Of these, prednisone, 7.5 mg orally daily for the first 2 years of active disease, substantively reduces progressive joint erosions (Shah, 2018).

Until recently, NSAIDs were the cornerstone of therapy, but they do not retard disease progression. The American College of Rheumatology recommends several disease-modifying antirheumatic drugs (DMARDs) that may reduce or prevent joint damage (Singh, 2016). According to Shah and St. Clair (2018), methotrexate has become the preferred DMARD outside of pregnancy. NSAIDs thus are important in pregnancy because methotrexate and leflunomide are contraindicated (Chap. 8, pp. 151–152). In one review of drug exposure, a fourth of women with rheumatoid arthritis took a DMARD within 6 months of conception (Kuriya, 2011). Of unplanned exposures during pregnancy, 4 percent of 393 pregnant women were given a category D or X medication—methotrexate was the most common at 2.9 percent.

Sulfasalazine and hydroxychloroquine are safe for use in pregnancy (Briggs, 2022; Partlett, 2011). These, combined with relatively low-dose prednisone—7.5 to 20 mg daily—usually successfully treat flares.

Biological DMARDs have revolutionized rheumatoid arthritis treatment. These include the tumor necrosis factor

alpha (TNF-α) inhibitors infliximab, adalimumab, golimumab, certolizumab, and etanercept (Shah, 2018). Their use in pregnancy is limited, but they appear to be safe for the fetus (Briggs, 2022). In one review, 13 percent of 393 pregnant women were given a biological cytokine-inhibiting DMARD—primarily etanercept (Kuriya, 2011). In another review of 300 exposures, no fetal effects were noted (Berthelot, 2009). A prospective study of 38 pregnant women found similar results (Hoxha, 2017). In 74 women exposed to adalimumab during pregnancy, no risks were identified (Burmester, 2017). Little is known regarding the pregnancy effects of anakinra, an interleukin 1 receptor antagonist, or of rituximab, an antagonist to the B-cell CD20 antigen. Other biologics are abatacept, tocilizumab, and tofacitinib.

■ Pregnancy and Rheumatoid Arthritis

In up to 70 percent of women with rheumatoid arthritis, disease will improve during pregnancy (Raine, 2020; Shah, 2018). Some studies suggest this may be due to regulatory T-cell alterations (Förger, 2020). Even so, some women develop disease during pregnancy, and others become worse. A downside to this respite during pregnancy is that postpartum exacerbation occurs in 40 to 50 percent of women (Eudy, 2018; Jethwa, 2019). This may stem from postpartum alterations in innate immunity (Häupl, 2008b).

Some studies report a protective effect of pregnancy against developing new-onset rheumatoid arthritis. In a case-control study of 88 affected women, pregnancy provided a degree of protection long term, but the likelihood of new-onset rheumatoid arthritis was increased sixfold during the first 3 postpartum months (Silman, 1992). Pikwer and colleagues (2009) reported a significant reduction in the risk of subsequent arthritis in women who breastfed longer than 12 months.

These findings may reflect the interference of sex hormones with several putative processes involved in arthritis pathogenesis, including immunoregulation (Förger, 2020; Häupl, 2008a,b). First, Unger and associates (1983) reported that amelioration of rheumatoid arthritis correlated with serum levels of *pregnancy-associated alpha$_2$-glycoprotein*. This compound has immunosuppressive properties. Second, Nelson and coworkers (1993) noted that disease improvement was associated with a disparity in HLA class II antigens between mother and fetus. They suggested that the maternal immune response to paternal HLA antigens may play a role in pregnancy-induced remission of arthritis. In addition to monocyte activations, there also may be T-lymphocyte activation (Förger, 2020).

Fertility is diminished in patients with rheumatoid arthritis, and adverse pregnancy outcomes are increased. Kishore and colleagues (2019) reported pregnancy outcomes from nearly 32,000 women with rheumatoid arthritis. Compared with unaffected women, those with rheumatoid arthritis had significantly greater rates of hypertensive diseases, preterm birth, hemorrhage, and fetal-growth restriction.

■ Juvenile Rheumatoid Arthritis

This group of diseases is the most frequent cause of chronic arthritis in children and persists into adulthood. In 76 pregnancies of 51 affected Norwegian women, pregnancy had no effects on clinical presentation, but disease activity usually became quiescent or remained so during pregnancy (Østensen, 1991). Similar to rheumatoid arthritis, postpartum flares were common. Joint deformities often developed in these women, and 15 of 20 cesarean deliveries were done for contracted pelves or joint prostheses. Results from a summary of 39 Polish women with juvenile rheumatoid arthritis were similar (Musiej-Nowakowska, 1999).

This arthritis portends few adverse pregnancy outcomes. The risk for preterm birth is elevated, but fetal development is normal (Mohamed, 2016; Rom, 2014; Wallenius, 2014). In a study of 1807 births, Remaeus and associates (2017) reported increased incidences of preterm birth, fetal-growth restriction, and preeclampsia. Disease severity in early pregnancy was predictive of preterm delivery and fetal-growth restriction in one cohort study (Bharti, 2015). And, patients with low disease activity scores in the first trimester are likely to have low disease activity or remission in the third trimester (Ince-Askan, 2017).

If the cervical spine is involved, particular attention is warranted during pregnancy. Subluxation is common, and pregnancy, at least theoretically, predisposes to this because of joint laxity. Importantly, there are anesthesia concerns during endotracheal intubation.

SYSTEMIC SCLEROSIS—SCLERODERMA

This is a chronic multisystem connective tissue disorder of unknown etiology. It is characterized by microvascular damage; inflammation from immune system activation; and excessive deposition of collagen in the skin, lungs, heart, gastrointestinal tract, and kidneys. It is uncommon, displays a 5-to-1 female dominance, and typically affects those aged 30 to 50 years (Clark, 2020; Varga, 2018).

This strong prevalence of scleroderma in women and its greater incidence in the years following childbirth give credence to the hypothesis that *microchimerism* is involved as discussed earlier (p. 1109) (Munira, 2020). Artlett and associates (1998) demonstrated Y-chromosomal DNA in almost half of women with systemic sclerosis compared with only 4 percent of controls. Rak and coworkers (2009) identified male microchimerism in peripheral blood mononuclear cells more frequently in women with limited versus diffuse scleroderma.

■ Clinical Course

The hallmark is overproduction of normal collagen. *Limited cutaneous systemic sclerosis* is the more benign form and progresses slowly. With *diffuse cutaneous systemic sclerosis*, skin fibrosis advances rapidly and is followed by gastrointestinal tract fibrosis, especially the distal esophagus (Varga, 2018). Pulmonary interstitial fibrosis along with vascular changes may cause pulmonary hypertension, which develops in 15 percent of patients. Antinuclear antibodies such as those listed in Table 62-1 are found in 95 percent of patients, and immunoincompetence often develops.

Raynaud phenomenon, which is typified by cold-induced, episodic, rapidly reversible digital ischemia, is seen in 95 percent of patients. There also may be swelling of the distal extremities

and face. Symptoms from esophageal involvement, especially fullness and epigastric burning pain, occur in half of patients. Pulmonary involvement is frequent and causes dyspnea. The 10-year cumulative survival rate is 70 percent in those with pulmonary fibrosis, and pulmonary arterial hypertension is the main cause of death (Clark, 2020; Varga, 2018). Women with limited cutaneous disease such as the *CREST syndrome—calcinosis, Raynaud phenomenon, esophageal involvement, sclerodactyly, and telangiectasia*—have milder disease.

Overlap syndrome refers to systemic sclerosis with features of other connective tissue disorders. *Mixed connective tissue disease* is a term used for the syndrome involving features of SLE, systemic sclerosis, polymyositis, rheumatoid arthritis, and high titers of anti-ribonucleoprotein (RNP) antibodies (Rudder, 2021). The disorder is also termed *undifferentiated connective tissue disease* (Radin, 2020; Zucchi, 2020).

Although systemic sclerosis is incurable, treatment directed at end-organ involvement can sometimes relieve symptoms and improve function. Renal involvement and hypertension are often comorbid. At times, ACE inhibitors may be required for blood pressure control despite their known teratogenicity. Obliterative vasculopathy of the renal cortical arteries characterizes *scleroderma renal crisis*, which develops in up to a fourth of these patients. This leads to renal failure and malignant hypertension. Interstitial restrictive lung disease is common and frequently becomes life threatening. Associated pulmonary hypertension is treated with bosentan or sildenafil (Chap. 52, p. 931).

■ Pregnancy and Systemic Sclerosis

The prevalence of scleroderma in pregnancy approximates 1 case in 22,000 pregnancies (Chakravarty, 2008). If baseline function is good, these women usually have stable disease during gestation. As perhaps expected, pregnancy aggravates dysphagia and reflux esophagitis (Steen, 1999). Dysphagia results from loss of esophageal motility due to neuromuscular dysfunction. A lower amplitude or disappearance of peristaltic waves in the lower two thirds of the esophagus is seen using manometry. Symptomatic treatment for reflux is described in Chapter 57 (p. 1017).

Women with renal insufficiency and malignant hypertension have a higher incidence of superimposed preeclampsia. With rapidly worsening renal or cardiac disease, pregnancy termination should be considered. Renal crisis is uncommon, but it is life threatening, and it does not improve with delivery (Zucchi, 2020). Pulmonary hypertension usually contraindicates pregnancy (Table 52-3, p. 919).

Vaginal delivery may be anticipated, unless the soft tissue thickening wrought by scleroderma produces dystocia requiring cesarean delivery. Tracheal intubation for general anesthesia has special concerns because of limited ability of these women to open their mouths widely (Sobanski, 2016). Because of esophageal dysfunction, aspiration is also more likely, and neuraxial analgesia is preferable. Warming the delivery room and intravenous fluids, extra blankets, and socks and gloves are considered to improve impaired circulation from Raynaud phenomenon. If corticosteroids were used frequently, stress doses of hydrocortisone, described earlier for SLE (p. 1113), are recommended (Sobanski, 2016).

Maternal and fetal outcomes correlate with underlying disease severity. In a review of 214 gravidas with systemic sclerosis, 45 percent had diffuse disease (Steen, 1999). Major complications included renal crisis in three and greater rates of preterm birth. A multicenter study of 109 pregnancies from 25 centers reported increased rates of preterm delivery, fetal-growth restriction, and very-low-birthweight newborns (Taraborelli, 2012). In a review of 307 affected pregnancies, risks for miscarriage, preterm births, and gestational hypertension were increased (Blagojevic, 2020). These are likely related to placental abnormalities that include decidual vasculopathy, acute atherosis, and infarcts (Sobanski, 2016). Somewhat related, perinatal outcomes are similar with undifferentiated connective tissue diseases (Radin, 2020; Zucchi, 2020).

Scleroderma may be associated with subfertility (Bernatsky, 2008; Lambe, 2004). For women who do not choose pregnancy, several reversible contraceptive methods are acceptable. However, hormonal agents, especially combination oral contraceptives, probably should not be used, especially in women with pulmonary, cardiac, or renal involvement. Due to the often unrelenting progression of systemic sclerosis, permanent sterilization also is considered.

VASCULITIS SYNDROMES

Inflammation and damage to blood vessels may be primary or caused by another disease. Immune-complex deposition is presumed to underlie most cases (Ross, 2020). Primary types are listed in Table 62-7 (Langford, 2018). Small vessel vasculitides such as *granulomatosis with polyangiitis* and *eosinophilic granulomatosis with polyangiitis* have antibodies directed against proteins in the cytoplasmic granules of leukocytes—*antineutrophil cytoplasmic antibodies (ANCA)* (Pagnoux, 2016). In general, women with a vasculitis syndrome have elevated rates of preterm birth and preeclampsia (Nguyen, 2021).

■ Polyarteritis Nodosa

This necrotizing vasculitis of small and medium-sized arteries is characterized clinically by myalgia, neuropathy, gastrointestinal disorders, hypertension, and renal disease (Goodman, 2014). A third of cases are associated with hepatitis B antigenemia (Langford, 2018). Symptoms are nonspecific, and fever, weight loss, and malaise are present in more than half of cases. Diagnosis is made by biopsy, and treatment is high-dose prednisone plus cyclophosphamide. Vasculitis due to hepatitis B antigenemia responds to antivirals, glucocorticosteroids, and plasma exchange (Chap. 58, p. 1037).

TABLE 62-7. Primary Vasculitis Syndromes

Polyarteritis nodosa
Wegener granulomatosis
Takayasu arteritis
Behçet disease
Churg-Strauss
Henoch-Schönlein
Giant cell arteritis

Only a few reports describe polyarteritis nodosa associated with pregnancy. Of 12 affected gravidas, polyarteritis first manifested during pregnancy in seven, and it was rapidly fatal by 6 weeks postpartum (Owen, 1989). The diagnosis was not made until autopsy in six of the seven women. Four women continued pregnancy, which resulted in one stillborn and three successful outcomes.

Granulomatosis with Polyangiitis—Wegener Granulomatosis

This is a small-vessel necrotizing granulomatous vasculitis affecting the upper and lower respiratory tract and kidney (Pagnoux, 2016). Disease frequently includes sinusitis and nasal disease (90 percent); pulmonary infiltrates, cavities, or nodules (85 percent); glomerulonephritis (75 percent); and musculoskeletal lesions (65 percent) (Sneller, 1995). At least 90 percent have polyangiitis (Langford, 2018). It is uncommon and usually encountered after age 50. Koukoura and associates (2008) reviewed 36 cases in association with pregnancy and found a higher preterm birth rate. In another report, a second woman had disease-related pneumonitis, but pregnancy did not appear to affect disease activity (Pagnoux, 2011). Because subglottic stenosis is found in up to a fourth of patients, the anesthesiology service is ideally consulted antepartum (Engel, 2011).

Therapeutic options are limited by teratogenicity and fetotoxicity (Daher, 2020). Corticosteroids are standard treatment, but azathioprine, cyclosporine, and IVIG therapy may also be used. For severe disease in the late second or third trimester, cyclophosphamide in combination with prednisolone is highly effective. Rituximab is also approved for this disorder and appears to be safe for the fetus (Briggs, 2022).

Takayasu Arteritis

Also called *pulseless disease*, this is a chronic inflammatory arteritis affecting large vessels (Abisror, 2020). Unlike *temporal arteritis*, which develops almost exclusively after age 55, the onset of Takayasu arteritis is almost always before age 40. It is associated with abnormal angiography of the upper aorta and its main branches and with upper extremity vascular impairment. Death usually results from congestive heart failure or cerebrovascular events. Computed tomography or magnetic resonance angiography can detect this disorder before the development of severe vascular compromise. Takayasu arteritis may respond symptomatically to corticosteroid therapy, however, it is not curative. Surgical bypass or angioplasty improves survival rates.

Comorbid severe renovascular hypertension, cardiac involvement, or pulmonary hypertension worsen pregnancy prognosis (Comarmond, 2020; Singh, 2015). Hypertension is relatively common and should be carefully controlled. Blood pressure is most accurately measured in the lower extremity. Overall, the prognosis for pregnancy is good (Kirshenbaum, 2018). A study of 43 pregnancies in 33 women with Takayasu arteritis reported that half had complications (Abisror, 2020). Authors described an increased risk of pregnancy-related hypertension and preeclampsia but overall favorable maternal and fetal outcomes. A review from Comarmond and colleagues (2020) cites a 5-percent life-threatening cardiovascular complication rate. Involvement of the abdominal aorta portends worse perinatal outcome (Sharma, 2000). Vaginal delivery is preferred, and epidural analgesia has been advocated for labor and delivery.

Other Vasculitides

Behçet disease is rare, and its prevalence approximates 1 case per 100,000 births (Lee, 2019). In one series of 298 pregnancies in 94 affected women, rates of miscarriage and smaller babies were higher than those in healthy controls (Gungor, 2014). Although greater risks for preeclampsia, preterm delivery, and venous thromboembolism are reported, pregnancy is not contraindicated (Elliot, 2019; Merlino, 2020).

Formerly *Churg-Strauss vasculitis*, eosinophilic granulomatosis with polyangiitis is rare in pregnancy (Jennette, 2013). One case report described a pregnant woman who responded to IVIG therapy (Hot, 2007). Another presented an affected 35-year-old woman at term whose necrotizing vasculitis involved the heart, and she subsequently underwent cardiac transplantation (Corradi, 2009). Edwards (2015) described one woman who developed postpartum relapses of this vasculitis in each of two pregnancies.

Henoch-Schönlein purpura is uncommon after childhood. Characteristic signs of the disorder include purpuric rash, arthralgia, abdominal pain, and gastrointestinal bleeding. In one review of 20 pregnancies complicated by this vasculitis, cutaneous lesions and arthralgias were present in three fourths and in approximately one half, respectively (Tayabali, 2012). Henoch-Schönlein purpura responds well to corticosteroid therapy, and pregnancy outcomes are generally good (Kalmantis, 2008).

INFLAMMATORY MYOPATHIES

These are acquired and potentially treatable causes of skeletal muscle weakness with a prevalence of 14 to 32 cases in 100,000 persons (Greenberg, 2018). Three major groups are polymyositis, dermatomyositis, and inclusion-body myositis, which all present with progressive asymmetrical muscle weakness. They have a variable association with connective tissue diseases, malignancy, drugs, systemic autoimmune disease such as Crohn disease, and viral, bacterial, and parasitic infections.

Polymyositis is a subacute inflammatory myopathy that is frequently associated with one of the autoimmune connective tissue disorders (Bitencourt, 2020; Munira, 2020). *Dermatomyositis* manifests as a characteristic rash accompanying or preceding weakness. Laboratory findings include elevated muscle enzyme levels in serum and an abnormal electromyogram. Confirmation is by biopsy, which shows perivascular and perimysial inflammatory infiltrates, vasculitis, and muscle fiber degeneration. It usually develops alone but can overlap with systemic sclerosis or mixed connective tissue disease.

Prevailing theories suggest that the syndromes are caused by viral infections, autoimmune disorders, or both. *Importantly, approximately 15 percent of adults who develop dermatomyositis have an associated malignant tumor*. The timing of myositis and tumor appearance may be separated by several years. The most common sites of associated cancer are breast, lung, stomach, and ovary. The disease usually responds to high-dose corticosteroid therapy, immunosuppressive drugs such as azathioprine or methotrexate, or IVIG (Dalakas, 2012; Linardaki, 2011).

Experiences in pregnancy are garnered mostly from case series and reviews. One cohort of 17 gravidas with polymyositis/dermatomyositis had higher rates of hypertension (23 percent), antepartum hemorrhage (11 percent), cesarean delivery (88 percent), and preterm birth (35 percent) compared with unaffected pregnant women (Chen, 2015). In another series of 60 women with dermatomyositis and 38 with polymyositis, 80 percent had no adverse effect on their disease. Similar results have been reported by others (Missumi, 2015; Pinal-Fernandez, 2014). Pregnancy outcome is related to dermatomyositis activity, and new-onset disease is particularly aggressive (Munira, 2020).

HEREDITARY CONNECTIVE TISSUE DISORDERS

Numerous inherited mutations involve genes that encode for structural proteins of bone, skin, cartilage, blood vessels, and basement membranes. Although connective tissues contain many complex macromolecules such as elastin and more than 30 proteoglycans, the most common constituents are fibrillar collagen types I, II, and III. Various mutations, some recessively and some dominantly inherited, result in clinical syndromes that include Marfan and Ehlers-Danlos syndromes, osteogenesis imperfecta, chondrodysplasias, and epidermolysis bulla. Of concern during pregnancy is the predilection for these disorders to result in aortic aneurysms (Schoenhoff, 2013).

Marfan Syndrome

This is an autosomal dominant connective tissue disorder that has a population prevalence of 1 case in 3000 to 5000 (Prockop, 2018). Marfan syndrome affects both sexes equally. The syndrome is due to abnormal fibrillin—a constituent of elastin—caused by any of several different mutations in the *FBN1* gene (Biggin, 2004). Located on chromosome 15q21, the *FBN1* gene has a high mutation rate. The lack of distinct genotype-phenotype correlation and large clinical variability limits the ability to predict disease severity in progeny. Currently, preimplantation genetic testing and prenatal diagnosis are limited to the 80 percent of cases in which the mutation in the *FBN1* gene is known (Smok, 2014).

In severe disease, the elastic lamina in the media of the aorta shows degeneration. This predisposes to aortic dilation or dissecting aneurysm, which appears more commonly during pregnancy (Curry, 2014; Roman, 2016). Marfan syndrome was found to underlie 65 percent of cases of aortic dissection in 27 pregnant women (Braverman, 2021). Marfan syndrome complicating pregnancy is discussed in more detail in Chapter 52 (p. 936).

Ehlers-Danlos Syndrome

This disease is characterized by various connective tissue changes, including skin hyperelasticity. Its prevalence is 7 cases per 100,000 births (Spiegel, 2020). Several disease types vary based on skin, joint, or other tissue involvement. In the more severe types, rupture of any of several arteries can cause either stroke or bleeding. Some types are autosomal dominant, some recessive, and some X-linked (Solomons, 2013). Types I, II, and III are autosomally dominant, and each accounts for approximately 30 percent of cases. Type IV is uncommon but is known to predispose to preterm delivery, great-vessel rupture, postpartum bleeding, and uterine rupture (Pepin, 2000). In most, the underlying molecular defect affects collagen or procollagen.

In general, women with Ehlers-Danlos syndrome have a higher frequency of preterm rupture of membranes, preterm delivery, antepartum and postpartum hemorrhage, placenta previa, and cervical insufficiency (Hurst, 2014; Spiegel, 2020). Several cases of spontaneous uterine rupture have been described (Rudd, 1983). Tissue fragility makes episiotomy repair and cesarean delivery difficult. A maternal and fetal death from spontaneous rupture of the right iliac artery has been reported (Esaka, 2009). In another case, a newborn was found to have multiple congenital skull fractures and intracranial hemorrhage caused by Ehlers-Danlos type VIIC (Bar-Yosef, 2008).

Osteogenesis Imperfecta

This disorder has a prevalence of 1 case in 20,000 births for type I and 1 case in 60,000 for type II (Prockop, 2018). It is characterized by brittle bones, and affected patients often have blue sclerae, hearing loss, multiple prior bone fractures, and dental abnormalities. There are up to 15 subtypes based on the causative gene and clinical picture, which ranges from mild to severe (Van Dijk, 2010). Genetic inheritance includes autosomal dominant, autosomal recessive, and sporadic patterns. Type I is the mildest form, and the typical mutation affects the *COL1A1* gene (Sykes, 1990). Type II is typically lethal in utero.

Women with osteogenesis imperfecta, most commonly type I, may have successful pregnancies. However, risks include fractures, complications related to scoliosis with restrictive lung disease, micrognathia, brittle teeth, an unstable cervical spine, uterine rupture, and cephalopelvic disproportion. A retrospective cohort of 295 women with osteogenesis imperfecta found greater risks of antepartum hemorrhage, placental abruption, fetal-growth restriction, congenital malformations, and preterm birth (Ruiter-Ligeti, 2016). It is not unusual for affected women to enter pregnancy with 20 to 30 prior fractures. Most require minimal treatment other than management of the fractures and consideration of bisphosphonates to decrease bone loss.

Depending on the type of osteogenesis imperfecta, the fetus may be affected and may also suffer fractures in utero or during delivery. Preimplantation genetic testing and prenatal diagnosis is available in many situations, if desired. In utero stem cell therapy is being evaluated (Couzin-Frankel, 2016).

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CHAPTER 63

Neurological Disorders

Many neurological disorders precede pregnancy. Most affected women will have successful perinatal outcomes, although some disorders carry specific risks. Other women will have new-onset neurological symptoms during pregnancy, and these must be distinguished from pregnancy complications. Neurovascular disorders are an important cause of maternal mortality and accounted for more than 7 percent of maternal deaths in the United States from 2007 through 2016 (Petersen, 2019). Psychiatric disorders can manifest with cognitive and neuromuscular abnormalities and should be considered in the evaluation of neurological symptoms.

CENTRAL NERVOUS SYSTEM IMAGING

Computed tomography (CT) and magnetic resonance (MR) imaging assist in the diagnosis, classification, and management of many neurological disorders. As discussed in Chapter 49, (p. 873), these can be used safely during pregnancy (Chansakul, 2017; Lum, 2020). CT scanning is often used when rapid diagnosis is necessary and is excellent for detecting recent hemorrhage. That said, MR imaging is often preferred and is particularly helpful to diagnose demyelinating diseases, arteriovenous malformations (AVMs), congenital and developmental nervous system abnormalities, posterior fossa lesions, and spinal cord diseases (Jamieson, 2020). Whenever either modality is employed, a woman with advanced pregnancy should be positioned in a lateral tilt with a wedge under one hip to prevent hypotension and to diminish aortic pulsations, which may degrade the image.

Cerebral angiography with contrast injection, usually via the femoral artery, is a valuable adjunct to the diagnosis and treatment of some cerebrovascular diseases. Fluoroscopy delivers more radiation but can be performed with abdominal shielding. Positron emission tomography (PET) and functional MR imaging (fMRI) have not been evaluated in detail for use in gravidas (van den Heuvel, 2016).

HEADACHE

In one national survey in the United States in 2012, 17 percent of persons aged 18 to 44 years reported a severe headache or migraine within the past 3 months (Blackwell, 2014). Burch and coworkers (2015) reported that 24 percent of nonpregnant women in this age group were similarly affected. Of pregnant women presenting with headache who received a neurological consultation, two thirds were due to primary disorders. The diagnosis was migraine in more than 90 percent. Of the other third due to secondary conditions, more than half stemmed from hypertensive disorders (Robbins, 2015). In one recent observational study at University of Texas Southwestern's Clements University Hospital, 20 percent of emergency department postpartum visits were for headache (Rodriguez, 2021).

TABLE 63-1. Headache Classification

Primary
Migraine
Tension-type
Trigeminal cephalalgia
Other

Secondary
Trauma
Vascular disorders
Substance abuse
Infection
Disorders of homeostasis
Craniofacial disorders
Psychiatric disorders

The classification by the International Headache Society (2018) is shown in Table 63-1. As discussed, in pregnant women, primary headaches are more common than those derived from secondary causes (Sperling, 2015). Migraine headaches are those most likely to be affected by the hormonal changes of pregnancy (Pavlovic, 2017). The incidences of different etiologies of severe headaches in pregnancy are shown in Figure 63-1 (Robbins, 2015).

Tension Headache

These are the most frequent cause of all headaches. They may be episodic or chronic. Their characteristic muscle tightness and mild to moderate pain in the back of the neck and head can persist for hours. Importantly, neurological disturbances or nausea are typically absent, which distinguishes them from migraines. The pain usually responds to rest, massage, local heat or ice, nonsteroidal antiinflammatory drugs (NSAIDs), or mild tranquilizers. Hospital admission is seldom necessary. For chronic headaches, amitriptyline can be effective (Goadsby, 2018).

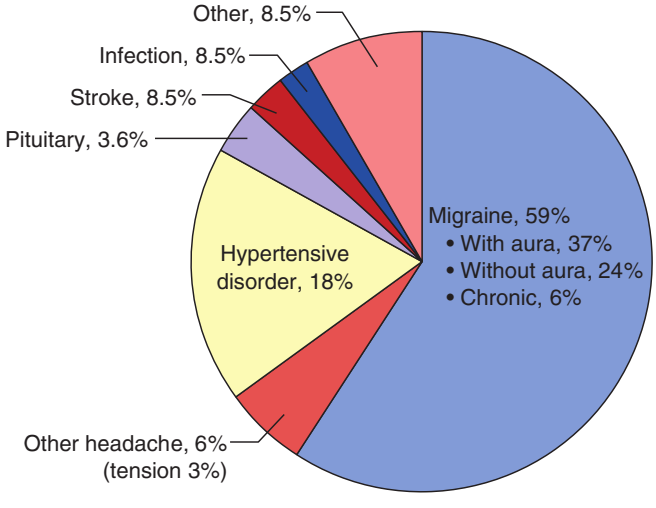

FIGURE 63-1 Incidences of headache causes in 140 consecutive pregnant women for whom in-hospital neurology consultation was requested.

Migraine Headache

This is a periodic, sometimes incapacitating neurological disorder with episodic attacks of severe headache and autonomic nervous system dysfunction (Ashina, 2020; Charles, 2017). The International Headache Society (2018) classifies three migraine types based on chronicity and on the presence or absence of an aura.

1. *Migraine without aura*-formerly termed common migraine-is characterized by a unilateral throbbing headache, nausea and vomiting, or photophobia.
2. *Migraine with aura*-formerly termed classic migraine-has similar symptoms preceded by premonitory neurological phenomena such as visual scotoma or hallucinations. A third of patients have this type, which sometimes can be averted if medication is taken at the *first premonitory sign.*
3. *Chronic* migraine is defined by a migraine headache occurring at least 15 days each month for more than 3 months.

Migraine headaches may begin in childhood, peak in adolescence, and tend to diminish in both frequency and severity with advancing years. According to Ashina (2020), their annual prevalence is 15 percent in women and 6 percent in men. Another 5 percent of women have *probable migraine*, that is, they have all criteria but one.

These headaches are especially common in young women and have been linked to hormone levels (Burch, 2020; Charles, 2017). Sensory sensitivity with migraines is likely caused by monoaminergic sensory control systems in the brainstem, hypothalamus, and cortex (Goadsby, 2018). The exact pathophysiology is uncertain, but symptoms develop when neuronal dysfunction leads to decreased cortical blood flow, activation of vascular and meningeal nociceptors, and stimulation of trigeminal sensory neurons. Importantly, migraines are not primarily a vascular disorder (Charles, 2017). Migraine headaches—especially those with aura in young women—are associated with increased risk for ischemic strokes (Tietjen, 2020). Other associated conditions are asthma, anxiety and depression, and other pain disorders.

Migraine in Pregnancy

Migraine headaches are frequently encountered during pregnancy. Most migraineurs have improvement during pregnancy (Lucas, 2019). Still, migraines—usually those with an aura—occasionally appear for the first time during pregnancy. Pregnant women with preexisting migraine symptoms may have other symptoms that suggest a more serious disorder, and new neurological symptoms should prompt a complete evaluation (Charles, 2017).

Migraines during pregnancy are associated with increased rates of preeclampsia, gestational hypertension, preterm birth, and other cardiovascular morbidities that include ischemic stroke (Grossman, 2017; Wabnitz, 2015). Bushnell and associates (2009) identified a migraine incidence during pregnancy of 185 cases per 100,000 deliveries. Of diagnoses associated in these gravid migraineurs, risks were significantly higher for stroke, 16-fo1d; myocardial infarction, fivefold; and heart disease, venous thromboembolism, and preeclampsia/gestational hypertension, each twofold. In a systematic review of 14

TABLE 63-2. Medications for Treatment of Acute Migraine in Pregnancy

Simple Analgesics
- Acetaminophen
- NSAIDs: naproxen, ibuprofen

5-HT Receptor Agonists
- Triptans: oral, nasal, parenteral

Dopamine-receptor Antagonists
- Metoclopramide
- Prochloroperzine
- Chlorpromazine

Antiemetics
- Ondansetron
- Metoclopramide

Other
- Opioids
- Transcranial magnetic stimulation

5-HT = 5-hydroxytryptamine (serotonin); NSAIDs = nonsteroidal antiinflammatory drugs.
From Ashina, 2020; Charles, 2017; Goadsby, 2018.

studies, risks for preeclampsia and low-birthweight neonates were significantly increased (Aukes, 2019).

Management

Several effective medications are shown in Table 63-2. Mild headaches respond to oral therapy in 50 to 70 percent of cases. Initial therapy with acetaminophen or an NSAID, along with an antiemetic, usually suffices for many early headaches. For severe headaches, parenteral therapy is indicated (Goadsby, 2018). Multitargeted drug therapy is necessary in most cases for migraine relief (Gonzalez-Hernandez, 2014). Headaches are treated aggressively with intravenous hydration, parenteral antiemetics, and triptans, and opioids are reserved for the most recalcitrant headaches. Although a 2-g infusion of magnesium sulfate has gained favor in the past few years, a metaanalysis reported no benefits (Choi, 2014). *Ergotamine derivatives are potent vasoconstrictors and are avoided in pregnancy because of their uterotonic effects* (Briggs, 2022).

Triptans are serotonin 5-$HT_{1B/2D}$-receptor agonists that effectively relieve headaches, nausea, and vomiting and greatly reduce analgesic needs. Triptans can be given as an oral tablet, injection, rectal suppository, or intranasal spray. They are best used in combination with NSAIDs (Goadsby, 2018). However, chronic NSAID use is avoided in pregnancy, especially later pregnancy because of fetal ductus arteriosus constriction and fetal urine production decline (Chap. 18, p. 151). The greatest triptan experience is with sumatriptan (Imitrex), and although not studied extensively in pregnancy, it is not a major teratogen (Saldanha, 2021; Spielmann, 2018). However, in one study at 36 months of children exposed to triptans in pregnancy, Wood and colleagues (2016) found neurodevelopment differences, including emotionality and activity problems.

Some women will benefit from peripheral nerve blocks, and Govindappagari and coworkers (2014) described their experiences with 13 pregnant women. For women with frequent migraine headaches, oral prophylactic therapy is warranted. Amitriptyline (Elavil), 10 to 175 mg daily; propranolol (Inderal), 40 to 120 mg daily; or metoprolol (Lopressor, Toprol), 25 to 100 mg daily, are successful options (Contag, 2010; Lucas, 2009).

Calcitonin gene-related peptide (CGRP) receptor antagonists to prevent migraines have garnered enthusiasm. Several of these monoclonal antibodies have been approved since 2018 for clinical use but not evaluated in pregnancy (Ashina, 2020; Tepper, 2018). Similarly, in a Cochrane review, botulinum toxin type A for chronic migraine may reduce migraine days per month by 2 days compared with placebo (Herd, 2018).

Cluster Headache

This rare primary headache disorder is characterized by severe unilateral lancinating pain radiating to the face and orbit, lasting 15 to 180 minutes, and occurring with autonomic symptoms and agitation. Pregnancy does not affect symptom severity. Affected women should avoid tobacco and alcohol. Acute management includes 100-percent oxygen therapy and sumatriptan given as a 6-mg dose subcutaneously (Vander Pluym, 2016). If recurrent, prophylaxis employs verapamil.

SEIZURE DISORDERS

After headaches, seizures are the next most prevalent neurological condition encountered in pregnancy. The Centers for Disease Control and Prevention reported that 3 million adults in 2015 had active epilepsy (Tian, 2018). Less than half were seizure free in the past year. Importantly, epilepsy accounted for 5 percent of maternal deaths in the United Kingdom from 2011 to 2013 (Knight, 2015).

Pathophysiology

A seizure is a transient combination of signs and symptoms stemming from abnormal excessive or synchronous neuronal activity in the brain (Lowenstein, 2018). Some identifiable causes of convulsive disorders in young adults include head trauma, alcohol- and other drug-induced withdrawals, cerebral infections, brain tumors, biochemical abnormalities, and arteriovenous malformations. A search for these is prudent with a new-onset seizure disorder in a pregnant woman. The diagnosis of idiopathic epilepsy is one of exclusion.

Classification

Epilepsy encompasses different syndromes whose cardinal feature is a predisposition to recurrent unprovoked seizures. The International League Against Epilepsy recently updated the following definitions (Fisher, 2017). Main categories describe seizure onset and include focal, generalized, and unknown groups.

Focal seizure onset describes those that originate in one localized brain area and affect correspondingly localized

neurological function. They are believed to result from trauma, abscess, tumor, or perinatal factors, although a specific lesion is rarely demonstrated. Seizures may occur with either intact or impaired awareness.

Focal seizures without dyscognitive features start in one region of the body and progress toward other ipsilateral areas of the body and produce tonic and then clonic movements. Seizures can affect sensory function or produce autonomic dysfunction or psychological changes. Cognitive function is not impaired, and recovery is rapid.

Focal seizures with dyscognitive features are often preceded by an aura and followed by impaired awareness manifested by sudden behavioral arrest or motionless stare. Involuntary movements such as picking motions or lip smacking are common.

Generalized seizure onset describes those that involve both brain hemispheres and may be preceded by an aura before an abrupt loss of consciousness. They may be motor or nonmotor. There is a strong hereditary component. In *generalized tonic-clonic seizures*, loss of consciousness is followed by tonic contraction of the muscles and rigid posturing, and then by clonic contractions of all extremities while the muscles gradually relax. Return to consciousness is gradual, and the patient may remain confused and disoriented for several hours. *Absence seizures*—also called petit mal seizures—are a form of generalized epilepsy that involve a brief loss of consciousness without muscle activity and are characterized by immediate recovery of consciousness and orientation.

Unknown seizure onset describes seizures with an unwitnessed onset. Thus, they remain unclassified as to focal or generalized onset until further information allows categorization. However, these can be further subgrouped as motor or nonmotor, or unclassified.

■ Preconceptional Counseling

Women with epilepsy ideally are counseled before pregnancy, and relevant points are presented also in Chapter 9 (p. 166). Oral folic acid supplementation with 0.4 mg per day is begun at least 1 month before conception. The dose is increased to 4 mg when the woman taking antiepileptic medication becomes pregnant. These medications are assessed and adjusted with a goal of monotherapy using the least teratogenic medication. If this is not feasible, attempts are made to reduce the number of medications and to use the lowest effective dose (Stephen, 2019; Tomson, 2019b). Medication withdrawal should be considered if a woman is seizure free for 2 years or more.

■ Pregnancy Complications

The major pregnancy-related risks to women with epilepsy are fetal malformations and convulsions. Seizure control is a priority to avoid its attendant morbidity and mortality. Early studies described worsening seizure activity during pregnancy, however, this is less common now because of more effective drugs (Pennell, 2020). Contemporary studies cite higher rates of seizure activity in only 20 to 30 percent of gravidas (Tomson, 2019b). Women who are seizure free for at least 9 months before conception will likely remain so during pregnancy (Harden, 2009b).

Greater seizure frequency is often associated with subtherapeutic anticonvulsant serum levels, a lower seizure threshold, or both. Numerous pregnancy-associated alterations can result in subtherapeutic serum levels. These include nausea and vomiting, slower gastrointestinal motility, antacid use that diminishes drug absorption, pregnancy hypervolemia offset by protein binding, induction of hepatic enzymes such as cytochrome oxidases, placental enzymes that metabolize drugs, and increased glomerular filtration that hastens drug clearance. Importantly, some women discontinue medication because of teratogenicity concerns. Last, the seizure threshold can be affected by pregnancy-related sleep deprivation and by hyperventilation and pain during labor (Tomson, 2019b).

Status epilepticus is a medical emergency. It is more likely to occur in women with refractory epilepsy (Kusznir Vitturi, 2019). In a randomized trial of 384 nonpregnant patients with benzodiazepine-refractory status, intravenous levetiracetam, fosphenytoin, or valproate yielded similar results (Kapur, 2019). Only one half of patients in each cohort had cessation of seizures and improved alertness by 60 minutes.

In addition to seizure-control challenges, women with epilepsy have a small increased risk of pregnancy complications that include miscarriage, hemorrhage, hypertensive disorders, placental abruption, preterm birth, fetal-growth restriction, and cesarean delivery (Salman, 2018; Viale, 2015). Importantly, MacDonald (2015) also reports a tenfold higher maternal death rate, and, as mentioned earlier, epilepsy accounted for 5 percent of maternal deaths in the United Kingdom. Postpartum depression rates also are increased in epileptic women (Turner, 2009). Last, children of epileptic mothers have a 10-percent risk of developing a seizure disorder.

With embryofetal malformations, it was difficult for years to separate the influence of epilepsy from that of its therapy as the primary cause. Now, untreated epilepsy is thought not to be associated with an elevated fetal malformation rate (Tomson, 2019b). That said, the fetus of an epileptic mother who takes certain anticonvulsant medications has an indisputably greater risk for congenital malformations. Moreover, monotherapy is associated with a lower rate of birth defects compared with multiagent therapy. Adherence to these principles has resulted in declining malformation rates from antiepileptic drugs (Tomson, 2019a).

Specific drugs, when given alone, raise the malformation rate (Chap. 8, p. 150). Some are listed in Table 63-3. Phenytoin and phenobarbital increase the major malformation rate two- to threefold above baseline (Perucca, 2005; Thomas, 2008). Valproate is a particularly potent teratogen, which has a dose-dependent effect and raises the malformation risk four- to eightfold (Klein, 2014; Tomson, 2019b). Valproate is also associated with lower cognitive performance (Kasradze, 2017). In general, with polytherapy, the risk rises with each drug added. A metaanalysis of 31 studies found lamotrigine and levetiracetam to carry the lowest malformation risk (Weston, 2016).

■ Management in Pregnancy

The American Academy of Neurology and the American Epilepsy Society have guidelines regarding treatment in pregnancy

TABLE 63-3. Teratogenic Effects of Common Anticonvulsant Medications

Drug (Brand Name)	Abnormalities Described	Affected	Embryofetal Risks[a]
Valproate (Depakote)	Neural-tube defects, clefts, cardiac anomalies; associated developmental delay; ADHD	7–10% with monotherapy; higher with polytherapy	
Phenytoin (Dilantin)	Fetal hydantoin syndrome: craniofacial anomalies, fingernail hypoplasia, growth deficiency, developmental delay, cardiac anomalies, clefts	5–11%	Yes
Carbamazepine; oxcarbazepine (Tegretol; Trileptal)	Fetal hydantoin syndrome, as above, spina bifida	2–5%	Yes
Phenobarbital	Clefts, cardiac anomalies, urinary tract malformations	6–20%	Suggested
Lamotrigine (Lamictal)	Increased risk for clefts (registry data)	Up to 2% (4- to 10-fold higher than expected)	Suggested
Topiramate (Topamax)	Clefts	2–3% (15- to 20-fold higher than expected)	Suggested
Levetiracetam (Keppra)	Theoretical: skeletal abnormalities; impaired growth in animals	1–3%	Suggested

ADHD = attention deficit hyperactivity disorder.
[a]Risk categories from Briggs, 2022; Bromley, 2017; Christensen, 2019; Food and Drug Administration, 2011; Harden, 2009b; Tomson, 2018, 2019b.

(Harden, 2009a,b,c). The major goal is seizure prevention. To accomplish this, treatment for nausea and vomiting is provided, seizure-provoking stimuli are avoided, and medication compliance is emphasized. The fewest necessary anticonvulsants are given at the lowest dosage needed for seizure control. Although some providers routinely monitor serum drug levels, these concentrations may be unreliable because of altered protein binding. Free or unbound drug levels, although perhaps more accurate, are not widely available. Importantly, no evidence suggests that such monitoring improves seizure control (Adab, 2006). For these reasons, drug levels may be most informative if measured following seizures or if noncompliance is suspected.

For women taking anticonvulsant drugs, a targeted sonographic examination in midpregnancy is recommended to evaluate for anomalies. Testing to assess fetal well-being is generally not indicated for women with uncomplicated epilepsy.

For women desiring to breastfeed, data regarding the safety of the various anticonvulsant medications are limited. However, no obvious deleterious effects, such as long-term cognitive issues, have been reported (Birnbaum, 2020; Briggs, 2022). Of birth control methods, combination oral contraceptive (COC) pill failure rates are higher with some of the anticonvulsant agents. For example, lamotrigine efficacy is substantially lowered by COCs. Thus, other more reliable methods should be considered (Chap. 38, p. 664).

CEREBROVASCULAR DISEASES

Abnormalities of the cerebrovascular circulation include both ischemic and hemorrhagic strokes and anatomical anomalies, such as AVMs and aneurysms. Cerebral ischemia is caused by reduction in blood flow that lasts longer than several seconds. Early, neurological symptoms may manifest. After a few minutes, however, infarction often follows. Hemorrhagic stroke is caused by bleeding directly into or around the brain. It produces symptoms by its mass effect, by blood's toxic effects, or by elevated intracranial pressure. Strokes in nonpregnant women are predominately ischemic. In gravidas, roughly half are ischemic, and the other half are hemorrhagic (Zofkie, 2018).

The obesity endemic in this country, along with a concomitant rise in rates of heart disease, hypertension, and diabetes, has increased the prevalence of strokes. Compared with men, women have a higher lifetime risk of stroke and associated mortality rate (Martinez-Sánchez, 2011; Virani, 2021). Moreover, pregnancy raises the immediate and lifetime risk of both ischemic stroke and hemorrhagic stroke (Jamieson, 2010; Jung, 2010).

With an incidence of 10 to 40 cases per 100,000 births, stroke is relatively uncommon in gravidas. However, it contributes disparately to maternal mortality rates (Leffert, 2016; Pacheco, 2019; Elgendy, 2021). The incidence is rising as measured by pregnancy-related hospitalizations for stroke (Callaghan, 2008; Kuklina, 2011). Most events are associated with hypertensive disorders or heart disease. Of the pregnancy-related mortality rate in the United States from 2007 to 2016, 7.2 percent was due to cerebrovascular accidents, and 7.8 percent was associated with hypertension (Petersen, 2019). Of maternal deaths after 42 days postpartum, 9.8 percent were attributable to stroke (Creanga, 2017).

Risk Factors

Most strokes in pregnancy manifest either during labor and delivery or in the puerperium. In a study of 2850 pregnancy-

related strokes, approximately 10 percent developed antepartum, 40 percent intrapartum, and 50 percent postpartum (James, 2005). Of 145 ischemic strokes, Leffert (2016) reported a timing of 45 percent antepartum, 3 percent intrapartum, and 53 percent postpartum.

Several risk factors both unrelated and related to pregnancy have been recognized. Unrelated causes are age; migraines, hypertension, obesity, and diabetes; cardiac disorders such as endocarditis, valvular prostheses, and patent foramen ovale; and smoking. Stroke etiologies related to pregnancy include hypertensive disorders, gestational diabetes, obstetrical hemorrhage, and cesarean delivery. *By far, the most common is pregnancy-associated hypertensive disorders*. A third of strokes are associated with gestational hypertension, and hypertensive women compared with normotensive counterparts have a three- to eightfold greater risk of stroke (Scott, 2012; Wang, 2011). Stroke is the major cause of maternal mortality associated with preeclampsia (Judy, 2019). Moreover, women with preeclampsia undergoing general anesthesia may be at higher risk of stroke compared with those given neuraxial anesthesia (Huang, 2010). Cesarean delivery raises the peripartum stroke risk 1.5-fold compared with vaginal delivery (Lin, 2008). Sepsis from any source increases the risk for postpartum stroke (Miller, 2019).

Pregnancy-induced effects on cerebrovascular hemodynamics include enhanced autoregulation that maintains blood flow despite changes in systemic blood pressure (van Teen, 2016). Although cerebral blood flow *decreases* by 20 percent from midpregnancy until term, it *increases* significantly with gestational hypertension (Zeeman, 2003, 2004b). Such hyperperfusion at least intuitively would be dangerous for women with certain vascular anomalies.

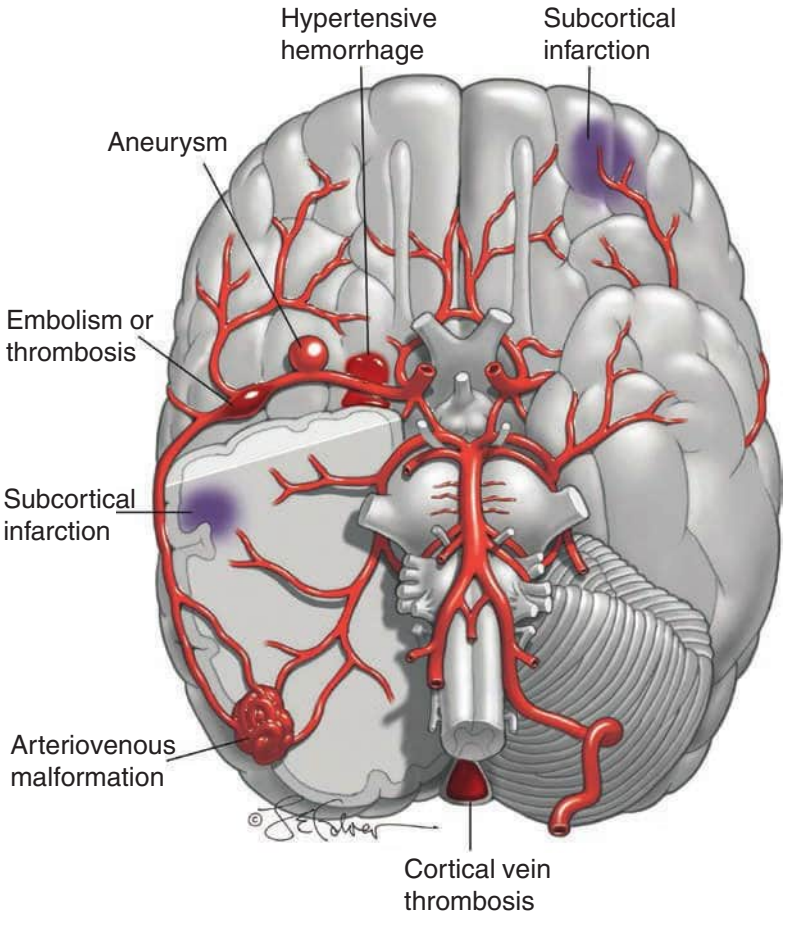

FIGURE 63-2 Illustrations of a brain showing various types of strokes seen in pregnancy: (1) subcortical infarction (preeclampsia), (2) hypertensive hemorrhage, (3) aneurysm, (4) embolism or thrombosis in middle cerebral artery, (5) arteriovenous malformation, and (6) cortical vein thrombosis.

■ Ischemic Stroke

Acute occlusion or embolization of an intracranial blood vessel causes cerebral ischemia, which may result in death of brain tissue (Fig. 63-2). The more commonly associated etiologies of ischemic stroke are shown in Table 63-4. A *transient ischemic attack (TIA)* is caused by reversible ischemia, and symptoms usually last less than 24 hours. Approximately 10 percent of these patients have a stroke by 1 year (Amarenco, 2016).

Stroke usually incites sudden severe headache, hemiplegia, or other neurological deficits. Seizures occasionally develop. Immediate assessment and CT scanning is indicated (Pacheco, 2019). Further evaluation includes echocardiography and additional cranial imaging with CT, MR imaging, or angiography. Serum lipids are measured with the caveat that their values are distorted by normal pregnancy (Appendix, p. 1231). Tests to detect antiphospholipid antibodies, lupus anticoagulant, other thrombophilias, and, if indicated, sickle-cell syndromes are performed (Buonanno, 2016).

TABLE 63-4. Some Associated Disorders or Causes of Ischemic and Hemorrhagic Strokes During Pregnancy or the Puerperium

Ischemic Stroke	Hemorrhagic Stroke
Preeclampsia syndrome	Chronic hypertension
Arterial thrombosis	Preeclampsia syndrome
Venous thrombosis	Arteriovenous malformation
Lupus anticoagulant	Saccular aneurysm
Antiphospholipid antibodies	Angioma
Thrombophilias	Cocaine, methamphetamines
Migraine	Vasculopathy
Paradoxical embolus	
Cardioembolic	
Sickle hemoglobinopathy	
Arterial dissection	
Vasculitis	
Moyamoya disease	
Cocaine, amphetamines	

From Smith, 2018; Yager, 2012; Zofkie, 2018.

These underlie up to a third of ischemic strokes in otherwise healthy young women.

With a thorough evaluation, most causes of embolism can be identified. Some of these include cardiac-associated embolism, vasculitis, or vasculopathy such as Moyamoya disease (Miyakoshi, 2009; Pacheco, 2019). Outcomes of embolic strokes are reported to be favorable and similar to those of nonpregnant women (Leffert, 2016). For some, thrombolysis for ischemic stroke during pregnancy should be considered (Pacheco, 2019). However, published experiences are sparse (Ryman, 2019). For some, mechanical thrombectomy can be used.

Preeclampsia Syndrome

In reproductive-age women, a significant proportion of pregnancy-related ischemic strokes are caused by gestational hypertension and preeclampsia (Miller, 2020; Zofkie, 2018). As shown in Figure 63-2, areas of subcortical edema and petechial hemorrhage may progress to cerebral infarction (Aukes, 2007, 2009; Zeeman, 2004a). Although these usually clinically manifest by an eclamptic convulsion, a few women will suffer a symptomatic stroke from a larger cortical infarction (Chap. 40, p. 700).

Other conditions with findings similar to preeclampsia are *thrombotic microangiopathies* (Chap. 59, p. 1060) and the *reversible cerebral vasoconstriction syndrome* (Chap. 40, p. 700). The latter, also termed *postpartum angiopathy*, can cause extensive cerebral edema, necrosis and widespread infarction, and areas of hemorrhage (Edlow, 2013; Miller, 2016).

Cerebral Embolism

These strokes usually involve the middle cerebral artery (see Fig. 63-2). The diagnosis can be made with confidence only after thrombosis and hemorrhage are excluded and is more certain if an embolic source is identified. Hemorrhage may be more difficult to exclude because both embolization and thrombosis can be followed by hemorrhagic infarction. Paradoxical embolism is an uncommon cause, even considering that more than a fourth of adults have a patent foramen ovale. Through the defect, right-sided venous thromboemboli are deported (Scott, 2012). Foraminal closure may not improve outcomes in these patients, however, this procedure has been performed during pregnancy (Dark, 2011). Assorted cardioembolic causes of stroke include arrhythmias—especially atrial fibrillation, valvular lesions, mitral valve prolapse, mural thrombus, infective endocarditis, and peripartum cardiomyopathy.

Management of embolic stroke in pregnancy consists of supportive measures and antiplatelet therapy. Thrombolytic therapy and anticoagulation in pregnancy are controversial (Li, 2012).

Cerebral Artery Thrombosis

Most thrombotic strokes affect older individuals and are caused by atherosclerosis, especially of the internal carotid artery. Many are preceded by one or more TIAs. Thrombolytic therapy with a recombinant tissue plasminogen activator (rtPA) is recommended. Alteplase is one of these. It is given intravenously within the first 3-hour window if neurological deficits are noted and if neuroimaging has excluded hemorrhage (Pacheco, 2019). A principal risk is hemorrhagic transformation of an ischemic stroke. This agent can be used in pregnancy, but published experiences of rtPA in this group are few (Ryman, 2019).

Cerebral Venous Thrombosis

In one study in the United States, 6 percent of cerebral venous thromboses were associated with pregnancy (Leavell, 2018). However, in more than 8 million deliveries from the Nationwide Inpatient Sample, cerebral venous thrombosis caused only 2 percent of pregnancy-related strokes (James, 2005). Predisposing causes are numerous, and for gravidas, late pregnancy and the puerperium are times of greatest risk (Silvis, 2019).

Thrombosis of the lateral or superior sagittal venous sinus usually occurs in the puerperium and often in association with preeclampsia, sepsis, or thrombophilia (see Fig. 63-2). It is more common in patients with inherited thrombophilias or antiphospholipid antibodies. Headache is the most frequent presenting symptom, neurological deficits are common, and up to a third of women have seizures (Pacheco, 2019). Oh and colleagues (2020) described a postpartum case in which cerebral vein thrombosis was misdiagnosed as postdural puncture headache. The diagnosis is made using MR venography.

Management includes anticonvulsants for seizures, and anticoagulation with heparin (Pacheco, 2019; Smith, 2018). Antimicrobials are given for septic thrombophlebitis, and fibrinolytic therapy is reserved for those women failing systemic anticoagulation. The acute prognosis for venous thrombosis in gravidas is better than in nonpregnant subjects, and mortality rates are <10 percent (McCau11ey, 2011).

In women with a prior cerebral venous thrombosis, one systematic review found only one recurrence in 217 pregnancies and five noncerebral venous thrombotic events in 186 pregnancies (Aguiar de Sousa, 2016). In a study of 52 women on prophylactic anticoagulation with prior cerebral venous thrombosis, recurrent thrombosis or bleeding did not develop. However, 24 percent had late obstetrical complications (Martinelli, 2016).

Ischemic Stroke Recurrence

Women with prior ischemic stroke have a low risk for recurrence during a subsequent pregnancy unless a specific, persistent cause is identified. During a 5-year follow-up of 441 reproductive-aged women with prior ischemic stroke or cerebral venous thrombosis, 13 had a recurrent ischemic stroke, and only two were associated with pregnancy. The authors concluded that the risk of stroke recurrence is low and a previous ischemic stroke is not a contraindication to pregnancy (Lamy, 2000). In one study of nonpregnant women, the ischemic stroke recurrence rate was similar between those with and without antiphospholipid antibodies as long as the former received warfarin or aspirin (Levine, 2004). The recurrence rate of reversible cerebral vasoconstriction syndrome in a subsequent pregnancy was noted to be 9 percent (Boitet, 2019).

Currently, no firm guidelines define prophylaxis in pregnant women with a stroke history (Smith, 2018). The American Heart Association stresses the importance of controlling risk factors such as hypertension and diabetes (Furie, 2011). As discussed in Chapters 52 and 55, those with antiphospholipid syndrome or certain cardiac conditions should be considered for prophylactic anticoagulation. For most of these

women, low-dose aspirin given throughout pregnancy seems reasonable.

Hemorrhagic Stroke

Intracerebral Hemorrhage

The symptoms of a hemorrhagic stroke are similar to those of an ischemic stroke, and their differentiation is possible only with CT or MR imaging (Hemphill, 2015; Smith, 2018). The two distinct categories of spontaneous intracranial bleeding are subarachnoid hemorrhage and intracerebral hemorrhage.

Intracerebral hemorrhage is bleeding into the brain parenchyma. It most often stems from the spontaneous rupture of Charcot-Bouchard aneurysms of small vessels damaged by chronic hypertension (see Fig. 63-2). Thus, pregnancy-associated hemorrhagic strokes such as the one shown in Figure 63-3 are often associated with chronic hypertension and superimposed preeclampsia (Cunningham, 2005; Martin, 2005). Because of its location, this type of hemorrhage has much higher morbidity and mortality rates than subarachnoid hemorrhage (Smith, 2018). Pressure-induced rupture causes bleeding into the putamen, thalamus, adjacent white matter, pons, and cerebellum. In the 28 women described by Martin and associates (2005), half died and most survivors had permanent disabilities. This underscores proper management of gestational hypertension, especially systolic hypertension.

Subarachnoid Hemorrhage

In a study of 639 cases of pregnancy-related subarachnoid hemorrhage from the Nationwide Inpatient Sample, the incidence was 8.5 per 100,000 pregnancies (Limaye, 2019). A remarkably similar incidence was reported in Japanese women (Yoshida, 2017). These bleeding events are more likely caused by an underlying cerebrovascular malformation in an otherwise normal patient (see Fig. 63-2). Ruptured saccular or "berry" aneurysms cause 80 percent of all subarachnoid hemorrhages (Lawton, 2017). The remaining cases stem from a ruptured AVM, coagulopathy, angiopathy, venous thrombosis, infection, drug abuse, tumors, or trauma. The mortality rate of subarachnoid hemorrhage during pregnancy is lower than that reported for nonpregnant women—8 versus 17 percent (Limaye, 2019).

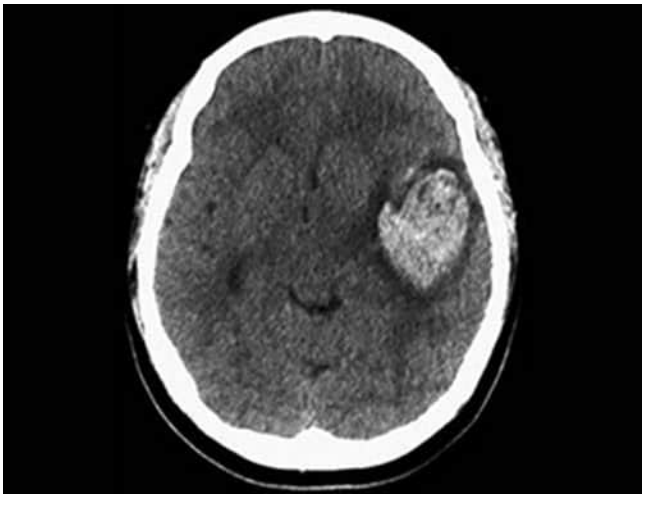

FIGURE 63-3 A noncontrast computed tomography axial head image demonstrates a large intraparenchymal hemorrhage in this woman with preeclampsia.

Intracranial Aneurysm. Approximately 1 to 2 percent of adults have this lesion (Lawton, 2017). Only a small percentage rupture. The rate approximates 0.1 percent for aneurysms <10 mm and 1 percent for those >10 mm (Smith, 2018). Most aneurysms identified during pregnancy arise from the circle of Willis, and in 20 percent of cases, lesions are multiple. Pregnancy does not raise the risk for aneurysmal rupture. However, because of their high population prevalence, they are more likely to cause subarachnoid bleeding than other etiologies (Hirsch, 2009; Tiel Groenestege, 2009). A systematic review of 44 women with 50 aneurysms in pregnancy reported that 72 percent ruptured during pregnancy, and 78 percent of these did so during the third trimester (Barbarite, 2016). This proclivity for rupture late in pregnancy is reported by others (Yoshida, 2017).

The cardinal symptom of aneurysmal rupture leading to subarachnoid hemorrhage is sudden severe headache that is accompanied by visual changes, cranial nerve abnormalities, focal neurological deficits, and altered consciousness. Signs of meningeal irritation, nausea and vomiting, tachycardia, transient hypertension, low-grade fever, leukocytosis, and proteinuria are typical. Prompt diagnosis and treatment may prevent potentially lethal complications. The American Heart Association recommends noncontrast cranial CT imaging as the first diagnostic test, although MR imaging may be superior (Smith, 2018).

Treatment of subarachnoid hemorrhage includes bed rest, analgesia, neurological monitoring, and strict blood pressure control. Repair of a potentially accessible aneurysm during pregnancy weighs surgical risks against the risk of recurrent hemorrhage. At least in nonpregnant patients, the risk of subsequent bleeding with conservative treatment is 20 to 30 percent for the first month and then 3 percent per year. The risk of rebleeding is highest within the first 24 hours, and recurrent hemorrhage leads to death in 70 percent (Smith, 2018).

Early repair after the sentinel hemorrhage is accomplished by open craniotomy or endovascular coil placement. In one systematic review of management in pregnancy, coil embolization yielded lower complication rates than aneurysmal clipping (Barbarite, 2016). For unruptured aneurysms, surgical management resulted in a third fewer complications than no treatment. For gravidas remote from term, repair without hypotensive anesthesia seems optimal. For women near term, cesarean delivery followed by aneurysm repair is a consideration. We have successfully done this in several cases.

For aneurysms repaired before or during pregnancy, most allow vaginal delivery if labor ensues remote from aneurysmal repair. Problems arise in defining "remote," and although some recommend 2 months, the time for complete healing is unknown. For women who survive subarachnoid hemorrhage, but in whom surgical repair is not done, we agree with Cartlidge (2000) and recommend against bearing down and favor cesarean delivery.

Arteriovenous Malformations. These are congenital focal abnormal conglomerations of dilated arteries and veins with subarteriolar disorganization (see Fig. 63-2). They

lack capillaries and have resultant arteriovenous shunting. Although unclear, the risk of bleeding during pregnancy may rise with gestational age. When AVMs bleed, half do so into the subarachnoid space, whereas half are intraparenchymal with subarachnoid extension (Smith, 2018). Uncommon, they affect an estimated 0.01 percent of the general population. Of identified AVM cases in pregnancy, 83 percent ruptured during pregnancy or postpartum, and more than 80 percent of these ruptured in the second or third trimester. Hemorrhage is associated with poor maternal outcome but does not appear to be more likely during pregnancy. (Lu, 2016). Although correspondingly rare during pregnancy, AVM bleeding accounted for 17 percent of hemorrhagic strokes in one study (Yoshida, 2017). At Parkland Hospital in a 35-year period and nearly 500,000 births, 62 women had a stroke, and five of these were due to a bleeding AVM (Simolke, 1991; Zofkie, 2018).

Treatment of AVMs in nonpregnant patients is individualized. No consensus guides whether all accessible lesions should be resected. Factors include AVM symptoms; its anatomy and size; an associated aneurysm, which is found in up to 60 percent of cases; and especially, prior AVM bleeding. After hemorrhage, the risk of recurrent bleeding in unrepaired lesions is 6 to 20 percent within the first year, and 2 to 4 percent per year thereafter (Friedlander, 2007; Smith, 2018). The mortality rate from a bleeding AVM is 10 to 20 percent. In pregnancy, the decision to operate is usually based on neurosurgical considerations. Because of the high risk of recurrent hemorrhage from an unresected or inoperable lesion, we favor cesarean delivery.

DEMYELINATING OR DEGENERATIVE DISEASES

The demyelinating diseases are neurological disorders characterized by immune-mediated focal or patchy destruction of myelin sheaths accompanied by an inflammatory response. The degenerative diseases are multifactorial and characterized by progressive neuronal death.

Multiple Sclerosis

This autoimmune demyelinating disease is second only to trauma as a cause of neurological disability in middle adulthood. The demyelinating effects stem predominantly from T cell–mediated autoimmune destruction of oligodendrocytes that synthesize myelin. It has a familial occurrence with an environmental trigger, it affects women twice as often as men, and it usually begins in the 20s and 30s (Cree, 2018; Fang, 2020). In one study, 0.03 percent of California deliveries were complicated by multiple sclerosis (MS) between 2001 and 2009 (Fong, 2018).

There are three clinical types of multiple sclerosis:

1. *Relapsing MS (RMS)* is the initial presentation in 90 percent of affected individuals. With it, unpredictable recurrent episodes of focal or multifocal neurological dysfunction usually are followed by full recovery. Over time, however, relapses lead to persistent deficits.
2. *Secondary progressive MS (SPMS)* is relapsing disease that begins to pursue a progressive downhill course after each relapse. All patients likely develop this type eventually.
3. *Primary progressive MS (PPMS)* accounts for 10 percent of cases. With it, disability gradually progresses from the time of initial diagnosis.

Classic findings of MS include sensory loss, visual symptoms from optic neuritis, weakness, and paresthesias. Clinical diagnosis is aided by MR imaging and cerebrospinal fluid analysis. In greater than 95 percent of cases, MR imaging shows characteristic multifocal white-matter plaques that represent discrete areas of demyelination (Fig. 63-4). Their appearance and extent are less helpful for predicting treatment response.

Formerly considered an MS variant, neuromyelitis optica spectrum disorder (NMOSD) is viewed as a distinct autoimmune disease. Antibodies target astrocytes and lead to autoimmune inflammation of the spinal cord and optic nerve. Some evidence suggests that pregnancy worsens this disorder (Mao-Draayer, 2020).

Multiple Sclerosis in Pregnancy

Women with MS experience fewer attacks during pregnancy, but with a significantly greater relapse rate postpartum (Cree, 2018). This may be related to higher pregnancy-induced numbers of T-helper lymphocytes and an increased T2/Tl ratio. In a metaanalysis of women with more than 1200 pregnancies complicated by MS, their relapse rate was 0.4 per year before pregnancy; 0.26 per year during pregnancy; and 0.7 per year after delivery (Finkelsztejn, 2011). A systematic review reported similar findings (Bove, 2014). Factors associated with postpartum relapse include a high relapse rate before pregnancy, relapses during pregnancy, and a high MS disability score (Portaccio, 2014). Breastfeeding has no effect on postpartum relapses (Hellwig, 2015; Portaccio, 2011).

With uncomplicated disease, pregnancy outcomes are usually not adversely affected (Bove, 2014; Fong, 2018). Some women

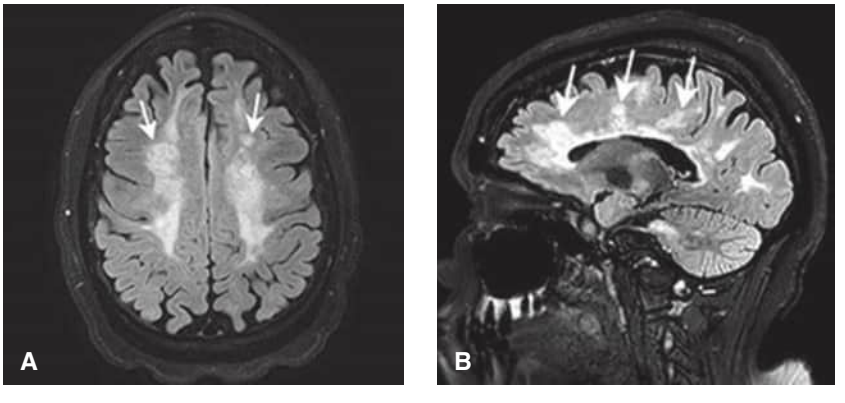

FIGURE 63-4 Magnetic resonance cranial images from a woman with multiple sclerosis. **A.** T2-weighted axial image shows bright signal abnormalities in white matter (*arrows*), typical for multiple sclerosis. **B.** Sagittal T2-FLAIR image shows periventricular hyperintense lesions (Dawson fingers; *arrows*) representative of demyelination in multiple sclerosis.

may fatigue more easily, those with bladder dysfunction are predisposed to urinary infection, and women with spinal lesions at or above T_6 are at risk for autonomic dysreflexia. In one study of 449 pregnancies in affected women, the labor induction rate was higher, and second-stage labor was longer (Dahl, 2006). The greater induction rate and elective operations contributed to the overall higher cesarean delivery rate. In an analysis of 649 affected women, the mean birthweight was lower, but the perinatal mortality rate was similar to controls (Dahl, 2005). In a study of 3875 pregnancies in women with MS, risks for infections and preterm delivery were increased (MacDonald, 2019).

Management

Goals in pregnancy are to arrest acute or initial attacks, employ disease-modifying agents, and provide symptomatic relief. Some treatments may require modification during pregnancy. Acute or initial attacks are treated with high-dose intravenous methylprednisolone—500 to 1000 mg daily for 3 to 5 days. This is followed by oral prednisone for 2 weeks. Plasma exchange may help those with fulminant attacks resistant to corticosteroid therapy. Symptomatic relief can be provided by analgesics. Carbamazepine, phenytoin, or amitriptyline are suitable after the first trimester for neurogenic pain; baclofen, for spasticity; α_1-adrenergic blocking agents, for bladder neck relaxation; and cholinergic and anticholinergic drugs, for bladder-contraction stimulation or inhibition, respectively.

Several disease-modifying therapies are now available to treat relapsing MS or for exacerbations. Examples include interferons, glatiramer, fingolimod, dimethyl fumarate, natalizumab, and ocrelizumab (Cree, 2018; Tintore, 2019). Data regarding their safety in pregnancy are limited (Briggs, 2022). In 246 women with MS, glatiramer was not teratogenic to their offspring (Herbstritt, 2016). In a review of 92 pregnancies, first-trimester natalizumab exposure was associated with an increased miscarriage risk (Portaccio, 2018). Fetal exposure in 89 pregnancies to fingolimod was associated with six fetal malformations and nine spontaneous losses. Because of this and associated animal teratogenicity, its use in pregnancy is not recommended. Due to its prolonged persistence, contraception is recommended for 2 months after fingolimod cessation (Alroughani, 2016). Last, prevention of relapses postpartum has been reported with intravenous immunoglobulin (IVIG). A dose of 0.4 g/kg is given daily for 5 days during weeks 1, 6, and 12 (Argyriou, 2008).

Myasthenia Gravis

This autoimmune-mediated neuromuscular disorder is more common in women, and its incidence peaks in their 20s and 30s (Waters, 2019). The etiology is unknown, but genetic factors likely play a role. Of affected patients, 80 to 90 percent demonstrate antibodies to the acetylcholine receptor (Lee, 2019). Those that are seronegative often have antibodies to muscle-specific tyrosine kinase (MuSK), which regulates assembly of the acetylcholine receptor subunits at the neuromuscular junction.

Cardinal features of myasthenia are weakness and easy fatigability of facial, oropharyngeal, extraocular, and limb muscles. Deep-tendon reflexes are preserved. Cranial muscles are involved early and disparately, and diplopia and ptosis are common. Facial muscle weakness causes difficulty in smiling, chewing, and speaking. In 85 percent of patients, the weakness becomes generalized. Other autoimmune diseases may coexist, and hypothyroidism should be excluded. The clinical course is marked by exacerbations. These can be life threatening and include *myasthenic crises*, which are characterized by severe muscle weakness, inability to swallow, and respiratory muscle paralysis (Lee, 2019). Another is a *cholinergic crisis*, which is caused by excessive cholinergic medication and leads to nausea, vomiting, muscle weakness, abdominal pain, and diarrhea.

Management

Myasthenia gravis is manageable but not curable. The oral anticholinesterase pyridostigmine (Mestinon) is first-line treatment. Thymectomy is recommended but postponed until after pregnancy (Amato, 2018a; Wolfe, 2019). Anticholinesterase medications improve symptoms by impeding acetylcholine degradation but seldom produce normal muscle function. Ironically, overdose is manifest by the cholinergic crisis mentioned earlier and may be difficult to differentiate from myasthenic symptoms. Most gravidas refractory to anticholinesterase therapy respond to immunosuppressive therapy with glucocorticoids, azathioprine, or cyclosporine. When short-term, rapid improvement is needed—such as for a surgical procedure or a myasthenic crisis—high-dose IVIG or plasma exchange is usually effective (Amato, 2018a; Sanders, 2016).

Myasthenia Gravis and Pregnancy

The greatest period of risk is within the first year following diagnosis. Thus, postponing pregnancy until improvement is sustained is reasonable. Antepartum management of myasthenia gravis includes close observation, liberal rest, and prompt treatment of infection (Waters, 2019). Women in remission who become pregnant while taking corticosteroids or azathioprine should continue these. Acute onset or exacerbation of myasthenia gravis demands prompt hospitalization and supportive care. Plasmapheresis and high-dose IVIG are options for emergencies (Waters, 2019). In refractory cases, thymectomy has been successfully performed during pregnancy.

Although pregnancy does not appear to affect the overall course of myasthenia gravis, fatigue common to most pregnancies may be exacerbated, and the expanding uterus may compromise respiration. Maternal hypotension or hypovolemia are ideally avoided because they can trigger crises. The clinical course of myasthenia gravis during pregnancy is unpredictable, and frequent hospitalizations are the norm. Up to a third of women have worsening symptoms during pregnancy, and exacerbations develop equally in all three trimesters (Djelmis, 2002; Podciechowski, 2005). In women with stable disease, most will remain stable throughout pregnancy but likely worsen in the first few months postpartum (Sanders, 2016).

Myasthenia gravis has no significant adverse effects on pregnancy outcomes (Wen, 2009). Preeclampsia is a concern because magnesium sulfate may precipitate a severe myasthenia crisis (Hamaoui, 2009; Heaney, 2010). Although phenytoin use also is problematic in this regard, its adverse effects are less troublesome.

Because smooth muscle is unaffected, most women have normal labor. Oxytocin is given for the usual indications, and cesarean delivery is reserved for obstetrical indications. Narcotics may cause respiratory depression, and close observation and respiratory support are essential during labor and delivery. Curariform drugs are avoided. Examples include magnesium sulfate, muscle relaxants used with general anesthesia, and aminoglycosides. Neuraxial analgesia is accomplished with amide-type local agents. Regional analgesia is preferred unless bulbar involvement or respiratory compromise is significant (Almeida, 2010; Blichfeldt-Lauridsen, 2012). During second-stage labor, some women may have impaired voluntary expulsive efforts that may warrant operative vaginal delivery.

Neonatal Effects

As discussed, 80 percent of mothers with myasthenia gravis have immunoglobulin G (IgG) antibodies against the acetylcholine receptor. These and anti-MuSK antibodies cross transplacentally, and the fetus can be affected. Poor fetal swallowing may yield hydramnios (Heaney, 2010). Similarly, 10 to 20 percent of neonates manifest myasthenia symptoms (Jovandaric, 2016). Transient symptoms usually include a feeble cry, poor suckling, and respiratory distress. Symptoms usually respond to anticholinesterase agents and resolve within a few weeks as maternal IgG antibodies clear.

NEUROPATHIES

Peripheral neuropathy is a general term for peripheral nerve(s) disorders, in which one or more nerves are affected. *Mononeuropathies* are relatively common in pregnancy and signify focal involvement of a single nerve trunk. These imply local causation such as trauma, compression, or entrapment. For example, traumatic pudendal, obturator, femoral, and common fibular mononeuropathies can stem from childbirth (Chap. 36, p. 644). *Polyneuropathies* can be axonal or demyelinating and can be acute, subacute, or chronic (Amato, 2018b). These are often associated with systemic diseases such as diabetes, with drug or environmental toxin exposure, or with genetic disease. Late-stage syphilis is a rare cause (Ghanem, 2020).

■ Guillain–Barré Syndrome

In 75 percent of cases, this acute demyelinating polyradiculoneuropathy has clinical or serological evidence of an acute infection. Common associated infections are *Campylobacter jejuni*, cytomegalovirus, Zika virus, and Epstein-Barr virus; surgical procedures; and immunizations (Leonhard, 2019). Guillain–Barré syndrome is thought to be immune-mediated from antibodies formed against nonself antigens. Demyelination causes sensory and motor conduction blockade, and remyelination yields recovery in most cases.

Clinical features include an areflexic, ascending paralysis, with or without sensory disturbances. Autonomic dysfunction is common. The full syndrome develops over 1 to 3 weeks. Some manifest as chronic inflammatory demyelinating polyneuropathy, and our experiences indicate that this may be relatively common in these young women.

Guillain-Barré syndrome is not more common in pregnancy, and its clinical course mirrors that for nonpregnant individuals. After an insidious onset, paresis and paralysis most often continue to ascend to cause ventilatory weakness.

Management is supportive and incorporates venous thromboembolism prophylaxis, pressure ulcer prevention, and enteral nutrition. In the worsening phase, patients are hospitalized, and a fourth require ventilatory assistance. IVIG or plasmapheresis are beneficial if begun within 1 to 2 weeks of motor symptoms, but neither decreases mortality rates (Leonhard, 2019). Up to 10 percent of patients deteriorate after initial improvement on therapy, and re-treatment with 2 g/kg IVIG over 5 days is recommended. Although most patients recover fully within several months to a year, the mortality rate is 5 percent, mainly due to pulmonary complications and arrhythmias (Pacheco, 2016).

■ Bell Palsy

This disfiguring palsy is usually a mononeuropathic acute facial paralysis that is relatively common in reproductive-aged women (Fig. 63-5). It has a female predominance, and rates in pregnancy may be increased (Beal, 2018; Choi, 2020). The disease is characterized by facial nerve inflammation and often is associated with reactivation of herpes simplex virus or herpes zoster virus. Other causes are Lyme disease and borreliosis.

Bell palsy usually has an abrupt and painful onset with maximum weakness by 48 hours. In some cases, hyperacusis and loss of taste accompany paralysis (Beal, 2018). Management includes supportive care with facial muscle massage and eye protection against corneal injury from drying. Consensus supports that prednisone, 1 mg/kg given orally daily for 5 days, will improve outcomes and shorten the recovery period (Beal, 2018; Madhok, 2016). It is controversial whether added valacyclovir or acyclovir will hasten recovery (Beal, 2018; Gagyor, 2019).

It is unclear if pregnancy alters the prognosis for spontaneous facial palsy recovery. In one study, compared with 90 percent of nonpregnant women and men, only half of pregnant women recovered to a satisfactory level after 1 year (Gillman,

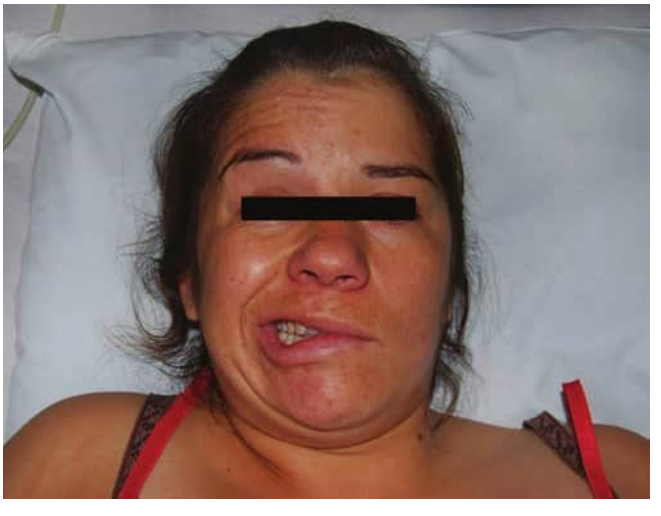

FIGURE 63-5 Bell facial nerve palsy developing on the day of cesarean delivery for dichorionic twins. This woman was treated with prednisone and antiviral medication, and 3 weeks postpartum, the palsy had almost resolved.

2002). In another report, pregnancy-associated Bell palsy had worse long-term outcomes compared with those of nonpregnant cohort (Phillips, 2017). Some prognostic markers for incomplete recovery are bilateral palsy, recurrence in a subsequent pregnancy, greater percentage of nerve function loss, and a faster rate of loss (Cohen, 2000; Gilden, 2004). Other than a fivefold greater rate for gestational hypertension or preeclampsia, women with Bell palsy do not have increased adverse pregnancy outcomes rates (Katz, 2011).

Carpal Tunnel Syndrome

This syndrome results from compression of the median nerve and is the most frequent mononeuropathy in pregnancy (Oliveira, 2019). Symptoms include burning, numbness, or tingling along the inner half of one or both hands. Others are wrist pain and numbness extending into the forearm and sometimes into the shoulder. Symptoms are bilateral in 80 percent of gravidas, and 10 percent have evidence for severe denervation. Differential diagnosis includes cervical radiculopathy of C_6–C_7 and de Quervain tendonitis. The latter is caused by swelling of the conjoined tendons and their sheaths near the distal radius. Nerve conduction studies may help to clarify.

In pregnancy, the reported incidence of carpal tunnel syndrome is 7 to 43 percent and varies greatly because the range of symptoms is marked (Meems, 2015; Oliveira, 2019). Symptomatic treatment with a splint applied to a slightly flexed wrist during sleep lightens pressure and usually provides relief. Although symptoms typically are self-limited, occasionally surgical decompression and corticosteroid injections are necessary (Keith, 2009; Shi, 2011). Symptoms may persist in more than half of patients at 1 year and in a third at 3 years (Padua, 2010).

Meralgia paresthetica is another common pregnancy-induced compression neuropathy (Gooding, 2020). Compression of the lateral femoral cutaneous nerve creates pain, burning, and numbness on the outside of the thigh. For treatment, the site at which the nerve crosses the crease in the groin can be injected with corticosteroids. Oral gabapentin is another treatment.

SPINAL CORD INJURY

According to the National Spinal Cord Injury Statistical Center (2021), approximately 18,000 new spinal cord injuries are sustained each year. The average age is 42 years, and males account for 80 percent of new cases. Cord injury severity determines the short- and long-term prognosis and pregnancy prognosis. For women, many have altered sexual function and transient hypothalamic pituitary hypogonadism. Despite this, pregnancy is not uncommon, and in a review of nearly 2000 women, 2 percent reported pregnancy in the prior 12 months (Lezzoni, 2015).

Two serious and life-threatening events can complicate spinal cord injuries. First, if the cord is transected above T_{10}, the cough reflex is impaired, respiratory function may be compromised, and pneumonitis from covert aspiration can be serious. Pulmonary function tests are considered to assess this risk, and some women may need ventilatory support in late pregnancy or labor.

Second, women with lesions above T_5–T_6 are at risk for autonomic dysreflexia. With this, stimuli from structures innervated below the level of the spinal lesion lead to massive, disordered sympathetic stimulation. Abrupt catecholamine release can prompt vasoconstriction with severe hypertension and symptoms that include throbbing headaches, facial flushing, sweating, bradycardia, tachycardia, arrhythmias, and respiratory distress. Dysreflexia can be precipitated by various stimuli. These include distention or manipulation of reproductive tract or lower urinary tract organs or bowel (American College of Obstetricians and Gynecologists, 2020; Krassioukov, 2009). In one report, 12 of 15 women at risk for autonomic dysreflexia suffered at least one episode during pregnancy (Westgren, 1993).

Gravidas with spinal cord injury have an increased frequency of other complications. In a review of 37 affected pregnant women, 30 percent had pyelonephritis, 32 percent had lower urinary tract infections, and 9 percent had pressure sores (Le Liepvre, 2017). Two women developed autonomic dysreflexia, which caused cerebral hemorrhage in one. Urinary infections may be related to altered vaginal microbiota (Pires, 2016). Bowel dysfunction causes constipation in more than half, and anemia and pressure-necrosis skin lesions are common.

Vaginal delivery is generally successful (Robertson, 2020). Operative vaginal delivery is frequently necessary. Because uterine contractions are not affected by spinal cord lesions, labor is usually easy, comparatively painless, and at times precipitous. If the lesion is below T_{12}, uterine contractions are felt normally. For lesions above T_{12}, the risk of out-of-hospital delivery is substantial and can be minimized by teaching women to palpate for uterine contractions. This is especially important because up to 20 percent of women deliver preterm (Westgren, 1993). Some recommend tocodynamometry and weekly cervical examinations beginning at 28 to 30 weeks' gestation. Another reasonable option that we frequently employ at Parkland Hospital is elective hospitalization after 36 to 37 weeks. Spinal or epidural analgesia extending to T_{10} prevents autonomic dysreflexia and should be instituted at the start of labor (Kuczkowski, 2006). If severe symptoms are identified before epidural placement, steps are taken to abolish the provoking stimulus. A parenteral antihypertensive agent such as hydralazine or labetalol is given.

IDIOPATHIC INTRACRANIAL HYPERTENSION

Also known as *pseudotumor cerebri*, this disorder is typified by increased intracranial pressure without hydrocephalus. The cause is unknown, but it may result from overproduction or underabsorption of cerebrospinal fluid (CSF), or both. Symptoms include headache in at least 90 percent of cases, visual disturbances such as loss of a visual field or central visual acuity in 70 percent, and commonly occurring papilledema that may be sight-threatening (Heaney, 2010; Kesler, 2013). Other complaints are stiff neck, back pain, pulsatile tinnitus, and cranial nerve palsies (Dinkin, 2019).

The syndrome is often found in young women and is prevalent in those who are obese, who recently gained weight, or both (Fraser, 2011). Along with symptoms, other criteria for diagnosis include elevated intracranial pressure >25 cm H_2O,

normal CSF composition, normal cranial CT or MR imaging findings, papilledema, and no evidence for systemic disease. If papilledema is not present, other criteria are required (Friedman, 2013).

Idiopathic intracranial hypertension is usually self-limited, but long-term vision loss is common (Hatem, 2018). Visual defects can be prevented by lowering the CSF pressure, and agents include acetazolamide to reduce fluid production, furosemide, or topiramate.

Corticosteroids are now rarely used. Surgical intervention is occasionally necessary and is accomplished by either lumboperitoneal shunting of spinal fluid or optic nerve sheath fenestration. Another treatment is stenting of dural venous sinus stenosis (Dinkin, 2019). It is controversial if pregnancy is a risk factor for idiopathic intracranial hypertension. Certainly, symptoms may first appear in pregnancy, and women previously diagnosed may become symptomatic. Symptoms usually develop by midpregnancy, tend to be self-limited, and usually resolve postpartum.

Pregnancy does not alter management. Some recommend serial visual-field testing to forestall permanent vision loss. In a report of 16 pregnant women, visual-field loss developed in four, and it became permanent in one (Huna-Baron, 2002). Visual-field loss is often coincident with the development of papilledema, for which acetazolamide is given. Lee and associates (2005) reported successful treatment of 12 pregnant women. Although outmoded for treatment of nonpregnant individuals, repeated lumbar punctures are generally successful in providing temporary relief throughout pregnancy. In some pregnant women, surgical therapy becomes necessary, including optic nerve sheath fenestration (Thambisetty, 2007).

Pregnancy complications are likely due to associated obesity and not to intracranial hypertension. Rates of adverse maternal and perinatal outcomes are not increased (Kesler, 2013). The route of delivery depends on obstetrical indications, and conduction analgesia is safe (Aly, 2007; Karmaniolou, 2011).

MATERNAL VENTRICULAR SHUNTS

Pregnancies in women with previously placed ventricular shunts for obstructive hydrocephalus usually have satisfactory outcomes. Shunts may be ventriculoperitoneal, ventriculoatrial, or ventriculopleural. Partial obstruction of a shunt is common, especially late in pregnancy (Schiza, 2012). In one report of 17 such pregnancies, neurological complications were reported in 13 (Wisoff, 1991). Findings included headaches in 60 percent, nausea and vomiting in 35 percent, lethargy in 30 percent, and ataxia or gaze paresis, each in 20 percent. Most symptoms respond to conservative management. However, if CT scanning during symptom evaluation discloses acute hydrocephaly, the shunt is tapped or pumped several times daily. In some cases, surgical revision is necessary and may be emergently indicated (Murakami, 2010). Another shunting procedure is placement of an endoscopic third ventriculostomy for hydrocephalus. With this, a small hole is created in the floor of the third ventricle to allow CSF to flow directly into lower cisterns. One report described successful results in five gravidas who underwent endoscopic ventriculostomy (Riffaud, 2006).

Vaginal delivery is preferred in women with shunts, and unless there is a meningomyelocele, conduction analgesia is permitted. Antimicrobial prophylaxis is indicated if the peritoneal cavity is entered for cesarean delivery or puerperal sterilization.

MATERNAL BRAIN DEATH

Brain death is rare in obstetrics, and only a few institutional brain-death policies address pregnancy (Lewis, 2016). Life-support systems and parenteral alimentation for up to 20 weeks while awaiting delivery have been described (Hussein, 2006; Powner, 2003; Reinhold, 2019). Some women were treated with aggressive tocolysis and antimicrobial therapy. In one review of 17 women with persistent vegetative state who were given various levels of support, five women died after delivery, and most of the others remained in their vegetative state (Chiossi, 2006). The ethical, financial, and legal implications, both civil and criminal, that arise from providing or withdrawing such care are profound (Feldman, 2000). In some women, perimortem cesarean delivery is performed.

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CHAPTER 64

Psychiatric Disorders

Pregnancy and the puerperium are at times sufficiently stressful to provoke mental illness. Such illness may represent recurrence or exacerbation of a preexisting psychiatric disorder, or it may signal the onset of a new condition. Especially prevalent in pregnancy and the puerperium are depressive and anxiety disorders (Kendig, 2017). Many of these disorders are associated with less prenatal care, substance use, preterm delivery, and other poor obstetrical and neonatal outcomes. In affected gravidas, the postpartum psychiatric illness rate also is higher (Baer, 2016). Last, perinatal mood disorders can adversely hinder the mother-child relationship.

Despite these known risks, obstetrical providers often are reluctant to confront or fail to identify mental health issues during pregnancy. Lyell and colleagues (2012) found that the diagnosis of depression was not documented in nearly half of the records of affected women.

PSYCHOLOGICAL ADJUSTMENTS TO PREGNANCY

Biochemical factors and life stressors can markedly influence mental health and mental illness during the perinatal period (Meltzer-Brody, 2018b). Intuitively, pregnancy exacerbates some coexisting psychological disorders. Namely, a higher risk for mood disorders is linked with pregnancy-related shifts in sex steroid and monoamine neurotransmitter levels, dysfunction of the hypothalamic-pituitary-adrenal axis, thyroid dysfunction, and immune response alterations (Yonkers, 2011). These changes, coupled with familial clustering of depression cases, suggest that a subgroup of women may be at greater risk for developing a unipolar major depressive disorder during pregnancy.

Women respond variably to the stresses of pregnancy. Some express persistent concerns regarding fetal health, child care, lifestyle changes, or fear of childbirth pain. Anxiety, sleep disorders, and functional impairment are common (Romero, 2014; Vythilingum, 2008). The level of perceived stress is significantly higher for women whose fetus is at high risk for a malformation, for those with preterm labor or delivery, and for those with other medical complications (Alder, 2007; Ross, 2006). For example, Hippman and associates (2009) screened for depression in 81 women who had an increased risk for a fetus with aneuploidy. Half of these women had a positive depression screening score, whereas only 2.4 percent of those with a normal pregnancy did so.

Several steps can diminish psychological stress in the event of a poor obstetrical outcome. For example, following a stillbirth, parental contact with the newborn and provision of photographs and other infant memorabilia is encouraged (Gold, 2007). Addressing associated sleep disorders also seems reasonable (Juulia Paavonen, 2017).

The Puerperium

This is a particularly stressful time for women, and risks for mental illness are increased. Up to 15 percent of women develop a nonpsychotic postpartum depressive disorder within 6 months of delivery (Tam, 2007; Yonkers, 2011). Depressive disorders are more likely in women with obstetrical complications such as severe preeclampsia or fetal-growth restriction, especially if associated with early delivery. Prior psychiatric disorders or childhood trauma also raises the risk for postpartum depression (Tebeka, 2021). Instead, some have a psychotic illness following delivery, and half of these manifest as a bipolar disorder.

Importantly, stressors beyond those directly related to the pregnancy also can raise perinatal depression rates. Tarney and colleagues (2015) identified spouse military deployment as a factor for postpartum depression. But, among women with a history of bipolar disorder, these elements play a lesser role in the development of mania or depression (Yonkers, 2011).

Maternity Blues

Also called *postpartum blues*, this is a time-limited period of heightened emotional reactivity experienced by half of women within the first week after parturition. Prevalence estimates for the blues range from 26 to 84 percent depending on diagnostic criteria (O'Hara, 2014). This emotional state generally peaks on the fourth or fifth postpartum day and normalizes by day 10 (O'Keane, 2011).

The predominant mood during the puerperium is happiness, but affected mothers are more emotionally labile. They also may have insomnia, weepiness, depression, anxiety, poor concentration, and irritability. Mothers may be transiently tearful for several hours and then recover completely, only to be tearful again the next day. Supportive treatment is indicated, and affected women are reassured that the dysphoria is transient and most likely due to biochemical changes. They are monitored for development of depression and other severe psychiatric disturbances.

Perinatal Evaluation and Screening

Both the American College of Obstetricians and Gynecologists (2018b) and the United States Preventive Services Task Force now recommend screening at least once during the perinatal period for depression and anxiety (Siu, 2016). Indeed, it has recently been recommended that all obstetrical care providers complete a full assessment of mood and emotional well-being during the comprehensive postpartum visit (American College of Obstetricians and Gynecologists, 2018a). Identification of psychiatric disorders in pregnancy can be challenging because changes in behavior and mood are often attributed to pregnancy. To differentiate these, Yonkers and associates (2011) recommend assessment of cognitive symptoms—for example, loss of concentration. Excessive anxiety and insomnia—even during periods of infant sleep—also can suggest postpartum depression. Specific factors for depression are reviewed and include a prior personal or family history of depression.

Universal screening programs for depression continue to evolve (Venkatesh, 2016). One major step forward is state-level support for screening. Beginning July 1, 2018, mothers who take newborns for Texas Health Steps routine examination are able to receive testing and counseling (Texas Health and Human Services, 2019). At Parkland Hospital, mental illness screening is completed at the first prenatal visit using a brief risk-based query and again postpartum using a recognized screening tool for postpartum depression. Questions search for psychiatric disorders, related therapy, prior or current use of psychoactive medications, and current symptoms. Women with a history of sexual, physical, or verbal abuse; illicit substance use; and personality disorders are also at greater risk for depression (Meltzer-Brody, 2014). Smoking and nicotine dependence and obesity also raise rates of *all* mental disorders in pregnancy (Molyneaux, 2014). Last, because eating disorders may be exacerbated by pregnancy, affected women are followed closely (p. 1149).

Several screening instruments shown in Table 64-1 are available and have been validated for use during pregnancy and the puerperium (Bhat, 2017). Use of one of these is encouraged because symptom- or risk-based screening alone may be insufficient. Cerimele and colleagues (2013) found that obstetrician-gynecologists failed to identify 60 percent of depressed women in clinical practice. In one study at Parkland Hospital, 17,000 women were screened during their first postpartum visit using the Edinburgh Postnatal Depression Scale (EPDS). Of these, 6 percent had scores that indicated either minor or major depressive symptoms, and 12 women had thoughts of self-harm (Nelson, 2013). In another study, Kim and coworkers (2015) assessed suicidal ideation in more than 22,000 women screened

TABLE 64-1. Depression Screening Tools

Screening Tool	Items	Time to Complete (min)	Available Resources Online
Edinburgh Postnatal Depression Scale	10	<5	www.fresno.ucsf.edu/pediatrics/downloads/edinburghscale.pdf
Patient Health Questionnaire 9	9	<5	www.integration.samhsa.gov/images/res/PHQ%20-%20Questions.pdf
Center for Epidemiologic Studies Depression Scale	20	5–10	www.perinatalweb.org/assets/cms/uploads/files/CES-D.pdf

These screening tools are also available in Spanish.

using the EPDS both during pregnancy and postpartum. They found rates of depression as high as 3.4 percent during the puerperium. A small fraction of those with thoughts of self-harm had a credible plan, intent, and means for attempted suicide.

Screening for perinatal depression alone was previously considered insufficient, however, evidence now suggests that screening itself has clinical benefit (American College of Obstetricians and Gynecologists, 2018b). One systematic review of six randomized trials that screened pregnant or postpartum women found that follow-up of these women weeks to months later demonstrated an absolute risk reduction in the depression rate by a range of 2.1 to 9.1 percent (O'Connor, 2016). However, this review included studies with and without treatment components compared with usual care. Another limitation is that four of the six studies did not exclude women previously known to be depressed. Findings from this analysis prompted an interim update by the American College of Obstetricians and Gynecologists (2018b) to state that screening alone can have clinical benefit, although treatment initiation or referral to a mental health care provider offers maximum benefit.

Mechanisms to ensure adequate ensuing care can be problematic. Nelson and associates (2013) found that more than three fourths of the 1106 women with abnormally elevated EPDS scores did not keep their later appointment for more formal psychiatric evaluation. Barriers include access to care, personal perception of depression, and societal stigmata. Women referred to a behavioral health provider located at the same site as their obstetrical care are four times more likely to access treatment than those referred elsewhere (Smith, 2009). To take advantage of this, at Parkland Hospital, mental health counselors also practice at postpartum clinic sites.

Other promising interventions for puerperal depression include home visits, telephone-based peer support, and interpersonal psychotherapy (Dennis, 2013; Lavender, 2013; Yonemoto, 2017). A report from Kaiser Permanente, which describes the benefits and hurdles of system-based perinatal mental health care, provides a glimpse into the possible future of universal perinatal screening and treatment (Avalos, 2016; Flanagan, 2016).

Treatment Considerations

Once a positive mental health screen result is identified, a stage-based response protocol is triggered (Kendig, 2017). In brief, the initial response focuses on maternal and infant safety, and if possible, onsite patient assessment by either a mental health provider or mental health counselor. Integrating on-site assessment and access to counselors quadruples later attendance rates to mental health appointments (Byatt, 2015).

For women with suicidal or homicidal ideation, perinatal care providers first determine a working diagnosis. Second, emergency psychiatric consultation is sought and ambulance transport is implemented if needed. Concurrently, perinatal care and psychiatric teams ideally communicate closely. Last, the patient, her family, and clinical staff are emotionally supported. Appreciation for this issue's significance has grown with the recent national emphasis on maternal mortality. For example, Palladino and associates (2011) found that pregnancy-associated homicide and suicide were significant contributors to maternal mortality in a multistate sample from the National Violent Death Reporting system.

Many psychiatric disorders can be improved with counseling and psychotherapy. In some instances, medications are needed. Shared decision making is employed by patients and their health-care providers. In particular, women taking psychotropic medication are informed of likely side effects. Many of these drugs are discussed in Chapter 8, and some are discussed subsequently.

Pregnancy Outcomes

As noted, maternal psychiatric illness can be linked to untoward outcomes such as preterm birth, low birthweight, and perinatal mortality (Grigoriadis, 2013; Jarde, 2016; Steinberg, 2014). In a study of 16,334 deliveries, a significant association between posttraumatic stress disorder (PTSD) and spontaneous preterm delivery was identified (Shaw, 2014). Domestic abuse—another aforementioned risk factor for perinatal mood disorder—also is linked with adverse perinatal outcomes (Yost, 2005).

CLASSIFICATION OF PSYCHIATRIC DISORDERS

The *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5)* is the most recent version from the American Psychiatric Association (2013). The manual assists in classifying mental disorders and specifies criteria for each diagnosis. It is presumed that correct diagnosis leads to specific treatment.

MOOD DISORDERS

Historically, depressive disorders include major depression—a unipolar disorder—and manic-depression—a bipolar disorder with both manic and depressive episodes. It also includes dysthymia, which is chronic, mild depression.

Major Depression

This is the most common depressive disorder, and the 12-month prevalence of major depressive episodes among adult women is 8.2 percent (Center for Behavioral Health Statistics and Quality, 2015). From 2011 to 2014, 16 percent of women had used an antidepressant in the prior month (Pratt, 2017). The diagnosis is made by identifying symptoms listed in Table 64-2, but very few patients manifest all of these.

Major depression is multifactorial and prompted by genetic and environmental factors. Families of affected individuals often also have members suffering with alcohol abuse and anxiety disorders. Provocative conditions leading to depression include substance abuse, certain medications, other medical disorders, and life events that prompt grief reactions. Although life events can trigger depression, genes influence the response to these events and render the distinction between genetic and environmental factors difficult.

TABLE 64-2. Symptoms of Depressive Illness[a]

Hopelessness and/or pessimism
Persistent sad, anxious, or "empty" feelings
Guilt, worthlessness, and/or helplessness
Irritability, restlessness
Loss of interest in activities once pleasurable, including sex
Fatigue and decreased energy
Difficulty concentrating, remembering details, and making decisions
Insomnia, early-morning wakefulness, or excessive sleeping
Overeating or appetite loss
Thoughts of suicide, suicide attempts
Persistent aches, or pains, headaches, cramps, or digestive problems that do not ease with treatment

[a]Not all patients experience the same symptoms.
From National Institute of Mental Health, 2019.

Pregnancy and Depression

Pregnancy is a major life stressor that can precipitate or exacerbate depressive tendencies. In addition, various pregnancy-induced effects are implicated. Hormones certainly affect mood, as evidenced by premenstrual syndrome and menopausal depression. Estrogen has been linked to enhanced serotonin synthesis, decreased serotonin breakdown, and serotonin-receptor modulation (Deecher, 2008). Concordantly, women who experience postpartum depression often have higher pre-delivery serum estrogen and progesterone levels and experience a greater decline postpartum (Ahokas, 1999).

The prevalence of antenatal depression averaged 11 percent in one Cochrane Database review (Dennis, 2007). In more than 1800 women enrolled for prenatal care at a single clinic, Melville and coworkers (2010) found rates of nearly 10 percent. A higher rate has been seen in those after antepartum complications (Toscano, 2021).

Postpartum Depression

Major or minor depression develops postpartum in 10 to 20 percent of women (Mental Health America, 2019). Postpartum depressive symptoms are associated with young maternal age, antenatal depression, unmarried status, smoking, newborns requiring intensive care, and stressors during pregnancy (Ko, 2017; Silverman, 2017). Specifically, physical or verbal abuse is a potent risk for postpartum depression (McFarlane, 2014). Last, serious adverse obstetrical events, especially those involving the neonate, are strongly linked (Nelson, 2013, 2015).

Depression is frequently recurrent. Up to 70 percent of women with previous postpartum depression have a subsequent episode. Women with both prior puerperal depression and a current episode of "maternity blues" carry an inordinately high risk for major depression. Indeed, 2 to 9 months postpartum, assistance with postpartum depression was the fourth most common challenge identified in women in the Pregnancy Risk Assessment Monitoring System—PRAMS (Kanotra, 2007).

Postpartum depression is generally underrecognized and undertreated. Major depression during pregnancy or after delivery can have devastating consequences for affected women, their children, and families. One of the most significant contributions to the mortality rate among new mothers is suicide, which is most frequent among women with mental illness (Koren, 2012; Palladino, 2011). If left untreated, up to 25 percent of women with postpartum depression will be depressed 1 year later. As the duration of depression increases, so too does the number of sequelae and their severity. Maternal depression during the first weeks and months after delivery can lead to insecure attachment and later behavioral problems in the child (Mezzacappa, 2017; Viktorin, 2017).

Depression Treatment

Therapy for mood disorders during pregnancy and postpartum has evolved. Babbitt (2014) and Pozzi (2014) and their associates have reviewed principles of perinatal care of women with major mental disorders. In general, for mild and mild-moderate depression, psychological treatment options, such as cognitive behavioral therapy, are considered first (Yonkers, 2011). Light- to moderate-intensity exercise may be beneficial (McCurdy, 2017).

Antidepressant medications together with some form of psychotherapy are indicated for moderate to severe depression during pregnancy or the puerperium (American College of Obstetricians and Gynecologists, 2018b). Shown in Figure 64-1 is one algorithm regarding mood disorder treatment. Some of these medications are listed in Table 64-3. For women with severe depression, a selective serotonin-reuptake inhibitor (SSRI) is selected initially. If depressive symptoms improve during a 6-week trial, the medication is continued for a minimum of 6 months to prevent relapse (Wisner, 2002).

If the response is suboptimal or a relapse occurs, another SSRI is substituted, or psychiatric referral is considered. At least 60 percent of women taking antidepressant medication before pregnancy have symptoms during pregnancy. In one study, approximately three fourths of women taking antidepressants before pregnancy stopped taking them before or during early pregnancy (Hayes, 2012). For those who discontinue treatment, almost 70 percent have a relapse compared with approximately 25 percent who continue therapy.

In one metaanalysis, women using antidepressants during pregnancy had higher rates of preterm birth and low-birthweight neonates (Huang, 2014). Some of the included studies failed

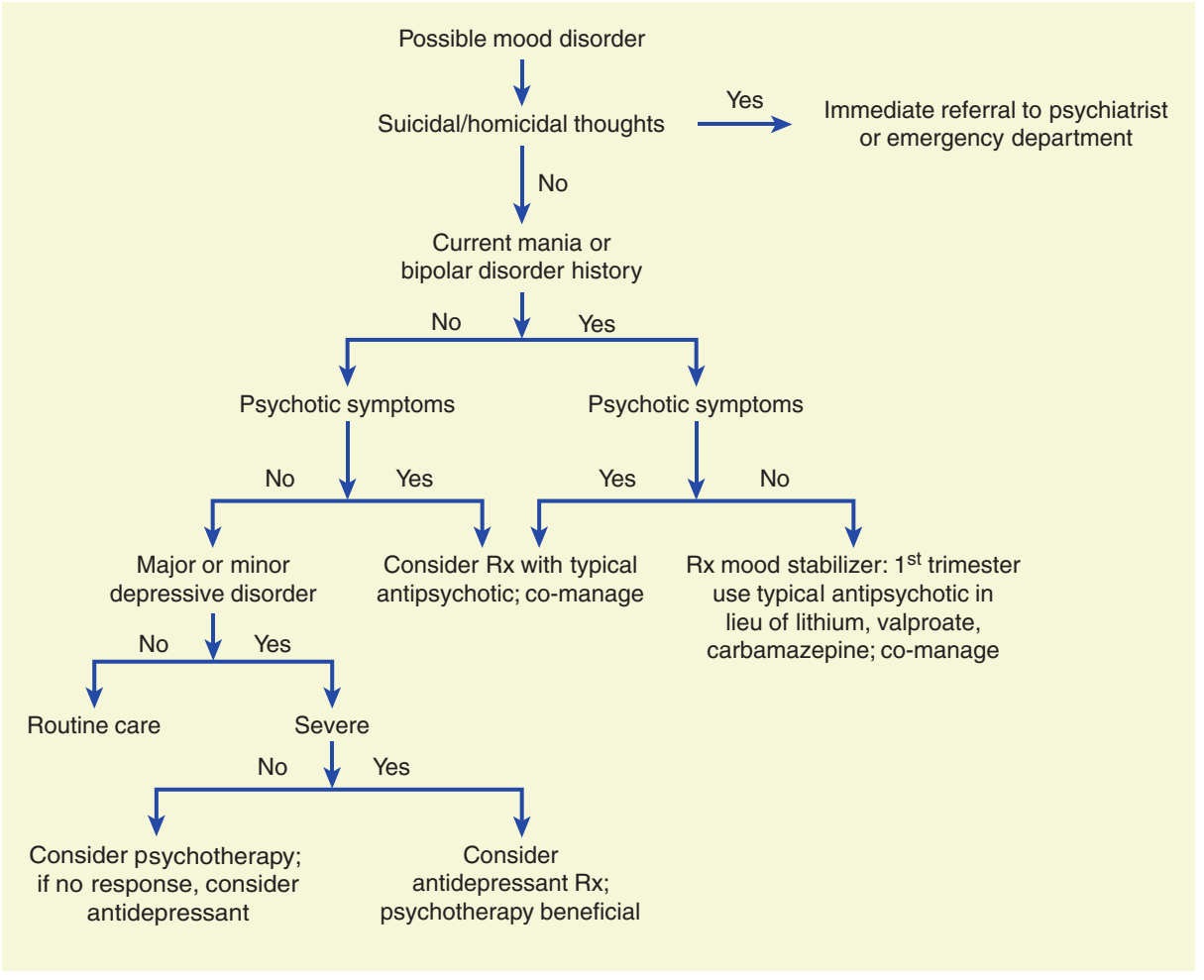

FIGURE 64-1 Treatment algorithm for pregnant women with mood disorders. Rx = prescription.

TABLE 64-3. Drugs Used for Treatment of Major Mood Disorders in Pregnant Women

Indication	Examples	Comments
Antidepressants		
SSRIs[a]	Citalopram, sertraline, fluoxetine, paroxetine	Some have possible link with heart defects, neonatal withdrawal syndrome, and pulmonary hypertension
Others	Bupropion, duloxetine, nefazodone, venlafaxine	
Tricyclics	Amitriptyline, desipramine, doxepin, imipramine, nortriptyline	No evidence of teratogenicity, not commonly used
Antipsychotics		
Typical	Chlorpromazine, fluphenazine, haloperidol, thiothixene	
Atypical	Aripiprazole, clozapine, olanzapine, risperidone, ziprasidone	
Bipolar Disorders		
Lithium[a]	Lithium carbonate	Manic episodes; teratogenic for cardiac defects (Ebstein anomaly)
Valproic acid[b]		Teratogenic for neural-tube defects
Carbamazepine[b]		Antiepileptic; hydantoin syndrome

[a]Chapter 8 (p. 150).
[b]Chapter 63 (p. 1130).
SSRI = selective serotonin-reuptake inhibitor.
Data from American College of Obstetricians and Gynecologists, 2018c; Briggs, 2017; Huybrechts, 2015; Koren, 2012.

to control for the underlying depressive illness (Susser, 2016). Nevertheless, in their review, Ray and Stowe (2014) concluded that the relative reproductive safety data are reassuring and that antidepressants remain a reasonable treatment option. Furthermore, recurrence sometime after medication is discontinued develops in 50 to 85 percent of women with an initial postpartum depressive episode. Surveillance includes monitoring for thoughts of suicide or infanticide, emergence of psychosis, and response to therapy. For some women, the course of illness is severe enough to warrant hospitalization.

Fetal and Neonatal Effects of Therapy. Some known and possible fetal and neonatal effects of treatment are listed in Table 64-3. Some studies suggest that SSRIs pose an elevated teratogenic risk for fetal cardiac defects, and these have mainly focused on paroxetine (Paxil). Associations were most consistent for ventricular septal defects. The estimated risk is no greater than 1 case in 200 exposed newborns (Koren, 2012). Nevertheless, the American College of Obstetricians and Gynecologists (2018b) recommends that paroxetine be avoided in women who are either pregnant or planning pregnancy. In women exposed to paroxetine in the first trimester, fetal echocardiography is considered. In one analysis of SSRIs, exposure to SSRIs during pregnancy and perinatal mortality were not linked (Jimenez-Solem, 2013). Andersen and associates (2014) found that women discontinuing SSRI treatment in early pregnancy had a small increased risk of miscarriage. However, the risk was similar to that in women discontinuing SSRI treatment months before pregnancy. These investigators concluded that treatment with SSRIs during pregnancy should not be discontinued for fear of miscarriage.

Of other potential effects, the risk of persistent pulmonary hypertension of the newborn is sixfold higher in neonates exposed to SSRIs after 20 weeks' gestation (Chambers, 2006). This translates to an overall pulmonary hypertension risk of less than 1 case in 100 exposed newborns (Koren, 2012). A population-based cohort study of 1.6 million pregnancies identified a twofold greater rate in exposed neonates. This yields an estimated attributable risk of 2 cases per 1000 births (Kieler, 2012). In a study of more than 120,000 women prescribed antidepressants, an attributed risk of 1 case per 1000 births was found (Huybrechts, 2015).

The maternal risk associated with discontinuing or tapering SSRI use during pregnancy must be weighed against marginally elevated neonatal risks (Ornoy, 2017). Women who abruptly discontinue either serotonin- or norepinephrine-reuptake inhibitor therapy typically experience some form of withdrawal.

Not surprisingly, up to 30 percent of exposed neonates also may exhibit withdrawal symptoms. Symptoms are similar to opioid withdrawal but typically are less severe. Neonatal SSRI withdrawal is usually self-limited, and the newborn rarely remains in the nursery more than 5 days (Koren, 2009). Recent magnetic resonance imaging studies show brain volume differences in SSRI-exposed fetuses compared with unexposed ones (Lugo-Candelas, 2018). Still, at this time, convincing evidence of long-term neurobehavioral effects of fetal exposure to these medications is lacking (Grzeskowiak, 2016; Man, 2017; Mezzacappa, 2017; Viktorin, 2017).

Some psychotropic medications pass into breast milk. In most cases, however, levels are very low or undetectable. Effects may be transient irritability, sleep disturbances, and colic.

Allopregnanolone. A recent Food and Drug Administration (FDA)-approved therapeutic agent for treatment of postpartum depression is brexanolone, which is an allopregnanolone analogue. Plasma allopregnanolone levels rise in connection with progesterone throughout pregnancy, and after childbirth these concentrations drop abruptly. Failure of gamma-aminobutyric acid type A (GABA-A) receptors to adapt to these changes following delivery is a suggested antecedent to postpartum depression. In small randomized trials, intravenous infusions of brexanolone significantly reduced Hamilton Rating Scale for Depression scores compared with placebo (Kanes, 2017; Meltzer-Brody, 2018a). Treatment is prohibitively expensive, and further studies are needed before its use is widely accepted.

Ketamine. This anesthetic drug is given intravenously for refractory depression, but studies in pregnant or postpartum women are lacking. Similarly, the recent FDA-approved esketamine nasal spray has not been studied in these women.

Electroconvulsive Therapy. This form of depression treatment is occasionally necessary during pregnancy for women with major mood disorders unresponsive to pharmacotherapy. Women undergoing electroconvulsive therapy (ECT) should be fasting for at least 6 hours. They are given a rapid-acting antacid before the procedure, and their airway is protected to decrease the likelihood of aspiration. After midpregnancy, a wedge is placed under the right hip to prevent sudden maternal hypotension from aortocaval compression. Other important preparatory steps include assessment of the cervix, discontinuation of nonessential anticholinergic medication, uterine and fetal heart rate monitoring, and intravenous hydration. During the procedure, excessive hyperventilation is avoided. In most cases, maternal and fetal heart rate and maternal blood pressure and oxygen saturation remain normal throughout the procedure.

With proper preparation, the risks to both mother and fetus appear to be reasonable (Ray-Griffith, 2016). Such therapy is relatively safe in the first trimester (Calaway, 2016). That said, adverse maternal and perinatal outcomes have followed ECT. Balki and associates (2006) reported a pregnancy in which fetal brain damage likely was caused by sustained maternal hypotension associated with treatment of status epilepticus stimulated by ECT.

At least two extensive reviews have evaluated ECT outcomes in pregnancy. In one, Miller (1994) found 300 cases and reported complications in 10 percent. These included fetal arrhythmias, vaginal bleeding, abdominal pain, and self-limited contractions. Women not adequately prepared had higher risks for aspiration, aortocaval compression, and respiratory alkalosis. In another review, Anderson and Reti (2009) described 339 cases, undoubtedly with some homology with the earlier study. In most cases, ECT therapy was done to treat depression, and it was 78-percent effective. They reported a 5-percent maternal ECT-related complication rate. The associated perinatal complication rate was 3 percent and included two fetal deaths.

In sum, we agree with Richards (2007) that ECT in pregnancy is not "low risk" and that it should be reserved for women whose severe depression is resistant to intensive pharmacotherapy.

Suicide

Self-harm is a primary cause of death among women during the perinatal period, and major depression is among the strongest predictors (Melville, 2010). Between 2004 and 2012, self-harm, suicide, or drug overdose was the leading cause of maternal death in Colorado (Metz, 2016). During a similar time period in Ontario, perinatal suicide accounted for 5.3 percent of all maternal deaths (Grigoriadis, 2017). Fetal loss is associated with a three- to fivefold greater risk for suicide (Weng, 2018). And, 54 percent of pregnancy-associated suicides reportedly involved intimate-partner conflict (Palladino, 2011).

Bipolar and Related Disorders

According to the National Institute of Mental Health (2017a), the lifetime prevalence for manic-depression illness is 4.4 percent. The prevalence of bipolar disorder does not vary between gravidas and nonpregnant reproductive-aged women (Yonkers, 2011). It has a strong genetic component and has been linked to possible mutations on chromosomes 16 and 8 (Jones, 2007). The risk that monozygotic twins are both affected is 40 to 70 percent, and the risk for first-degree relatives is 5 to 10 percent (Muller-Oerlinghausen, 2002).

Periods of depression last at least 2 weeks. At other times, patients are manic, in which mood is abnormally raised, expansive, or irritable. Potential organic causes of mania include substance abuse, hyperthyroidism, and central nervous system tumors. These are all excluded during an acute event. Importantly, pregnancy frequently prompts medication discontinuation, which poses a substantially increased risk for relapse. Approximately one third of patients with manic-depression illness will attempt suicide during their lifetime (Novick, 2010).

Bipolar Disorder in Pregnancy

This disorder has also been associated with adverse perinatal outcomes such as preterm birth (Mei-Dan, 2015). Women who experience pregnancy complications are more likely to exhibit periods of mania or depression (Di Florio, 2013). Moreover, symptomatic women during pregnancy more likely have postpartum relapses that can be severe (Taylor, 2018). Women who tend to be manic present with exacerbations earlier in the postpartum period.

Typical therapy for bipolar disorder includes mood stabilizers such as lithium, valproic acid, and carbamazepine and antipsychotic medications (see Table 64-3). Treatment of bipolar disorder in pregnancy is complex and is ideally managed concurrently with a psychiatrist. Decisions include risks versus benefits of mood stabilizers, some of which are teratogenic (Clark, 2018). For example, lithium has been linked to Ebstein anomaly in exposed fetuses. More recent data, however, suggest a lower risk of cardiac malformations than previously indicated (Munk-Olsen, 2018; Patorno, 2017). Nevertheless, many recommend fetal echocardiography for lithium-exposed fetuses. Some limited evidence suggests that lithium in breast milk, when its elimination is impaired as in dehydration or immaturity, can adversely affect the infant (Davanzo, 2011). However, lithium use in mothers with a healthy, term fetus is considered moderately safe. Children born to bipolar women do not appear to suffer long-term adverse effects (Santucci, 2017). A more detailed discussion of other mood stabilizers and antipsychotic medications side effects is found in Chapter 8 (p. 153).

Postpartum Psychosis

This severe mental disorder is usually a bipolar disorder, but it may be due to major depression (American Psychiatric Association, 2013). Its estimated incidence is 1 case in every 1000 deliveries, and it is more common in nulliparas, especially those with obstetrical complications (Bergink, 2016; Tinkelman, 2017). In most cases, illness manifests within 2 weeks of delivery and lasts 2 to 3 months. Because those with underlying psychiatric disease have a 10- to 15-fold risk for recurrence postpartum, close monitoring is recommended.

Women with a history of bipolar disease typically exhibit symptoms within 1 to 2 days after delivery (Heron, 2007, 2008). Manic symptoms include feeling excited or elated, being active or energetic, feeling "chatty," and suffering insomnia. Affected women may display confusion and disorientation but may also have lucid episodes.

Postpartum psychosis has a 50-percent recurrence risk in the next pregnancy. As a result, Bergink and associates (2016) recommend initiating lithium therapy immediately after delivery in women with a history of postpartum psychosis.

The clinical course of bipolar illness with postpartum psychosis is comparable with that for nonpregnant women. Patients usually require hospitalization, pharmacological treatment, and long-term psychiatric care. Psychotic women may have delusions leading to thoughts of self-harm or harm to their infants. Unlike women with nonpsychotic depression, these women commit infanticide, albeit uncommonly (Kim, 2008). In most instances, women with postpartum psychosis ultimately develop relapsing, chronic, psychotic manic-depression.

Anxiety Disorders

The prevalence of anxiety disorder in the prior year among women in the United States is 23 percent (National Institute of Mental Health, 2017b). These relatively common disorders include panic attack, panic disorder, social anxiety disorder, specific phobia, separation anxiety disorder, and generalized anxiety disorder. All are characterized by irrational fear, tension, and worry, which are accompanied by physiological changes such as trembling, nausea, hot or cold flashes, dizziness, dyspnea, insomnia, and frequent urination (Schneier, 2006). They are treated with psychotherapy and medication, which may be an SSRI, tricyclic antidepressant, monoamine oxide inhibitor, or other.

Anxiety Disorders in Pregnancy

Despite the relatively high prevalence in childbearing-aged women, data regarding anxiety disorders in pregnancy are few. Most reports conclude that rates between pregnant

and nonpregnant women do not differ. One analysis of 268 gravidas with generalized anxiety disorder demonstrated that both symptoms and anxiety severity decline across pregnancy (Buist, 2011).

From their review, Thorsness and colleagues (2018) concluded that some of the anxiety disorders may have important maternal-fetal implications. Some researchers, but not all, have linked these disorders to preterm birth, fetal-growth restriction, and poor neurobehavioral development (Yonkers, 2017). Children with a history of in utero exposure to maternal anxiety are felt to be at greater risk for various neuropsychiatric conditions such as attention-deficit/hyperactivity disorder (ADHD).

Anxiety Disorder Treatment

Anxiety disorders can be effectively treated during pregnancy with psychotherapy, cognitive behavioral therapy, or medication (Williams, 2018). Mood and anxiety disorders coexist in more than half of women identified with either diagnosis. Thus, antidepressants—specifically, SSRIs—listed in Table 64-3 are often the first line of pharmacotherapy. As with other medication exposures in pregnancy, choosing a single SSRI agent at the lowest effective dose is preferred.

Benzodiazepines also are commonly used to treat anxiety or panic disorders (Thorsness, 2018). Earlier case-control studies linked their use to a possible increased risk for cleft lip and palate. A metaanalysis of more than 1 million exposed pregnancies, however, did not identify a teratogenic risk (Enato, 2011). Benzodiazepines, especially when taken during the third trimester, can cause neonatal withdrawal syndrome, which persists for days to weeks after delivery. Importantly, benzodiazepines should be avoided in women with current or past history of substance misuse (Thorsness, 2018).

SCHIZOPHRENIA SPECTRUM DISORDERS

This major form of mental illness affects 1.1 percent of adults (National Institute of Mental Health, 2016). Schizophrenia spectrum disorders are defined by abnormalities in one or more of the following domains: delusions, hallucinations, disorganized thinking, grossly disorganized or abnormal motor behavior, and negative symptoms. Brain-scanning techniques such as positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) show that schizophrenia is a degenerative brain disorder. Subtle anatomical abnormalities are present early in life and worsen with time.

Schizophrenia has a major genetic component, and concordance was 33 percent in monozygotic twins in large database (Hilker, 2018). If one parent has schizophrenia, the risk to offspring is 5 to 10 percent (Rasic, 2014). Some data, including a strong association between schizophrenia and the velocardiofacial syndrome, suggest associated genes. Some cases are related to chromosome 22q11, but sophisticated gene mapping studies clearly show that schizophrenia is not related to a single gene or mutation (Kukshal, 2012). Other putative risks for subsequent schizophrenia in an exposed fetus remain unproven, for example, the association with maternal influenza A infection (Chap. 67, p. 1187).

Signs of illness begin approximately at age 20 years, and work and psychosocial functioning typically deteriorate over time. Women have a slightly later onset than men. Thus, many investigators theorize that estrogen is protective. With appropriate treatment, patients can experience a decline or cessation of symptoms. Within 5 years from the first signs of illness, 60 percent have social recovery, 50 percent are employed, 30 percent are mentally handicapped, and 10 percent require continued hospitalization (American Psychiatric Association, 2013).

■ Schizophrenia in Pregnancy

Most studies have reported no adverse maternal outcomes, although some earlier ones found higher rates of low birthweight, fetal-growth restriction, and preterm delivery. In a study of more than 3000 pregnancies in schizophrenic women, the rate of placental abruption was elevated threefold and that of "fetal distress"—vaguely defined—was increased 1.4-fold (Jablensky, 2005).

Because schizophrenia has a high recurrence rate if medications are discontinued, continued therapy during pregnancy is advised. That said, "typical" antipsychotic drugs listed in Table 64-3 are associated with adverse fetal or maternal sequelae in some, but not all studies (Coughlin, 2015; Robinson, 2012). Because less is known about "atypical" antipsychotics, the American College of Obstetricians and Gynecologists (2018c) recommends against their routine use in pregnant and breastfeeding women. The FDA (2011) issued a safety communication concerning the potential risk for abnormal muscle movements and withdrawal symptoms in newborns of mothers treated with antipsychotic drugs during the third trimester.

EATING DISORDERS

These include *anorexia nervosa*, in which the patient refuses to maintain normal body weight, and *bulimia nervosa*, in which binge eating is usually followed by purging or excessive fasting to maintain normal body weight (American Psychiatric Association, 2013). Eating behavior disturbances largely affect adolescent females and young adults. With anorexia and bulimia, the lifetime prevalence for each is 2 to 3 percent (National Institute of Mental Health, 2016a).

Bulik and coworkers (2009) studied pregnancy outcomes in almost 36,000 Norwegian women screened for eating disorders. Approximately 0.1 percent had anorexia nervosa, 0.85 percent had bulimia nervosa, and 5.1 percent reported a binge-eating disorder. This 6-percent pregnancy prevalence is similar to the 6-month prevalence for nonpregnant individuals (National Institute of Mental Health, 2016a). The last subtype had a higher risk for large-for-gestational age neonates with a concomitantly increased cesarean delivery rate. All eating disorders begin with the desire to be slim, and women with chronic eating disorders may migrate between subtypes (Andersen, 2009).

■ Eating Disorders in Pregnancy

Early pregnancy complication rates are increased with both eating disorders, but especially in women with bulimia nervosa

(Hoffman, 2011). Generally, eating disorder symptoms improve during pregnancy, and remission rates may reach 75 percent. In contrast, a typical case of hyperemesis gravidarum may actually be a new or relapsing case of bulimia nervosa or of binge-purge type anorexia nervosa. As perhaps expected, anorexia is associated with low-birthweight, smaller head circumference, and small-for-gestational-age newborns (Micali, 2016). Children born to these mothers are more likely to have psychopathology at 7 years (Barona, 2016). Additional maternal risks associated with eating disorders include poor wound healing and difficulties with breastfeeding. At a minimum, closely monitoring gestational weight gain in women with a suspected history of an eating disorder seems prudent.

Care for these women involves a multidisciplinary team that includes an obstetrician, mental health provider, and either dietician or nutritionist. Psychological treatment is the cornerstone for treatment in women with eating disorders and frequently includes cognitive behavioral therapy. Anorexia nervosa often responds to motivational interactions with meal planning (Cardwell, 2013). After delivery, women with eating disorders are more prone to postpartum depression. Women with bulimia are at particular risk for disease rebound after delivery because of body image concerns.

SUBSTANCE USE DISORDERS

According to the American Psychiatric Association (2013), substance-related disorders encompass 10 classes of drugs that include caffeine, tobacco, cannabis, hallucinogens, opioids, anxiolytics, and stimulants. Their essential feature is a cluster of cognitive, behavioral, and physiological symptoms indicating that the individual continues to use the substance despite significant related problems. Central to these disorders is an underlying change in brain circuits that may persist beyond detoxification and characterized by repeated relapses.

It is estimated that 10 percent of fetuses are exposed to one or more illicit drugs. Agents may include heroin and other opiates, cocaine, amphetamines, barbiturates, and marijuana (American College of Obstetricians and Gynecologists, 2019). Well-documented sequelae include fetal-growth restriction, low birthweight, and drug withdrawal soon after birth. Adverse effects of marijuana are being delineated with expanding legalization. As noted by Metz and Borgelt (2018), adverse perinatal outcomes associated with marijuana use are especially seen with heavy use. Moreover, later childhood neurobehavioral consequences may follow prenatal exposure. Thus, women are currently advised to refrain from using marijuana during pregnancy and lactation. Women who use such drugs frequently do not seek prenatal care, which in itself is associated with risks for preterm and low-birthweight newborns.

Opioid Use Disorder

These disorders have reached epidemic proportions in the United States. The rates of maternal opioid-related diagnoses at delivery (0.8 percent) and of neonatal abstinence syndrome (0.7 percent) in 2017 in the United States were significantly higher than those in 2010 (Hirai, 2021). Because of this, the American College of Obstetricians and Gynecologists and the American Society of Addiction Medicine (2017) recommend universal screening by questionnaire at the first prenatal visit. Urine drug testing to detect or confirm substance use is performed only with patient consent and in compliance with state laws.

Medication-Assisted Treatment

For women who abuse opioids, *methadone maintenance* can be initiated within a registered treatment program to reduce opioid use complications and narcotic withdrawal, to encourage prenatal care, and to avoid drug culture risks (American College of Obstetricians and Gynecologists, 2017). Buprenorphine also may be offered and managed by physicians with specific credentialing (Boyars, 2018; Jones, 2018). Available programs can be found through the treatment locator of the Substance Abuse and Mental Health Services Administration at www.samhsa.gov. Methadone dosages usually are initiated at 10 to 30 mg daily and titrated as needed. Concomitant chronic use of naloxone with buprenorphine is discouraged given risks of precipitating neonatal withdrawal.

Medically Supervised Withdrawal

In some women, careful *medication-assisted withdrawal* may be an appropriate option. This is controversial because of the relatively high relapse rate, and it is discouraged by the American College of Obstetricians and Gynecologists and the American Society of Addiction Medicine (2017). From their review of more than 600 treated women, Boyars and Guille (2018) caution against this approach but concluded that assisted withdrawal is a reasonable approach. At Parkland Hospital, pregnant opioid users who decline maintenance therapy are offered inpatient hospitalization for controlled methadone taper. The goal is reduction of neonatal opioid withdrawal syndrome rates (Dashe, 2002; Stewart, 2013). In 2017, 69 women who were enrolled in our opioid perinatal intervention program delivered at Parkland Hospital. Of these women, 37 (54 percent) delivered without use of opioids at delivery. Their neonates' median length of stay was 4.5 days, which was significantly shorter than the 23.5 days required for newborns whose mothers were using opioids at delivery.

Neonatal Opioid Withdrawal Syndrome

This is a drug withdrawal syndrome that most commonly follows maternal opioid use. It is discussed in Chapter 33 (p. 605).

POSTTRAUMATIC STRESS DISORDER

This is included in trauma– and stressor–related disorders (American Psychiatric Association, 2013). The essential feature of PTSD is development of characteristic symptoms following exposure to one or more traumatic events. One example in obstetrics is PTSD following hyperemesis gravidarum (Chap. 57, p. 1014). Symptoms may be anxiety or fear but can be anhedonia, dysphoria, or dissociative behavior. According to Yonkers and coworkers (2014), 8 percent of pregnant women have facets of this syndrome. Psychotherapy is one first-line therapy (National Institute of Mental Health, 2019). These

women are also treated with benzodiazepines or antidepressants. Those with concordant major depression are at high risk for preterm birth.

PERSONALITY DISORDERS

These disorders are characterized by the chronic use of certain coping mechanisms in an inappropriate, stereotyped, and maladaptive manner. They are rigid and unyielding personality traits. The American Psychiatric Association (2013) recognizes three clusters of personality disorders:

1. Paranoid, schizoid, and schizotypal personality disorders, which are characterized by oddness or eccentricity.
2. Histrionic, narcissistic, antisocial, and borderline disorders, which are all characterized by dramatic presentations along with self-centeredness and erratic behavior.
3. Avoidant, dependent, compulsive, and passive-aggressive personalities, which are characterized by underlying fear and anxiety.

In the United States, the prevalence of any personality disorder in the past year approximates 9 percent (National Institute of Mental Health, 2017c). Genetic and environmental factors are thought important in their genesis. Psychotherapy is appropriate treatment, but most affected individuals do not recognize their problem, and thus only 20 percent seek help. In an observational study of 202 women with borderline personality disorder, De Genna and associates (2012) noted that affected women become pregnant during the most severe trajectory of their illness. They are at higher risk for adolescent and unintended pregnancies. Notably, Conroy and coworkers (2010) found that a mother's ability to care for her newborn was impaired only when a personality disorder was coupled with depression.

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CHAPTER 65

Dermatological Disorders

PREGNANCY-SPECIFIC DERMATOSES

Four dermatoses considered unique to pregnancy are pemphigoid gestationis (PG), pruritic urticarial papules and plaques of pregnancy (PUPPP), atopic eruption of pregnancy (AEP), and intrahepatic cholestasis of pregnancy. Descriptions of these are given in Table 65-1. Their gross appearance can be similar to each other or to other skin disorders, and pruritus is a common feature. Of these four, adverse fetal outcomes are linked only with PG and intrahepatic cholestasis. The latter is discussed in detail in Chapter 58 (p. 1032). It generally lacks primary skin lesions, but pruritus is usually associated with abnormally elevated serum bile acid levels and mildly increased hepatic transaminase levels.

Pemphigoid Gestationis

In this rare autoimmune bullous disease, pruritic papules and urticarial plaques initially form. Vesicles or bullae usually follow after 1 to 2 weeks. Lesions frequently involve umbilicus and other skin surfaces but typically spare mucous membranes, scalp, and face (Fig. 65-1).

Previously termed *herpes gestationis*, PG is not related to the herpesvirus. Instead, maternal immunoglobulin G (IgG) antibodies target collagen XVII found in the basement membrane of skin and amnionic epithelium (Kelly, 1988; Sadik, 2016). Collagen XVII is also termed *bullous pemphigoid 180 (BP180)*. Autoantibody binding to BP180 activates complement to promote eosinophil chemotaxis to the antigen-antibody complexes. Eosinophilic degranulation damages the dermal–epidermal junction and leads to blistering.

Pregnancy

In most cases, PG develops during a first pregnancy. Most subsequent pregnancies also are affected, usually earlier and more severely (Tani, 2015). Additionally, other autoimmune diseases, especially Graves disease, are frequent in affected women (Jenkins, 1999; Shornick, 1992).

PG usually begins during the second or third trimester, but postpartum onset or exacerbation is common (Lawley, 1978). The disease course is often marked by antepartum flares and remissions. In cases with early-onset and blistering, PG can be associated with preterm birth, oligohydramnios, and fetal-growth restriction (Al-Saif, 2016; Chi, 2009; Dabas, 2018). One theory suggests mild placental insufficiency stems from IgG and complement deposition along the amnionic basement membrane (Huilaja, 2013). Thus, surveillance for and management of these complications in affected pregnancies is reasonable.

In 5 to 10 percent of cases, IgG antibodies passively transfer from the mother to cause similar skin lesions in the newborn (Erickson, 2002). These eruptions in the neonate require only wound care and clear spontaneously within a few weeks as the passively acquired IgG levels drop. After delivery, maternal lesions resolve without scarring, and most women are disease-free after 6 months (Jenkins, 1999). In some, however, resolution is protracted. Disease may be exacerbated during menses or by oral contraceptives (Fania, 2017; Semkova, 2009).

Diagnosis and Treatment

Before bullae form, these lesions may resemble PUPPP. Other diagnoses include bullous pemphigoid, pustular psoriasis,

TABLE 65-1. Pregnancy-specific Dermatoses

Disorder	Frequency	Characteristic Lesion	Adverse Pregnancy Effects	Treatment
PUPPP	Common	Erythematous pruritic papules or plaques; patchy or generalized on abdomen, thighs, buttocks, especially within striae, but with umbilical sparing	None	Oral antipruritics, emollients, topical corticosteroids, and if severe, oral steroids
AEP			None	
Eczema in pregnancy	Common	Dry, red scaly patches on extremity flexures, neck, face		
Prurigo of pregnancy	Common	1–5 mm pruritic red papules on extensor surfaces, trunk		
Pruritic folliculitis of pregnancy	Rare	Small red papules, sterile pustules on trunk		
Pemphigoid gestationis	Rare	Erythematous pruritic papules, plaques, vesicles, and bullae; abdomen often with umbilical involvement, extremities	Preterm birth, fetal-growth restriction, transient neonatal lesions	
Cholestasis of pregnancy	Common	No primary lesions, secondary excoriations from scratching	Increased perinatal morbidity	Oral antipruritics, cholestyramine, ursodeoxycholic acid

AEP = atopic eruptions of pregnancy; PUPPP = pruritic urticarial papules and plaques of pregnancy.

erythema multiforme, linear IgA bullous dermatosis, urticaria, dermatitis herpetiformis, allergic contact dermatitis, and AEP (Lipozenčić, 2012). Potentially life-threatening drug-induced blistering syndromes, such as Stevens-Johnson syndrome and toxic epidermal necrolysis, also must be excluded (Stern, 2012).

Diagnostically, immunofluorescent staining of a skin punch biopsy sample is the most accurate. With this, C3 complement and sometimes IgG are seen deposited along the basement membrane between the epidermis and the dermis (Katz, 1976; Tani, 2015). Circulating IgG antibodies against BP180 also can be detected in maternal serum using enzyme-linked immunosorbent assay (ELISA) (Al Saif, 2017; Sitaru, 2004).

Pruritus with PG can be severe. Early in its course, topical high-potency corticosteroids and oral antihistamines may be effective (p. 1158). For refractory lesions, an oral corticosteroid is provided, and prednisone or prednisolone is preferable. Either is inactivated by placental 11-β-hydroxylase enzyme, which significantly lowers fetal exposure (Benediktsson, 1997). Oral prednisone, 0.5 to 1 mg/kg daily and gradually tapered to a maintenance dose, is one option. In rare intractable cases,

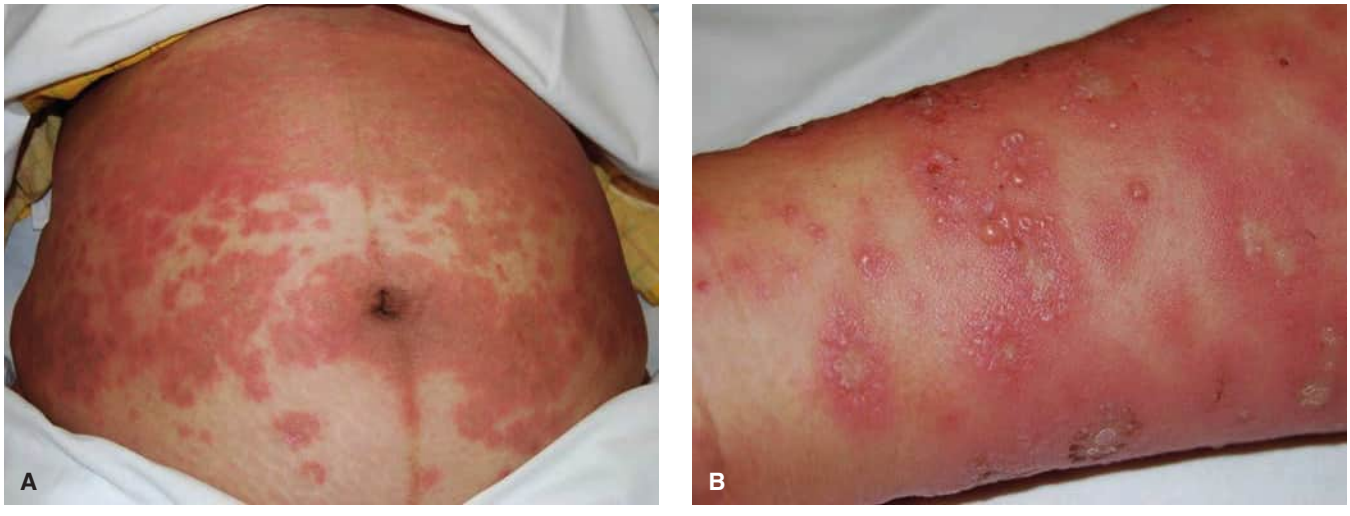

FIGURE 65-1 Pemphigoid gestationis. **A.** Abdominal plaques classically involve the umbilicus. **B.** Blistered lesions on the wrist and forearm. (Reproduced with permission from Dr. Kara Ehlers.)

intravenous immunoglobulin (IVIG) therapy, cyclosporine, or plasmapheresis has been used (Huilaja, 2015; Marker, 2011; Yang, 2018). Rituximab early in pregnancy also is described, but its later use carries the risk of transient newborn immunosuppression risks (Chakravarty, 2011; Tourte, 2017).

Pruritic Urticarial Papules and Plaques of Pregnancy

This common pregnancy-specific dermatosis is characterized by intensely pruritic, 1- to 2-mm erythematous papules that coalesce to form urticarial plaques. Also known as *polymorphic eruption of pregnancy*, PUPPP usually appears late in pregnancy (Rudolph, 2005). Rarely, onset is postpartum (Park, 2013). The rash affects the abdomen and proximal thighs in 97 percent of women (Fig. 65-2). Lesions often initially form within striae but spare periumbilical skin. The face, palms, and soles are rarely involved (High, 2005). It is more frequent in whites and nulliparas, those with multifetal gestation, and those carrying a male fetus (Regnier, 2008). PUPPP seldom recurs in subsequent pregnancies. Its cause is unknown, but an autoimmune basis is not implicated (Ambros-Rudolph, 2011; Lawley, 1979).

PUPPP mimics several other skin eruptions. Some include contact dermatitis, drug eruption, viral exanthem, insect bites, scabies infestation, pityriasis rosea, and the other pregnancy-specific dermatoses (Brandão, 2017). Specifically, it may appear similar to early PG that has not yet blistered. In unclear cases, skin biopsy and negative serum BP180 antibody levels help to differentiate the two.

Pruritus will usually respond to treatment with oral antihistamines, skin emollients, and topical corticosteroids (Lehrhoff, 2013). A few women will need short-course systemic corticosteroids to relieve severe itching (Scheinfeld, 2008).

PUPPP carries no adverse pregnancy effects. It usually resolves within several days following delivery and does not scar. In 15 to 20 percent of women, however, symptoms persist for 2 to 4 weeks postpartum (Vaughan Jones, 1999).

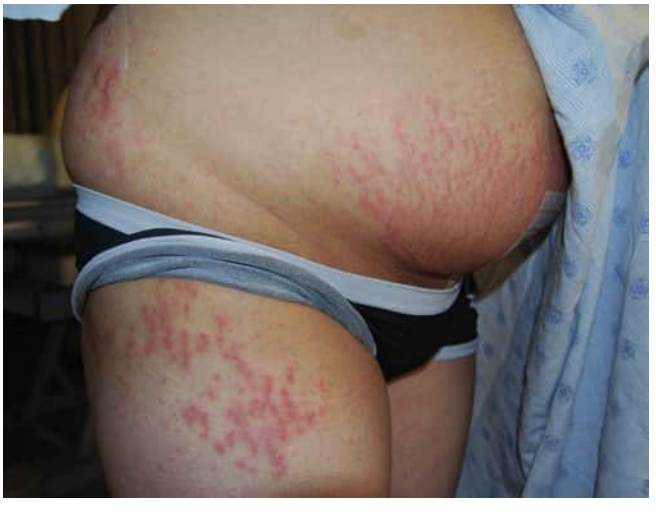

FIGURE 65-2 Pruritic urticarial papules and plaques of pregnancy (PUPPP) shows small papules on the buttock and proximal thigh and within abdominal striae.

Atopic Eruption of Pregnancy

This umbrella term encompasses three conditions previously considered separately: eczema in pregnancy, prurigo of pregnancy, and pruritic folliculitis of pregnancy (Ambros-Rudolph, 2006). Two thirds of women with AEP have widespread eczematous changes, whereas the other third have papular lesions (American Academy of Dermatology, 2019). Diagnosis is greatly aided by a history of prior atopy and by rash characteristics. As a group, these three pose no risk to the fetus (Roth, 2016).

Eczema in pregnancy appears as traditional eczema but with a pregnancy onset. It is the most common pregnancy-specific dermatosis, and affected skin shows dry, thickened, scaly, red patches involving extremity flexures, nipples, neck, and face (Ambros-Rudolph, 2011). In contrast, *prurigo of pregnancy*, also known as *prurigo gestationis,* is characterized by 5- to 10-mm, itchy, erythematous papules or nodules commonly found on the extensor surfaces and trunk. Last, *pruritic folliculitis of pregnancy* is rare and notable for small, erythematous follicular papules and sterile pustules predominantly on the trunk. Of AEP cases, 75 percent develop in the first or second trimesters (Ambros-Rudolph, 2006). All lesions usually resolve with delivery but may persist for up to 3 months postpartum. Recurrence with subsequent pregnancies is variable but common.

Diagnosis is one of exclusion. Biopsy findings and serology results specific for PG are negative (p. 1155). Serum bile acid levels help exclude cholestasis of pregnancy. Many women with eczema of pregnancy have elevated serum immunoglobulin E (IgE) levels (Ambros-Rudolph, 2006).

For all three AEP manifestations, skin lesions and pruritus are usually controlled with chronic emollient use, as-needed oral antihistamines, and low- or moderate-potency topical corticosteroid preparations (Roth, 2016). With the latter, twice-daily application is continued for several weeks to achieve improvement. For maintenance, moisturizer alone or once- or twice-weekly topical corticosteroid use is reasonable. For severe eczema, second-line agents include short-course ultrapotent topical corticosteroids. In some cases, topical tacrolimus, narrow-band ultraviolet B therapy, an oral corticosteroid, or cyclosporine is required (Eichenfield, 2014; Vestergaard, 2019).

OTHER DERMATOLOGICAL CONDITIONS

Acne Vulgaris

This is a common chronic dermatosis that may worsen, improve, or remain stable during pregnancy. In symptomatic gravidas, either 2.5- to 5-percent benzoyl peroxide or 15- to 20-percent azelaic acid is a suitable topical, antiinflammatory, comedolytic agent (Chien, 2016). If needed, 5-percent benzoyl peroxide can instead be coupled with either topical erythromycin or clindamycin, and combined solutions are available. In these combinations, benzoyl peroxide minimizes development of *Propionibacterium acnes* drug resistance (Zaenglein, 2016). Topical retinoids include tretinoin and adapalene. Large studies have not found higher rates of major birth defects with their topical use (Jick, 1993; Shapiro, 1997). However, these are probably best avoided during pregnancy, especially the first trimester (Kaplan, 2015; Panchaud, 2012). The topical retinoid tazarotene is

contraindicated. For more severe cases, oral antibiotics that include erythromycin, azithromycin, cephalexin, or amoxicillin may be coupled with benzoyl peroxide. Systemic antibiotics are ideally delayed until the second trimester, and therapy duration limited to 4 to 6 weeks (Chien, 2016). Refractory cases often merit dermatological consultation. Also, for severe cases, a short course of oral corticosteroid or intralesional injection is an option. Of these, oral agents are delayed until after the first trimester due to the small risk for facial clefts (Chap. 8, p. 153).

Psoriasis and Pustular Psoriasis of Pregnancy

Psoriasis is a common dermatosis with a variable course during pregnancy, however, postpartum flares are common (Murase, 2005). The National Psoriasis Foundation offers pregnancy guidelines (Bae, 2012). Emollients alone are given initially, and low- or moderate-potency topical corticosteroids can be added. In resistant cases, restrained use of high-potency or ultrapotent topical corticosteroids appears safe in the second and third trimesters. Ultraviolet B phototherapy is a second-line option. Last, cyclosporine, oral corticosteroids, or tumor necrosis factor alpha (TNF-α) antagonists that include adalimumab, etanercept, and infliximab are third-tier agents for pregnancy. Overall, psoriasis itself does not pose a higher risk of adverse pregnancy outcomes (Bobotsis, 2016). With severe disease, a small increased risk of low birthweight, gestational diabetes, and preeclampsia was found by some (Bröms, 2018; Yang, 2011).

Psoriasis is most commonly of the chronic plaque variety. In contrast, with *pustular psoriasis of pregnancy*, severe systemic symptoms may develop and can mimic sepsis. Formerly called *impetigo herpetiformis*, this rare pustular form has an erythematous background and pruritic plaques ringed by sterile pustules that enlarge, coalesce, and then crust (Fig. 65-3). Plaques initially involve intertriginous areas but may spread to the torso, extremities, and oral mucosa. Extensive lesions can lead to massive fluid loss with hypovolemia, placental insufficiency, and fetal compromise and may also become secondarily infected.

Testing reveals leukocytosis, elevated erythrocyte sedimentation rate, hypocalcemia, and hypoalbuminemia (Umezawa, 2003). Blood cultures and skin viral/bacterial cultures to exclude infection and a diagnostic skin biopsy are obtained. Classically, the former are sterile, and the latter reveals epidermal pustules of neutrophils.

First-line treatment is with oral prednisone (15–80 mg/d), cyclosporine (2–3 mg/kg/d), infliximab (Remicade), topical corticosteroids, or topical calcipotriene (Robinson, 2012; Trivedi, 2018). Selection of a systemic or topical agent and its dose is directed by disease severity. As needed, fluid resuscitation, electrolyte correction, and intravenous antibiotics for secondary infections are adjuncts (Huang, 2011). Pustular psoriasis of pregnancy typically resolves quickly postpartum, and thus early delivery can be considered individually. Recurrences are reported in subsequent pregnancies and with menses or oral contraceptive use (Roth, 2011).

Erythema Nodosum

This skin condition reflects subcutaneous fat inflammation and is associated with many disorders, including pregnancy. Other triggers are infections, sarcoidosis, drugs, Behçet syndrome, inflammatory bowel disease, or malignancy (Mert, 2007; Papagrigoraki, 2010). Characteristically, tender, red, warm, 1- to 6-cm nodules and plaques develop rapidly on extensor surfaces. After a few days, lesions flatten, and color evolves like a bruise—from dark red and purple to yellow green. Constitutional symptoms also may be present. Initial evaluation and treatment focuses on the underlying etiology. Symptoms spontaneously resolve in 1 to 6 weeks without scarring but may leave residual hyperpigmentation (Acosta, 2013).

Pyogenic Granuloma

This lesion is frequently seen in pregnancy (Fig. 65-4) (Bett, 2019). Poorly named, *pyogenic granuloma* is actually a lobular

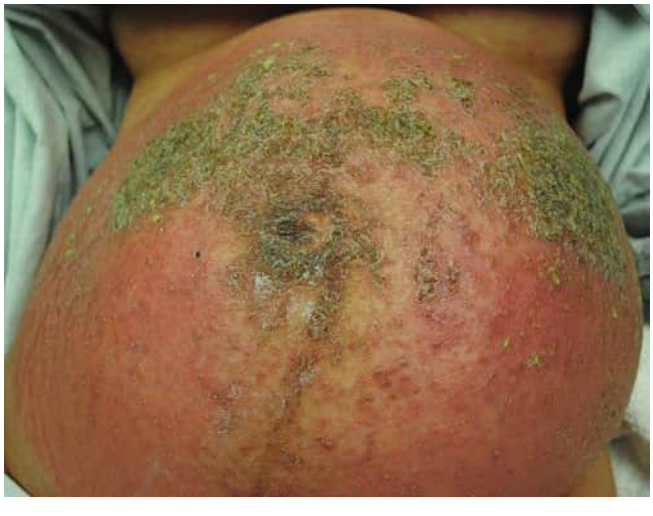

FIGURE 65-3 Generalized pustular psoriasis of pregnancy displays erythematous, sometimes pruritic plaques ringed by sterile pustules that enlarge and then form a scaling crust. (Reproduced with permission from Dr. Paul Slocum.)

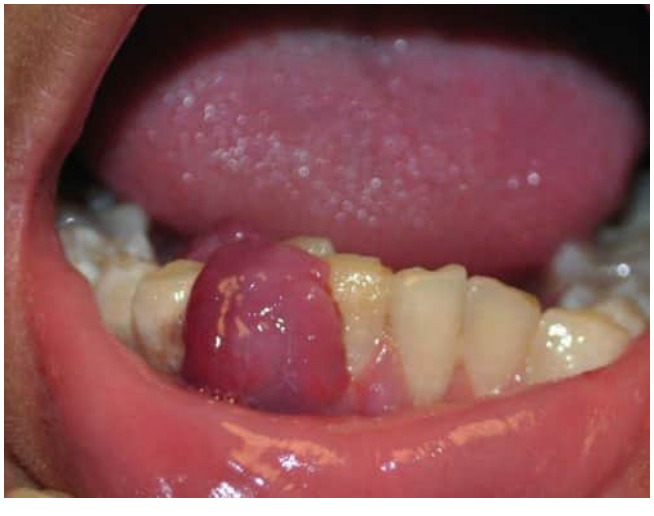

FIGURE 65-4 Pyogenic granuloma is characterized grossly by a lobulated red growth on a pedunculated or sessile base. With minimal trauma, these vascular lesions bleed easily. (Reproduced with permission from Dr. Sarah White.)

capillary hemangioma. Pregnancy-associated elevations in angiogenic factors that include vascular endothelial growth factor are implicated (Yuan, 2000, 2004). It commonly forms on the gingiva, other oral/nasal surfaces, or hand in response to low-grade local irritation or trauma (Cardoso 2013). Lesions grow quickly and bleed with minimal provocation. Active bleeding can be controlled with pressure and application of a silver nitrate stick or Monsel (ferric subsulfate) paste. These growths often resolve within months postpartum and thus may be observed antepartum. But, with a symptomatic antepartum growth, a persistent postpartum lesion, or an unclear diagnosis, excision is preferred. An option is scalpel excision plus suturing, electrosurgical curettage, laser photocoagulation, or cryotherapy. Oral lesions are best referred to specialists.

Miscellaneous Conditions

Hidradenitis suppurativa is a chronic inflammatory skin disease. Keratin plugging of hair follicles and recurrent inflammation lead to painful nodules and abscesses that rupture to create sinus tracts. Hurley stages I–III range from transient, widely spaced inflammatory papules to diffuse involvement with multiple deep sinus tracts between skin abscesses (Hurley, 1989). For most, symptoms during pregnancy are unchanged or improved (Kromann, 2014; Vossen, 2017).

Treatment aims to decrease cutaneous inflammation and provide antibacterial effects. For active stage I/II disease, 1-percent clindamycin is topically applied twice daily for 12 weeks (Alikhan, 2019). As alternatives, 0.75-percent metronidazole or 2-percent erythromycin gel are suitable (Perng, 2017). For stage II/III disease, a 300-mg clindamycin plus a 300-mg rifampin dose orally twice daily for 10 weeks has evidence-based support (Alikhan, 2019). Adalimumab (Humira) is an FDA-approved biological agent that targets TNF-α and offers a second-line option for advanced-stage disease in pregnancy (Jemec, 2019; Perng, 2017).

Neurofibromatosis lesions are typified by benign cutaneous neurofibromas, café-au-lait spots, axillary and inguinal freckling, benign iris nodules (Lisch nodules), and optic nerve gliomas. Neurofibromas may grow in size and number during pregnancy (Cesaretti, 2013; Dugoff, 1996). With neurofibromatosis type 1, higher rates of preeclampsia and preterm birth complicate pregnancy (Leppävirta, 2017; Terry, 2013). With type 2, some evidence suggests a risk for preeclampsia (Terry, 2015). Prenatal genetic diagnosis is available for both types (Merker, 2015).

Rosacea fulminans, also known as *pyoderma faciale,* is rare and typified by facial pustules and coalescing draining sinuses but without comedones. Its marked presentation usually merits dermatological consultation. Topical or oral antibiotics are primary treatment, and topical corticosteroids may be added. Less often, short-course oral corticosteroids or focal surgical drainage is a needed adjunct (Angileri, 2021; Fuentelsaz, 2011; Jarrett, 2010).

Other skin conditions discussed elsewhere in this book are hirsutism and melanoma (Chap. 66, p. 1176), cutaneous lupus (Chap. 62, p. 1111), hyperpigmentation (Chap. 4, p. 55), and skin lesions seen with infections (Chaps. 67 and 68, p. 1182).

DERMATOLOGICAL TREATMENT

Local skin care, oral antihistamines, and topical corticosteroids are commonly used for many dermatoses. Oral antihistamines are given for pruritus. Suitable options include first-generation agents such as diphenhydramine (Benadryl), 25 to 50 mg every 6 hours, or chlorpheniramine (Chlor-Trimeton), 4 mg every 6 hours. Second-generation agents—loratadine (Claritin) 10 mg daily or cetirizine (Zyrtec) 5 or 10 mg daily—may produce less sedation and are also safe for pregnancy.

Numerous topical corticosteroid preparations are available, and in the United States, these are categorized by potency (Table 65-2). For initial treatment of dermatological disorders, low- or moderate-potency agents are preferred. Low-potency agents include 1-percent hydrocortisone and 0.05-percent desonide (DesOwen). Moderate-potency drugs are 0.1-percent triamcinolone acetonide (Aristocort) and 0.1-percent mometasone furoate (Elocon). High-potency medications include 0.05-percent betamethasone dipropionate (Diprolene). Ultrapotent agents, such as 0.05-percent clobetasol propionate (Temovate), are best reserved for refractory disorders and used for only 2 to 4 weeks on small surface areas.

Mild and moderate strengths are not associated with adverse pregnancy outcomes, whereas high-potency and ultrapotent agents pose a small risk for fetal-growth restriction with large cumulative doses (Chi, 2013, 2015). Even then, this risk is less than that with oral corticosteroids. Importantly, with any topical agent, factors that raise systemic absorption include a large surface area treated, compromised epidermal barrier, occlusive dressing, prolonged treatment duration, and coadministration of other topical agents that enhance absorption.

TABLE 65-2. Commonly Used Topical Corticosteroids in Pregnancy

Low-Potency Agents	Moderate-Potency Agents	High-Potency Agents	Ultrapotency Agents
Hydrocortisone 0.5–1% *cream, ointment*	Triamcinolone acetonide 0.1% *cream, ointment*	Triamcinolone acetonide 0.5% *cream, ointment*	Clobetasol propionate 0.05% *cream, ointment*
Dexamethasone 0.1% *cream*	Mometasone furoate 0.1% *cream*	Mometasone furoate 0.1% *ointment*	
Desonide 0.05% *foam, cream, ointment*	Betamethasone valerate 0.1% *cream, ointment*	Betamethasone dipropionate 0.05% *cream, ointment*	

TABLE 65-3. Some Dermatological Agents and Their Suitability for Pregnancy

Group	Action	Pregnancy Recommendation
Topical Agents		
Corticosteroids	Antiinflammatory	Suitable
Benzoyl peroxide	Antiinflammatory, comedolytic, antibacterial	Suitable
Azelaic acid		Suitable
Antibiotics: Clindamycin, erythromycin	Antibacterial	Suitable
Calcineurin inhibitors: Tacrolimus, pimecrolimus	Antiinflammatory	Suitable
Calcipotriene	Antiinflammatory, vitamin D analogue	Possible poor ossification in animals; no human data Probably suitable in dermatological dosages
Coal tar	Antiinflammatory; keratinocyte regulation	Possible animal mutagen/carcinogen; no human data If used, delay until 2nd trimester
Retinoids:	Antiinflammatory, comedolytic	
Tretinoin, adapalene		Large studies show no harm, but experts suggest avoiding
Tazarotene		Teratogenic; contraindicated
Crisaborole	Antiinflammatory	Limited pregnancy data; avoidance currently suggested
Systemic Agents		
Oral antibiotics: Azithromycin, amoxicillin, cephalexin, erythromycin	Antibacterial	Suitable
Oral corticosteroids	Antiinflammatory	1st-trimester use linked to small risk of oral clefts
Cyclosporine	Immunomodulator	Low birthweight, preterm birth; nonteratogenic
TNF-α inhibitors: Infliximab, adalimumab, etanercept	TNF-α inhibition	Suitable

From Bae, 2012; Briggs, 2017; Murase, 2014; Park-Wyllie, 2000; Rademaker, 2018; Robinson, 2012; Sekhon, 2018; Vestergaard, 2019.

For use in pregnancy and lactation, Murase (2014) and Butler (2014) have compiled tables and evidence-based descriptions of most. Table 65-3 reflects more commonly encountered agents. Notable therapeutic agents to avoid during pregnancy include methotrexate, psoralen plus ultraviolet A, mycophenolate mofetil, podophyllin, and systemic retinoids. These teratogens are discussed in Chapter 8. Bacterial infections are a potential secondary complication of skin disorders and are treated promptly with oral antimicrobial agents with gram-positive coverage.

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CHAPTER 66

Neoplastic Disorders

Any of the many neoplasms that affect reproductive-aged women can complicate pregnancy. Fortunately, most encountered neoplasms are benign, and uterine leiomyomas and ovarian cysts are the most frequent. Despite this, the incidence of malignancy approximates 1 case per 1000 to 2000 pregnancies (Korenaga, 2020; Ma, 2020). A third are diagnosed prenatally, and the remainder within 12 months of delivery. The distribution of some of these is shown in Figure 66-1 (de Haan, 2018). In another report from the Cancer Research Network, breast malignancies made up 25 percent and thyroid cancers, 20 percent. Melanoma and hematological and cervical cancers each contributed approximately 10 percent (Cottreau, 2019).

During pregnancy, cancer management poses unique problems related to fetal concerns, and treatment is individualized. Considerations include the type and stage of malignancy, the desire for pregnancy continuation, and inherent risks associated with modifying or delaying cancer treatment. Last, adverse pregnancy outcomes have been associated in general with gravidas with cancer (Ma, 2020; Momen, 2018).

CANCER THERAPY IN PREGNANCY

Surgery

Operative procedures may be indicated to aid cancer diagnosis, staging, or therapy. Fortunately, most surgeries that do not

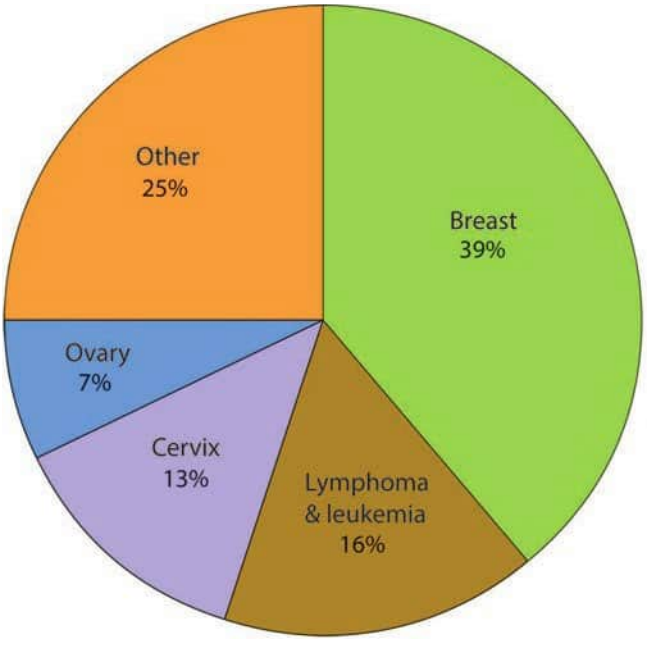

FIGURE 66-1 Distribution of cancer in 1170 pregnant women form the International Network on Cancer, Infertility, and Pregnancy (INCIP).

interfere with the reproductive tract are well tolerated by both mother and fetus (Chap. 49, p. 867). Although many operations have classically been deferred until after 12 to 14 weeks' gestation to minimize miscarriage risks, this probably is unnecessary. We believe that surgery should be performed at any gestational age if maternal well-being is imperiled.

Both pregnancy and malignancy are risk factors for venous thromboembolism (VTE). From studies of women with cancer during pregnancy, the risk of VTE is higher in pregnancy and in the postpartum period than in gravidas without a malignancy (Bleu, 2016; Greiber, 2021). Current guidelines lack specific recommendations for pregnant women undergoing surgeries for cancer. Thus, depending on the complexity of the planned procedure, it seems reasonable to consider prophylactic low-molecular-weight heparin combined with elastic stockings and/or intermittent pneumatic compression (Chap. 55, p. 989).

Diagnostic Imaging

Sonography is a preferred imaging tool during pregnancy. Even so, the American College of Obstetricians and Gynecologists (2019c) notes that most diagnostic radiographic procedures deliver very low x-ray doses and should not be delayed if they would directly affect therapy (Chap. 49, p. 872). Magnetic resonance (MR) imaging can safely be performed in any trimester, but delay until after the first trimester may lower potential risks. Gadolinium should not be used in the first trimester and should be used later in pregnancy only when the benefits overwhelmingly outweigh risks (American College of Radiology, 2021; Kanal, 2013). Computed tomography (CT) is less often selected due to ionizing radiation, and procedure-related doses are listed in Chapter 49 (p. 874). Thus, CT imaging is used in pregnancy most often to evaluate acute concerns that include pulmonary embolism, bowel or renal obstruction, and acute neurological events. To enhance CT imaging, oral and intravenous contrasts may be added. These lack known fetal harm, and postpartum breastfeeding need not be interrupted. In pregnancy, some radioisotopes are relatively safe (Table 49-10, p. 876).

Radiation Therapy

Therapeutic radiation is used to *treat* cancers and delivers a higher radiation dose than that with diagnostic imaging. Radiotherapy may significantly expose the fetus depending on the dose, tumor location, field size, and gestational age. Potential adverse effects include fetal malformation, intellectual disability, growth restriction, sterility, and carcinogenesis (Brent, 1999; Stovall, 1995). In the 2 weeks following fertilization, exposure typically leads to chromosomal damage and embryonic death. The next most susceptible period is during organogenesis in weeks 2 through 8, and exposure can create malformations. These might develop above a threshold dose of 0.1 to 0.2 Gy. During weeks 8 through 25, the fetal central nervous system is especially vulnerable. The threshold dose for intellectual disability at 8 to 15 weeks' gestation approximates 0.06 Gy, and at 16 to 25 weeks it is about 0.25 Gy (Kal, 2005; Otake, 1996). After 25 weeks' gestation, susceptibility is less, although no gestational age is considered safe for therapeutic radiation exposure. Thus, radiotherapy to the maternal abdomen is contraindicated. With some head and neck cancers, however, radiotherapy to supradiaphragmatic areas can be used relatively safely with abdominal shielding of the fetus (Amant, 2015a).

Chemotherapy

Various antineoplastic drugs may be given as primary or adjunctive therapy. Although chemotherapy often improves long-term maternal outcomes, many are reluctant to employ it during pregnancy. Concerns for the fetus include malformations, growth restriction, intellectual disability, and the risk of future childhood malignancies. Risks depend primarily on fetal age at exposure, and most agents are potentially detrimental in the first trimester during organogenesis. Indeed, in one review, 14 percent of major malformations were attributable to first-trimester exposure to cytotoxic drugs (National Toxicology Program, 2013).

After the first trimester, most antineoplastic drugs are without immediate obvious adverse fetal sequelae (Korenaga, 2020; Vercruysse, 2016). Similarly, late mutagenic effects appear limited (Amant, 2015b; Cardonick, 2015). Although not always practicable, some recommend that chemotherapy be withheld in the 3 weeks before expected delivery because neutropenia or pancytopenia might cause undue risk for maternal infection or hemorrhage. Another concern is that neonatal hepatic and renal clearance of chemotherapy metabolites is limited (Ko, 2011). For these reasons, most cytotoxic chemotherapy agents are contraindicated with breastfeeding (Pistilli, 2013).

Molecular Therapy

Biological agents designed to stimulate hemopoiesis are commonly used with cancer treatments. Some of these include the granulocyte colony-stimulating factors filgrastim (Neupogen) and pegfilgrastim (Neulasta). If required in pregnancy, limited data support the safety of these agents (Boxer, 2015). Red blood cells can be stimulated by erythropoietin alfa (Procrit), which from case reports also appears safe in pregnancy (Sienas, 2013). However, maternal hypertension is a known potential risk. Last, for chemotherapy-induced thrombocytopenia, romiplostim and eltrombopag are thrombopoietin-receptor agonists that appear to be safe in pregnancy (Chua, 2020; Michel, 2020).

Targeted Therapy

The two main types of targeted therapy are monoclonal antibodies and small-molecule inhibitors. Both block the actions of specific enzymes, proteins, or other molecules involved in cancer cell growth (Tsao, 2019). Another is nanotherapy using drugs incorporated into encapsulated nanoparticles (Pereira, 2020). These drugs are designed to treat an ever-expanding list of cancers, and some are described in later discussions of specific tumors. Most of these compounds are labeled by the Food and Drug Administration as class D, and data are limited regarding their pregnancy or breastfeeding effects.

Many of these drugs target tyrosine kinase, an important enzyme that regulates signaling pathways involved with cell division, differentiation, and apoptosis. With first-trimester

use, embryo toxicity or teratogenicity has been attributed to these. Thus, use balances potential maternal benefit and potential fetal risk (Lodish, 2013).

Of other agents, the monoclonal antibody trastuzumab (Herceptin) inhibits the human epidermal growth factor receptor type 2 (HER2), which some breast cancers express. Although not teratogenic, its use in the second and third trimesters is associated with oligohydramnios, which appears to be reversible upon stopping the drug (McCormick, 2018; Zagouri, 2013b). Because of sparse available data, other HER2 inhibitors are best avoided in pregnancy (Lambertini, 2015).

Fertility and Pregnancy after Cancer Therapy

Oncofertility is an emerging discipline to preserve fertility in young adults diagnosed with cancer (Robson, 2020). Fertility may be diminished after chemotherapy or radiotherapy. Counseling ideally takes place before cancer treatment, and guidelines have been developed by the American Society for Reproductive Medicine (ASRM) (2018) and other major groups (Oktay, 2018; van de Kooi, 2021). Prior to therapy, embryo or oocyte cryopreservation is a recognized option. Ovarian tissue cryopreservation is available in research settings (American Society for Reproductive Medicine, 2013a,b, 2014). In addition, many cancer survivors conceive by assisted reproductive technologies (ART), which by itself has associated obstetrical risks (Chap. 9, p. 169).

If pelvic radiation is planned, surgical transposition moves ovaries and their intact primary blood supply out of the pelvis. The ovary is then fixed to the lateral abdominal wall at a site 3 to 4 cm above the level of the umbilicus. Metal clips are placed to help identify the ovary in future imaging (Moawad, 2017). In one review, functional preservation was reported in 65 to 94 percent, depending on radiotherapy type (Gubbala, 2014).

In counseling cancer survivors, evidence suggests that exposure to most radiotherapy or chemotherapy agents does not significantly raise the risk of congenital anomalies or genetic disease in their offspring (Signorello, 2012; Winther, 2012). In those treated as children, chemotherapy does not show a consistent link to adverse obstetrical outcomes (Melin, 2015; Reulen, 2009). Data are limited in those with cancer treated as an adult, and some studies show slightly higher rates of preterm birth and cesarean delivery (Haggar, 2014; Stensheim, 2013).

Prior abdominopelvic radiation more convincingly affects neonatal outcomes, including elevated rates of abortion, low birthweight, stillbirth, and preterm birth (Signorello, 2006, 2010; Winther, 2008). Radiation may reduce uterine volume, thin the endometrium, and impair uterine blood flow (Critchley, 1992; van de Loo, 2019). Radiotherapy directed to the uterus and given at a younger age shows greater effects (Teh, 2014).

Placental Metastases

Tumors infrequently metastasize to the placenta. The most common types are malignant melanomas, leukemias, lymphomas, and breast cancer (Chap. 6, p. 112). Placentas from pregnancies in all women with cancer should be sent for histological evaluation. Tumor cells are usually confined within the intervillous spaces, and fetal metastases are rare (Al-Adnani, 2007; Rubrecht, 2020).

REPRODUCTIVE TRACT NEOPLASMS

Benign neoplasms of the reproductive tract are common and include leiomyomas, ovarian tumors, and endocervical polyps. Cancer in these organs may also complicate pregnancy, and of these, cervical neoplasia makes up most (de Haan, 2018).

Cervix

Endocervical Polyp

These are overgrowths of endocervical stroma covered by epithelium. They typically appear as single, red, elongated fleshy masses of variable size that extend outward from the endocervical canal. Usually benign, they can bleed and can be a source of Pap test results reported as *atypical glandular cells of undetermined significance—AGUS*. With removal and histological polyp evaluation, dysplasia is diagnosed in up to 0.5 percent, and cancer is found in approximately 0.1 percent (Park, 2020).

Few formal data guide management in pregnancy. Small asymptomatic lesions may be left alone to slough during delivery or puerperal remodeling. Removal and histological evaluation is reasonable if malignancy is suspected or if bleeding is troublesome. For most, the polyp is grasped with ring forceps and twisted repeatedly about its base to strangulate feeding vessels. With repeated twisting, the base narrows and avulses. Monsel paste, which is ferric subsulfate, can be applied with pressure to the stalk stub for hemostasis. A thick-pedicle polyp may infrequently warrant surgical ligation and excision.

Cervical Neoplasia

Pregnancy provides an opportune time to screen for cervical intraepithelial neoplasia (CIN) and invasive cervical cancer. With Pap test screening, pregnancy status should be noted on the requisition form as cytological interpretation may be influenced by normal pregnancy-associated changes. Presence of decidual cells and, less often, an Arias-Stella reaction are examples. The latter gives an appearance of endocervical gland hyperplasia, which can make differentiating this from truly atypical glandular cells difficult.

Current screening guidelines apply to both nonpregnant women and gravidas (American College of Obstetricians and Gynecologists, 2021b; U.S. Preventive Services Task Force, 2018). Recommendations for average-risk women include: (1) no screening until age 21, (2) cytology alone every 3 years in those aged 21 to 29 years, and (3) in women aged ≥30 years, three options are suitable. These are human papillomavirus (HPV) *plus* cytology, termed co-testing, every 5 years; primary HPV testing every 5 years; or cytology every 3 years.

Higher-risk women with altered immune systems include women with human immunodeficiency virus (HIV) infection, systemic lupus erythematosus, organ transplant, or immunosuppressant medication use (Perkins, 2020). Others include those with past CIN or prior early cervical cancer or in utero diethylstilbestrol (DES) exposure. Affected women are screened earlier and more often using current guidelines for HIV-affected individuals (Panel on Opportunistic Infections in Adults and Adolescents with HIV, 2020). Germane to gravidas aged ≤30 years, these guidelines recommend Pap test screening at the time of initial HIV diagnosis and then

yearly. Once three consecutive Pap test findings are normal, screening may be spaced to every 3 years. Co-testing is not recommended. For those aged >30 years, similar Pap testing is applied. Co-testing is suitable for this group, and if negative, the next test can repeated in 3 years.

Human Papillomavirus. This virus infects cervical epithelia. The infection usually clears, but in some, the virus may promote benign, premalignant, or cancerous neoplastic growth. The prevalence of HPV infection in pregnant women approximates 15 percent (Hong, 2013; Liu, 2014). Of the many HPV serotypes, several are associated with high-grade squamous intraepithelial (HSIL) lesions and invasive cancer. Serotypes 16 and 18 are preeminent. HPV testing targets only high-risk types associated with cervical neoplasia, and identification of types 16 or 18 prompts colposcopic evaluation. There is no indication for low-risk HPV testing.

Serotypes HPV 6 and 11 are linked with benign maternal genital warts. Congenital HPV infection resulting from vertical transmission, which is mother to fetus/newborn passage, beyond transient skin colonization is rare. Still, conjunctival, laryngeal, vulvar, or perianal warts present at birth in the neonate or that develop within 1 to 3 years of birth are most likely due to perinatal exposure to these maternal HPV serotypes (Chap. 68, p. 1216). Importantly, cesarean delivery does not lower the risk of neonatal laryngeal papillomatosis.

The clear link between HPV infection and cervical neoplasia led to development of approved vaccines that reduce cervical cancer risk (Lei, 2020). Only one vaccine is currently available in the United States. Gardasil 9 is a nonavalent HPV vaccine (9vHPV) against HPV types 6, 11, 16, 18, 31, 35, 45, 52, and 58. This vaccine is not administered during pregnancy and is compatible with breastfeeding (Chap. 10, p. 189).

Abnormal Cytology and Histology. The incidence of abnormal cervical cancer screening test results and their management is similar for gravidas and nonpregnant women. Current 2019 management consensus guidelines from the American Society of Colposcopy and Cervical Pathology focus on the individual's risk for CIN 3 or cervical cancer, rather than on specific screening results (Perkins, 2020).

Management has become complex and derives from large database analyses. Factors include the abnormal cytology and HPV results, age, and previous screening results. As a result, algorithms now calculate the best clinical approach to abnormal screening test results (www.asccp.org/management-guidelines). In overview, certain cytological abnormalities and HPV test results warrant colposcopy, and the main goal during pregnancy is to exclude invasive cancer. Thus, lesions suspicious for high-grade disease or cancer are biopsied. Endocervical sampling, endometrial biopsy, and treatment of preinvasive lesions are unacceptable during pregnancy.

Women with histologically confirmed CIN from biopsy during pregnancy are allowed to deliver vaginally. Further evaluation is planned at least 4 weeks postpartum. Alternatively, for clinical findings with higher cancer risk, repeat colposcopy and cytology/HPV testing are performed at intervals no more frequently than 12 weeks. Biopsy is repeated only if a lesion appears worse or invasive cancer is suspected (Perkins, 2020).

Postpartum reassessment may reveal lesions missed previously due to either cervical changes of pregnancy or advancing lesion severity. Instead, CIN regression is common during pregnancy or puerperium. In one study of 1079 pregnant women with cervical dysplasia in which biopsy correlated with colposcopic findings, 61 percent of lesions reverted to normal postpartum (Fader, 2010). In another study, lesions regressed postpartum in 70 percent of women with CIN 2 or 3. However, 7 percent of CIN 2 lesions progressed to CIN 3, but no lesion advanced to invasive cancer (Yost, 1999). In another study of 77 women with carcinoma in situ (CIS) diagnosed antepartum, a third had postpartum regression of their lesion, two thirds had persistent CIS, and only two women had microinvasive cancer on cone biopsy after delivery (Ackermann, 2006).

Adenocarcinoma in situ (AIS) is managed in a manner similar to CIN 3 (Dunton, 2008). Thus, unless invasive cancer is identified, treatment of AIS is not recommended until 6 weeks postpartum. Referral to a gynecologist with advanced colposcopic skills is recommended (Perkins, 2020).

Cervical Conization. If invasive epithelial lesions are suspected, conization is indicated and may be done with loop electrosurgical excisional procedure (LEEP) or by cold-knife conization. However, the epithelium and underlying stroma within the endocervical canal cannot be extensively excised without the risk of membrane rupture. Logically, residual disease is common. Of 376 cone biopsies during pregnancy, residual neoplasia was later found in 43 percent of subsequent specimens (Hacker, 1982). In another series, nearly 10 percent of 180 pregnant women required transfusion after conization (Averette, 1970). Thus, if possible, conization is avoided in pregnancy because of its higher risks for abortion, membrane rupture, hemorrhage, and preterm delivery.

Women with CIN treated *before* pregnancy may also encounter pregnancy complications. First, distal cervical stenosis is uncommon but may follow conization, LEEP, or laser surgery. Cervical stenosis almost always yields during labor. A so-called *conglutinated cervix* may undergo almost complete intrapartum effacement without dilation. Spontaneous dilation usually promptly follows firm pressure with a fingertip, although instrumented dilation or cruciate incisions may be required.

Second, preconceptional cold-knife conization is associated with cervical insufficiency and preterm birth. However, the relationship between preterm birth and LEEP continues to be debated (Castanon, 2012; Conner, 2014; Stout, 2015). The size of tissue excised seems to be directly related to adverse outcomes (Weinmann, 2017).

Invasive Cervical Cancer

This cancer is found in approximately 1 in 1200 to 10,000 pregnancies (Bigelow, 2017; McCormick, 2018). The diagnosis is confirmed with biopsies taken during colposcopy, with conization, or from a grossly abnormal lesion. Of the histological types, squamous cell carcinomas account for 75 percent, whereas adenocarcinomas compose the remainder (Schorge, 2017). Cancers may appear as exophytic or endophytic growth; as a polyp, papillary tissue, or barrel-shaped cervix; or as focal

ulceration or necrosis. A watery, purulent, foul, or bloody discharge may be present. The sensitivity of a single Pap test is poor. Thus, biopsy with Tischler forceps is warranted for suspicious lesions. Abnormal tumor vessels may cause heavier than expected biopsy-site bleeding, which is usually controlled by Monsel paste and pressure.

Historically, cervical cancer was solely staged clinically. The current staging system now incorporates radiological and surgical evaluation (Bhatla, 2019). Lymph node metastasis is now also included in staging**.** Allowable components of clinical staging are cold-knife conization, pelvic examination under anesthesia, cystoscopy, intravenous pyelogram (or this portion of MR imaging can be used), proctoscopy, and chest radiography. Notably, physiological pregnancy changes may limit physical assessment of cancer extent, which is more likely to be underestimated in gravidas. Specifically, induration of the broad ligament base, which characterizes tumor spread beyond the cervix, may be less prominent due to cervical, paracervical, and parametrial pregnancy-induced softening. MR imaging can be used without gadolinium contrast to ascertain involvement of the urinary tract, parametrium, and lymph nodes (Beharee, 2019).

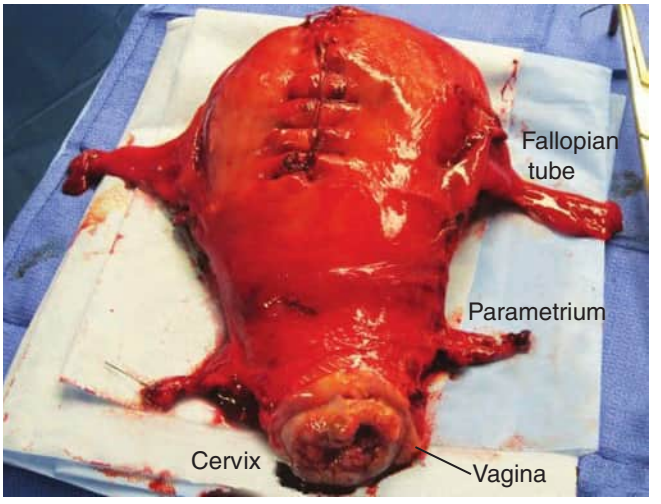

FIGURE 66-2 Radical hysterectomy specimen with invasive cervical squamous cell carcinoma. With radical hysterectomy, the parametrium and 2 to 3 cm of vagina are excised to help achieve a tumor-free resection. (Reproduced with permission from Dr. Debra L. Richardson.)

Management and Prognosis. Cervical cancer treatment in pregnant women is individualized, and factors include the clinical stage, fetal age, and individual desire to continue pregnancy. Stage IA1 is termed *microinvasive disease* and describes lesions with deepest invasion <3 mm (Bhatla, 2019). If diagnosed by cone biopsy, treatment follows guidelines similar to those for intraepithelial disease. In general, continuation of pregnancy and vaginal delivery are considered safe, and definitive therapy is reserved until 6 weeks postpartum.

In contrast, cancer with greater invasion demands relatively prompt therapy. During the first half of pregnancy, immediate treatment is advised by most, but the decision whether to continue pregnancy is a factor. During the latter half of pregnancy, the risk of early delivery versus delayed treatment are weighed (McCormick, 2018). In two studies with a total of 40 women past 20 weeks' gestation with either stage I or stage IIA carcinoma, delayed treatment was considered reasonable in women without bulky lesions (Takushi, 2002; van Vliet, 1998). Another option is to complete staging using laparoscopic lymphadenectomy and to delay treatment if metastases are excluded (Alouini, 2008; Favero, 2010). In a metaanalysis, preoperative neoadjuvant chemotherapy with platinum derivatives was found to be promising for treatment in pregnancy (Zagouri, 2013a).

Although surgical therapy and radiation are equally effective, radical hysterectomy plus pelvic lymphadenectomy is the preferred treatment for invasive cervical cancer in most young women with stage I and early stage IIA lesions. Disadvantageously, radiotherapy for cervical cancer destroys ovarian and possibly sexual function and frequently causes intestinal and urinary tract injury. In 49 women with pregnancy-associated stage IB cancer, a 30-percent severe complication rate accompanied radiotherapy compared with that of only 7 percent with radical surgery (Nisker, 1983). With surgery before 20 weeks' gestation, radical hysterectomy is usually performed with the fetus in situ. In later pregnancy, however, hysterotomy and delivery is often performed first (Fig. 66-2).

Although rarely selected during pregnancy, Ungár and colleagues (2006) performed abdominal radical trachelectomy before 20 weeks' gestation for stage IB1 cancer in five pregnant women. One cases series describes four women with stage IA1 adenocarcinoma at 16 to 23 weeks' gestation treated with laser conization, and all delivered at term (Yahata, 2008).

For more advanced-stage cancer, radiotherapy is given. External beam radiation in early in pregnancy typically leads to spontaneous abortion. If miscarriage does not ensue, curettage is performed. During the second trimester, spontaneous abortion may not promptly occur and may necessitate hysterotomy in up to a fourth of cases. This is selected because labor induction or dilation and evacuation may pose serious hemorrhage risks from the cancer.

Pregnancy does not negatively affect cervical cancer prognosis, and survival outcomes are similar for pregnant and nonpregnant women (Amant, 2014; Mogos, 2013). For both of these groups, the overall 5-year survival rate approximated 80 percent in a case-control study of 44 women with pregnancy-associated cervical cancer (van der Vange, 1995).

Delivery

Adverse prognostic effects from vaginal delivery through a cancerous cervix are unknown. For this reason, the mode of delivery is controversial, especially for small, early-stage lesions. In some cases of bulky or friable tumors, hemorrhage from the cancer may complicate vaginal delivery. Also, recurrences in the episiotomy scar have been reported (Goldman, 2003). Thus, most favor cesarean delivery.

Pregnancy after Radical Trachelectomy

Radical trachelectomy for stage IB1 and IB2 cervical cancer before conception is one fertility-sparing option. During the typically vaginal procedure, the cervix is amputated at the level of the internal os, and a permanent-suture cerclage is placed around the isthmus to support future pregnancies. The uterine

isthmus is then reconstructed to the vagina. Following this, women continue to menstruate, and conception can occur naturally. Because of the permanent cerclage, a classical cesarean incision is required for delivery. Evidence suggests that cervical length <13 mm at 20 weeks' gestation is associated with preterm birth <34 weeks (Kasuga, 2017). In a systematic review of 2566 women after radical trachelectomy for early-stage cancer, the 5-year overall maternal survival rate was 97 percent (Smith, 2020). The pregnancy rate was 24 percent, and the live-birth rate was 75 percent.

Uterus

Leiomyomas

Also known as myomas and somewhat erroneously called *fibroids*, uterine leiomyomas are common benign smooth-muscle tumors. Their incidence during pregnancy approximates 2 percent, but the cited range depends on the frequency of routine sonography and population characteristics (Qidwai, 2006; Stout, 2010). In one study of 4271 women, the first-trimester myoma prevalence was highest in black women—18 percent—and lowest in whites—8 percent (Laughlin, 2009).

Leiomyomas vary in location and may develop as submucosal, subserosal, or intramural growths. Less often, these develop in the cervix or broad ligament. Rare parasitic types obtain their blood supply from adjacent structures such as the omentum. In another rare manifestation—*leiomyomatosis peritonealis disseminata*—numerous, small, benign subperitoneal smooth-muscle tumors mimic carcinomatosis but often regress after pregnancy.

In general, progesterone is considered the critical mitogen for uterine leiomyoma growth. In turn, estrogen functions to upregulate and maintain progesterone receptors (Ishikawa, 2010). In pregnancy, progesterone's effect on myoma growth is unpredictable, and tumor size may grow, regress, or remain unchanged (Laughlin, 2009; Neiger, 2006).

Especially during pregnancy, these masses can be confused with other pelvic masses, and sonographic imaging is indispensable (Fig. 66-3). Once diagnosed, myomas do not require sonographic surveillance unless associated complications are anticipated. With unclear sonographic findings, MR imaging may be necessary and ideally performed after the first trimester.

Symptoms. Most leiomyomas are asymptomatic, but acute or chronic pain or pressure may develop, especially with large masses (Doğan, 2016). For chronic pain, nonnarcotic analgesic drugs usually suffice. More acutely, some myomas can outgrow their blood supply and hemorrhagic infarction follows, which is termed *red* or *carneous degeneration*. Clinically, acute focal abdominal pain and tenderness are preeminent and often accompanied by leukocytosis or low-grade fever. Thus, tumor degeneration may be difficult to differentiate from other sources of acute abdominal pain. Sonography aids diagnosis, but close observation is requisite because an infarcted myoma is essentially a diagnosis of exclusion. Uncommonly, preterm labor is stimulated by associated inflammation.

Symptoms from a degenerated myoma usually abate within a few days. In severe cases, observation may be needed to exclude a septic cause. Although surgery is rarely needed during pregnancy, myomectomy in highly selected cases has yielded good outcomes. Of 23 reported cases, women were 14 to 20 weeks' gestation, and in almost half, surgery was performed because of pain (Celik, 2002; De Carolis, 2001). Except for one loss immediately following surgery at 19 weeks, most underwent cesarean delivery at term. Occasionally, a pedunculated subserosal myoma will undergo torsion with subsequent painful necrosis. Laparoscopy or laparotomy can be used to ligate the stalk and resect the necrotic tumor. That said, we believe that surgery should be limited to tumors with a discrete pedicle that can be easily clamped and ligated.

Pregnancy Complications. Myomas have been associated with several complications that include preterm labor, placental

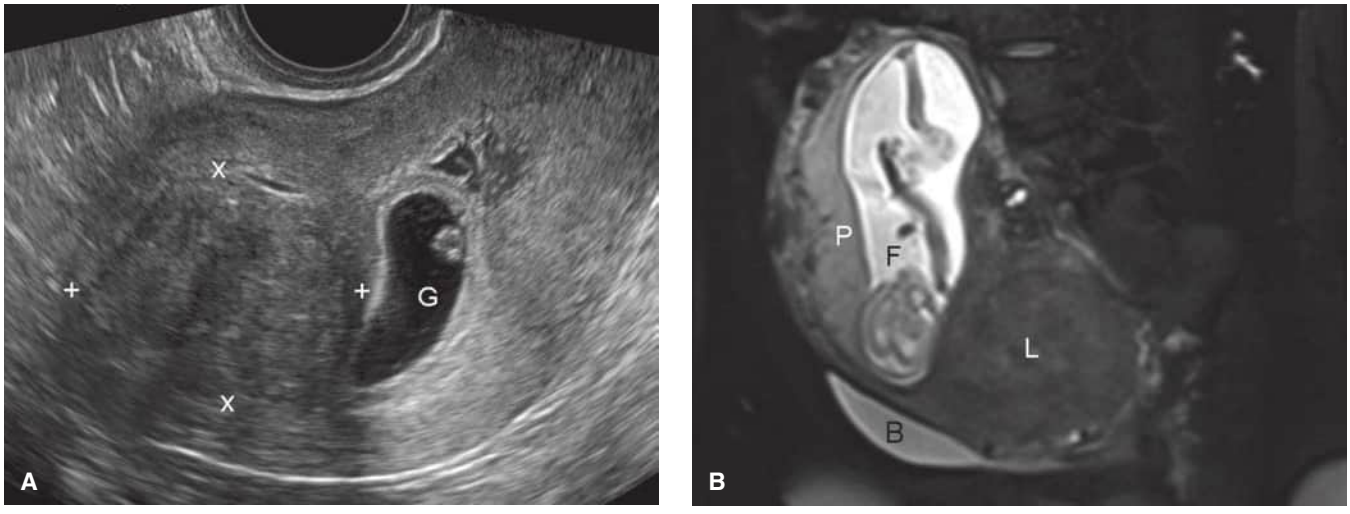

FIGURE 66-3 Leiomyoma imaging. **A.** In this sagittal view from transvaginal sonography, a large uterine leiomyoma (*calipers*) displays heterogeneous echoes and occupies the fundus. This mass lies adjacent to an early first-trimester gestational sac (*G*) that shows a yolk sac. **B.** MR imaging at 16 weeks' gestation shows a large leiomyoma (*L*) in the posterior uterine segment and cervix, which fills the pelvis. Associated ureteral compression and hydronephrosis required placement of a percutaneous nephrostomy tube. At term, planned cesarean delivery was done due to obstruction of the birth canal. B = bladder; F = fetus; P = placenta.

abruption, fetal malpresentation, obstructed labor, cesarean delivery, and postpartum hemorrhage. In a review of pregnancy outcomes in 2065 women with myomas compared with unaffected gravidas, placental abruption and breech presentation were each increased fourfold; first-trimester bleeding and dysfunctional labor, twofold; and cesarean delivery, sixfold (Coronado, 2000). In a report of 301 women with myomas, the preterm birth risk was 2.5-fold higher than in unaffected women (Girault, 2018). Another study reported an eightfold increased second-trimester abortion risk in affected women (Salvador, 2002).

Factors most important in determining morbidity in pregnancy are myoma number, size, and location (Ciavattini, 2015; Jenabi, 2018; Lam, 2014). If the placenta is adjacent to or implanted over a leiomyoma, the risks for abortion, preterm labor, placental abruption, and postpartum hemorrhage are all increased. Retroplacental myomas are also associated with fetal-growth restriction (Knight, 2016). Myoma-related bleeding may stem from miscarriage, preterm labor, placenta previa, and placental abruption. Rarely, bleeding results from a submucous myoma that has prolapsed from the uterus and into the cervix or vagina. In this case, although heavy or persistent bleeding may require earlier intervention, the stalk, if accessible, can be ligated vaginally near term to avoid avulsion during delivery.

Tumors in the cervix or lower uterine segment may obstruct labor (Fig. 66-4). Despite these complications, Qidwai and associates (2006) reported a 70-percent vaginal delivery rate even in women in whom myomas measured ≥10 cm. These data argue against empirical cesarean delivery, and we allow a trial of labor unless myomas clearly obstruct the birth canal. If cesarean delivery is indicated, uterine malrotation, which can be caused by a bulky lateral myoma, should be excluded by palpation of the fundus prior to hysterotomy (Chap. 3, p. 46). Myomas are generally left alone. Specifically, because of enucleation-associated hemorrhage, myomectomy during cesarean delivery is discouraged. Exceptions include recalcitrant intraoperative bleeding or a myoma that prohibits hysterotomy closure. With cesarean delivery in one study, mean hemoglobin levels dropped in those with myomas, but the transfusion rate was not increased (Pergialiotis, 2017). Importantly, cesarean hysterectomy may be technically difficult because of lateral ureteral displacement by the masses.

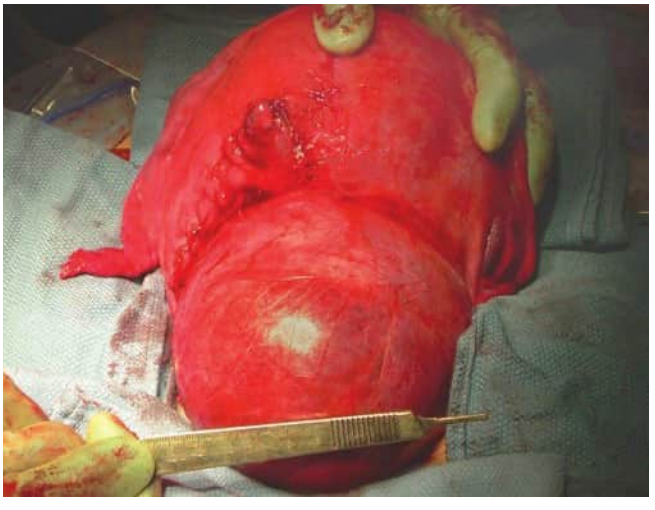

FIGURE 66-4 Cesarean delivery performed because of a large leiomyoma in the lower uterine segment. A classical vertical uterine incision, seen to the left of the myoma, was required for delivery of the fetus.

Fortunately, myomas rarely become infected (Genta, 2001). When infection develops, it usually is postpartum, especially if the tumor is located immediately adjacent to the implantation site (Lin, 2002). They also may become infected with an associated septic abortion or with myoma perforation by a sound, dilator, or curette.

Fertility Considerations. Despite their relatively high prevalence in young women, their negative effect on fertility is unclear. Moreover, evidence from one systematic review was inconclusive to support myomectomy for intramural or subserosal myomas to improve fertility (Metwally, 2020). As an exception, the American Society for Reproductive Medicine (2017) describes fair evidence for hysteroscopic myomectomy of submucous myomas to improve clinical pregnancy rates. In a systematic review of nearly 1400 pregnancies, myomas were not associated with a higher miscarriage rate (Sundermann, 2017).

Instead of an infertility indication, some women may elect myomectomy to treat bleeding or pressure symptoms yet still desire fertility preservation. Importantly, after myomectomy, the gravid uterus can rupture either before or during labor (American College of Obstetricians and Gynecologists, 2021a). Management is individualized, and review of the prior operative report is prudent. If resection resulted in a defect into or immediately adjacent to the endometrial cavity, cesarean delivery is usually done before labor. Timing of cesarean delivery is individualized, and the American College of Obstetricians and Gynecologists (2021b) cites between $37^{0/7}$ and $38^{6/7}$ weeks' gestation.

Uterine artery embolization of myomas is another option for women seeking symptom relief yet desiring fertility preservation (Ludwig, 2020). Women so treated have higher rates of miscarriage, cesarean delivery, and postpartum hemorrhage. The Society of Interventional Radiology considers myoma embolization relatively contraindicated in women who plan future pregnancies (Dariushnia, 2014). Even so, myoma embolization does not harm ovarian reserve (Shamy, 2020).

Endometrial Lesions

With *endometriosis*, studies have recently focused on a link with adverse obstetrical outcomes (Stephansson, 2009; Zullo, 2017). However, data are complicated by heterogeneity regarding disease stage and location, use of ART, and analysis methodologies (Leone Roberti Maggiore, 2016). Despite this, an association with placenta previa is the most consistent.

Occasionally, an *endometrioma* can develop after delivery from endometrial tissue implanted within laparotomy or episiotomy scars. Pfannenstiel incisions carry greater susceptibility than vertical ones (Ecker, 2014). These form a palpable mass and can cause cyclical localized pain. Endometriomas within an ovary are discussed in the next section.

Adenomyosis is traditionally found in late reproductive life and beyond. Its acquisition may be at least partially related to

disruption of the endometrial-myometrial border during sharp curettage for abortion (Curtis, 2002). In one systematic review, miscarriage, poor fetal growth, preeclampsia, placenta previa, and preterm delivery were associated risks (Nirgianakis, 2021).

Endometrial carcinoma is an estrogen-dependent neoplasia also usually found in women aged >40 years and thus seen only rarely with pregnancy (Korenaga, 2020). Of 27 cases that were identified during pregnancy or within the first 4 months postpartum, most were found in first-trimester curettage specimens (Hannuna, 2009). These are usually early-stage, well-differentiated adenocarcinomas for which treatment consists primarily of total abdominal hysterectomy and bilateral salpingo-oophorectomy.

For nonpregnant women, surgical management of early endometrial cancer is also the standard. However, to preserve fertility potential in a well-counseled woman with early-stage, well-differentiated, endometrioid endometrial cancer, treatment with oral or intrauterine progestin therapy can be used to prompt tumor regression (Hamilton, 2021). Notably, live birth rates are low, and a large percentage requires ART for conception (Harrison, 2019). Moreover, recurrences and deaths have been reported (Erkanli, 2010).

Ovary

Ovarian masses found during pregnancy are common. Incidences vary depending on the frequency of prenatal sonography, the ovarian size threshold, and study site designation as tertiary or primary care. Thus, the incidence of ovarian masses not surprisingly ranges from 1 in 100 to 2000 pregnancies (Bacalbaşa, 2020; Korenaga, 2020). Of ovarian malignancies, the incidence in the California Cancer Registry was 1 case in 19,000 pregnancies (Smith, 2003).

The most frequent types of ovarian masses are corpus luteum cysts, endometriomas, benign cystadenomas, and mature cystic teratomas (dermoid cysts). In one series of 53 endometriomas diagnosed in the first trimester, a fourth each remained stable or increased in size, and a third shrank (Bailleux, 2017).

Mature cystic teratomas enlarge infrequently during pregnancy. Rarely, a teratoma may express N-methyl-D-aspartate (NMDA) receptors within the tumor's neural-tissue component. Antibodies form against these receptors within the tumor and then attack similar-looking receptors in the brain. In one case, a pregnant woman developed encephalitis from these antibodies (Mizutamari, 2016).

Because pregnant women are usually young, malignant tumors and those of low malignant potential are proportionately uncommon. One study found that 1 percent of 9375 ovarian masses were frankly malignant and that another 1 percent were of low malignant potential (Leiserowitz, 2006). In surgically excised masses, rates of malignancy are higher, vary from 4 to 13 percent, and probably reflect a greater preoperative concern for cancer (Sherard, 2003).

Diagnosis

Most ovarian masses are asymptomatic. Some cause pressure or chronic pain, and acute abdominal pain may be due to torsion, rupture, or hemorrhage. Rarely, blood loss is sufficient to cause hypovolemia.

Ovarian masses are usually detected during routine prenatal sonography or during imaging for other indications, including symptom evaluation. For complicated anatomy, MR imaging can be used without contrast.

Cancer antigen 125 (CA125) is a tumor marker, and levels are frequently elevated with ovarian malignancy. Importantly, in early pregnancy and early puerperium, CA125 levels are normally elevated, possibly from the decidua. From the second trimester until term, levels are not normally higher than those in the nonpregnant woman (Appendix, p. 1229) (Korenaga, 2020; Szecsi, 2014). With severe preeclampsia, however, concentrations are abnormally elevated (Karaman, 2014). Other tumor markers that have been used for diagnosis or posttreatment surveillance in pregnancy include human chorionic gonadotropin (hCG), alpha-fetoprotein (AFP), inhibins A and B, carcinoembryonic antigen (CEA), and the multimarker OVA1 test (Liu, 2011).

Complications

Torsion and hemorrhage are significant complications of adnexal masses. Torsion usually causes acute constant or episodic lower abdominal pain and tenderness that is accompanied frequently by nausea and vomiting. Transvaginal sonography (TVS) often aids diagnosis, and an adnexal mass is typically comorbid. With color Doppler, absent flow strongly correlates with torsion. However, minimal or early twisting may compromise only venous flow, thus leaving the arterial supply intact. Other sonographic signs are ovarian stromal edema; follicle displacement to the ovarian periphery; free cul-de-sac fluid; the whirlpool sign, which displays twisted vessels of the involved pedicle; and the follicular ring sign (Moro, 2020; Yatsenko, 2021). This last sign is a 1- to 2-mm echogenic rim around antral follicles and may reflect edema and engorged capillaries.

If torsion is suspected, laparoscopy or laparotomy is warranted. Contrary to prior teaching, most now recommend untwisting to save the ovary (Fig. 66-5). Concerns for thrombus release and pulmonary embolism have been allayed (McGovern, 1999). A grossly necrotic adnexum is removed. With a salvageable

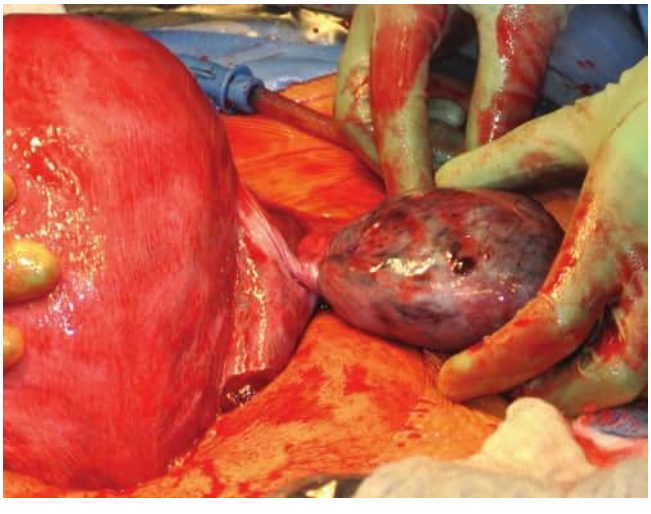

FIGURE 66-5 Ovarian torsion at term. The patient underwent cesarean delivery, and the left uteroovarian pedicle was untwisted. (Reproduced with permission from Dr. C. Edward Wells.)

ovary, within minutes of untwisting, congestion is relieved but the blue-black color typically persists.

If the adnexum is deemed viable, there are options. First, an associated neoplasm is resected. However, ovarian cystectomy in an edematous ovary may be technically difficult, and adnexectomy may be necessary. Less often, cystectomy may be delayed for low-risk lesions to allow easier enucleation following edema resolution (Adeyemi-Fowode, 2019). Second, oophoropexy, especially for a second case of torsion, can minimize recurrence risk (Djavadian, 2004). Techniques described include shortening of the uteroovarian ligament with a running stitch or fixing the uteroovarian ligament to the posterior uterus, the lateral pelvic wall, or the round ligament (Fuchs, 2010).

The most common cause of ovarian hemorrhage follows rupture of a corpus luteum cyst. Symptoms mirror those of hemoperitoneum, and diffuse lower abdominal pain is usual. TVS shows blood in the cul-de-sac and a collapsed ovarian cyst remnant (Fig. 12-5, p. 224). If the diagnosis is certain and symptoms abate, observation and surveillance is usually sufficient. Concern for ongoing bleeding will typically prompt surgical evaluation. If the corpus luteum is removed before 10 weeks' gestation, progestational support is recommended to maintain the pregnancy. Suitable regimens include: (1) micronized progesterone (*Prometrium*), 200 or 300 mg orally once daily; (2) 8-percent progesterone vaginal gel (*Crinone*), one premeasured applicator vaginally daily, plus micronized progesterone, 100 or 200 mg orally once daily; or (3) intramuscular 17-hydroxyprogesterone caproate, 150 mg. The first two regimens are given until 10 completed weeks. For the last, if given between 8 and 10 weeks' gestation, only one injection is required immediately after surgery. If the corpus luteum is excised between 6 and 8 weeks' gestation, two additional doses should be given 1 and 2 weeks after the first.

Asymptomatic Adnexal Mass During Pregnancy

Most of these are incidentally found, and decisions include necessity and timing of resection. A cystic benign-appearing mass measuring <5 cm often requires no additional antepartum surveillance. Early in pregnancy, this is likely a corpus luteum cyst, which typically resolves by the early second trimester. For cysts ≥10 cm, the risk of malignancy, torsion, or labor obstruction is substantial, and surgical removal is reasonable.

Tumors between 5 and 10 cm are carefully evaluated by TVS coupled with color Doppler and possibly MR imaging. Simple-appearing cysts can be managed expectantly with sonographic surveillance (Fig. 66-6) (American College of Obstetricians and Gynecologists, 2016; Schmeler, 2005). Resection is done if cysts grow, display malignant qualities, or become symptomatic. Those with classic findings of endometrioma or mature cystic teratoma may be resected postpartum or during cesarean delivery for obstetrical indications.

On the other hand, if sonographic findings suggest cancer, prompt resection is indicated (Caspi, 2000). Nodules, papillary excrescences, solid components, or thick, vascular septa within the mass or ascites are suggestive findings (Andreotti, 2020). In one review of 563 masses in pregnancy, approximately half were simple, and the other half complex (Webb, 2015). Among simple masses, 1 percent were malignant, and of complex masses, 9 percent were cancerous.

Approximately 1 in 1000 pregnant women undergoes surgical exploration for an adnexal mass (Boulay, 1998). In general, we plan resection at 14 to 20 weeks' gestation because most masses that will regress will have done so by this time. Laparoscopic removal is ideal (Chap. 49, p. 867) (Naqvi, 2015; Sisodia, 2015). Importantly, the American College of Obstetricians and Gynecologists (2016) recommends consultation with a gynecological oncologist for elements implicating cancer that include a very elevated CA125 level, a nodular or fixed pelvic mass, ascites, evidence of metastasis, or ultrasound findings suggesting malignancy.

Pregnancy-Related Ovarian Tumors

One group of ovarian masses results directly from the stimulating effects of various pregnancy hormones on ovarian stroma. These include pregnancy luteoma, hyperreactio luteinalis, and ovarian hyperstimulation syndrome.

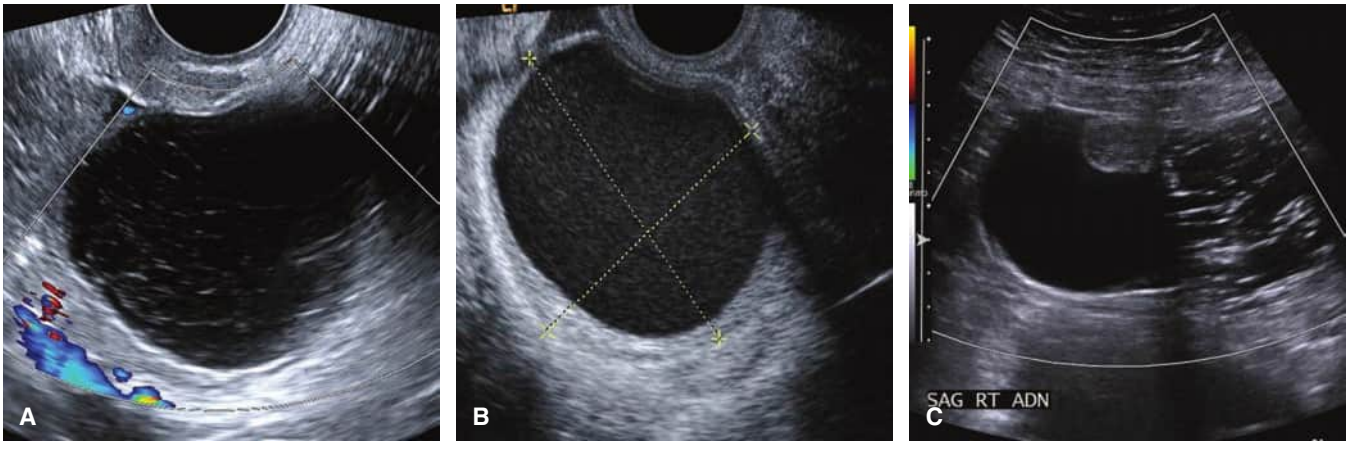

FIGURE 66-6 Sonographic characteristics of common adnexal masses in pregnancy. **A.** A simple hemorrhagic cyst with smooth walls and an internal reticular pattern is characteristic of a physiological corpus luteum cyst. **B.** Homogeneous cystic mass with diffuse internal low-level echoes suggestive of an endometrioma or hemorrhagic corpus luteum. **C.** Mature cystic teratoma (dermoid cyst) appears as a complex adnexal cyst. On the right side, hyperechoic lines and dots represent hair in both longitudinal and transverse planes. At the central superior aspect of this cyst, a mural nodule—the Rokitansky protuberance—is seen. A fat (*right side*)-fluid (*left side*) level is another common finding with these tumors.

Pregnancy Luteoma. This is a rare, benign ovarian neoplasm that arises from luteinized stromal cells and classically raises testosterone levels (Hakim, 2016; Irving, 2011). Up to 25 percent of affected women will be virilized, and of these affected women, nearly half of their female fetuses will have some degree of virilization. However, most mothers and their fetuses may be unaffected because the placenta rapidly converts testosterone to estrogen (Kaňová, 2011).

In typical cases, an adnexal mass along with maternal virilization will prompt sonography and measurement of testosterone and CA125 levels. Luteomas are variably sized, appear solid, may be multiple or bilateral, and may be complex because of internal hemorrhage (Choi, 2000). Concerns for malignancy may be further investigated with MR imaging (Kao, 2005; Tannus, 2009).

Total testosterone levels are increased, but notably, levels in normal pregnancy can be substantially elevated (Appendix, p. 1231). Differential diagnoses include granulosa cell tumors, thecomas, Sertoli-Leydig cell tumors, Leydig cell tumors, stromal hyperthecosis, and hyperreactio luteinalis.

Generally, luteomas do not require surgical intervention unless torsion, rupture, or hemorrhage complicate these (Masarie, 2010). Tumors spontaneously regress during the first few months postpartum, and androgen levels drop precipitously following delivery (Wang, 2005). Lactation may be delayed a week by hyperandrogenemia (Dahl, 2008). Recurrence in subsequent pregnancies is rare.

Hyperreactio Luteinalis. In this condition, one or both ovaries develop multiple, large theca-lutein cysts, typically after the first trimester. Cysts are caused by luteinization of the follicular theca interna layer, and most are stimulated by exceptionally high hCG levels (Russell, 2009). Thus, they are more common with gestational trophoblastic disease, twins, fetal hydrops, and other conditions with increased placental mass (Nassr, 2018). Maternal but not fetal virilization may develop (Malinowski, 2015). Serum testosterone levels are not predictive of maternal virilization (Condic, 2021).

Sonographically, these ovarian tumors have a "spoke wheel" pattern (Fig. 13-3, p. 238) (Baxi, 2014). If the diagnosis is confident, and unless complicated by torsion or hemorrhage, surgical intervention is not required. These masses resolve after delivery. Few data allow prediction of recurrence in a subsequent pregnancy, but in one case report, a woman had hyperreactio with three pregnancies (Bishop, 2016).

Ovarian Hyperstimulation Syndrome. This is typified by multiple ovarian follicular cysts accompanied by increased capillary permeability. It most often is a complication of ovulation-induction therapy for infertility, although it rarely may develop in an otherwise normal pregnancy. Its etiopathogenesis is thought to involve hCG stimulation of vascular endothelial growth factor (VEGF) expression in granulosa-lutein cells (Soares, 2008). This causes greater vascular permeability that can lead to ascites, pleural or pericardial effusion, hypovolemia with acute kidney injury, and hypercoagulability. Serious complications are renal dysfunction, adult respiratory distress syndrome, ovarian rupture with hemorrhage, and VTE. Unlike hyperreactio luteinalis, virilization is absent (Suzuki, 2004).

Management is outlined by the American Society for Reproductive Medicine (2016). Treatment is primarily supportive to maintain vascular volume and prevent VTE. In severe cases, paracentesis can be helpful.

Ovarian Cancer

Malignancies of the ovary are the leading cause of death from genital-tract cancers in all women (American Cancer Society, 2021). Still, the incidence of ovarian malignancy only ranges from 1 case in 20,000 to 50,000 births (Eibye, 2013; Smith, 2003). Of those found in pregnancy, 75 percent are early-stage cancers that carry a 5-year survival rate between 70 and 90 percent (Brewer, 2011). The types of malignancy are also markedly different in gravidas compared with those in older women. In pregnant women, these are, in decreasing order of frequency, germ cell and sex cord-stromal tumors, low-malignant-potential tumors, and epithelial cancers (Morice, 2012).

Pregnancy apparently does not alter the prognosis of most ovarian malignancies. Management is similar to that for nonpregnant women, with the usual proviso that it may be modified depending on gestational age. Thus, if frozen-section histopathological analysis verifies malignancy, surgical staging is done with careful inspection of all accessible peritoneal and visceral surfaces (Bacalbaşa, 2020). Peritoneal washings are taken for cytology, biopsies are obtained from the diaphragmatic surface and peritoneum, omentectomy is completed, and pelvic and infrarenal paraaortic lymph nodes are sampled, if accessible.

If disease is advanced, bilateral adnexectomy and omentectomy will decrease most tumor burden. In early pregnancy, hysterectomy and aggressive surgical debulking procedures may be elected. In other cases, minimal debulking described in the previous paragraph is done, and the operation is terminated. In some cases of aggressive or large-volume disease, chemotherapy can be given during pregnancy while awaiting pulmonary maturation. Monitoring maternal CA125 serum levels during chemotherapy is not accurate in pregnancy (Morice, 2012).

Preventively, increasing parity is one known factor (Fortner, 2019; Huang, 2020). A metaanalysis also found that prior miscarriage or abortion lowered risk (Lee, 2021). Of modifiable factors, combination oral contraceptives and breastfeeding lower ovarian cancer rates (Babic, 2020; Havrilesky, 2013; Iversen, 2018). Discussed in Chapter 39 (p. 682), rates of some ovarian cancers may decline following tubal interruption and perhaps salpingectomy.

■ Adnexal Cysts

Paratubal and paraovarian cysts either are distended remnants of the paramesonephric ducts or are mesothelial inclusion cysts. One autopsy series in nonpregnant women cited an incidence of 5 percent (Dorum, 2005). The most common paramesonephric cyst is the hydatid of Morgagni, which is pedunculated and typically dangles from one of the fimbria. Although these may undergo torsion, other complications are rare, and most are identified during cesarean delivery or puerperal sterilization. In these instances, they can simply be excised or drained by creating a large window in the cyst wall. Neoplastic paraovarian cysts are rare, sonographically and histologically resemble

tumors of ovarian origin, and rarely are of borderline potential or frankly malignant (Korbin, 1998).

Vulva and Vagina

Preinvasive disease in young women—vulvar intraepithelial neoplasia (VIN) and vaginal intraepithelial neoplasia (VAIN)—are seen more often than invasive disease and are commonly associated with HPV infection. As with cervical neoplasia, these premalignant conditions are treated after delivery.

Cancer of the vulva or vagina is generally a malignancy of older women, and thus, these are rarely associated with pregnancy (Amant, 2019; Korenaga, 2020). Even so, any suspicious lesion is biopsied. Most are squamous cell cancers, and treatment is individualized according to the clinical stage and depth of invasion. In a review of 23 cases, investigators concluded that radical surgery for stage I disease was feasible during pregnancy—including in the last trimester (Heller, 2000). It appears that vaginal delivery is not contraindicated if vulvar and inguinal incisions are well healed. In late pregnancy, resection and definitive therapy can often be delayed due to these tumors' typically slow progression (Anderson, 2001). Other vulvar cancer types and vaginal malignancies are rare in pregnancy and mainly the subjects of case reports (Korenaga, 2020; Matsuo, 2009).

BREAST CARCINOMA

Breast cancer incidence in women aged 25 to 40 years has been rising since the 1930s (American Cancer Society, 2021; Lima, 2020). It has an overall relatively high frequency in younger women and is the most frequent cancer complicating pregnancy (see Fig. 66-1) (Alfasi, 2019; de Hann, 2018). From the Nationwide Inpatient Sample, the incidence approximated 1 case in 15,000 births (Maor, 2017). Postponed childbearing was considered partially responsible for the increase in pregnancy-associated breast cancer in Sweden and Denmark (Andersson, 2015; Eibye, 2013). And, as more women choose to delay childbearing, the frequency of associated breast cancer is certain to rise. Genetic mutations underlie some breast cancer cases, and these are discussed in that section (p. 1174).

Diagnosis

More than 90 percent of gravidas with breast cancer have a palpable mass, and greater than 80 percent of cases are self-reported (Brewer, 2011). In pregnancy, clinical assessment, diagnostic procedures, and treatment of women with breast tumors are often slightly delayed (McCormick, 2018). This is partially attributed to pregnancy-induced growth of breast tissue that obscures masses.

Breast mass evaluation does not differ from that for nonpregnant women (Loibl, 2015; McCormick, 2018). Thus, any suspicious breast mass should be pursued to diagnosis. Pragmatically, a palpable discrete mass can be biopsied or excised. To distinguish between a solid and cystic lesion, sonography has high sensitivity and specificity (Navrozoglou, 2008). Mammography is appropriate if indicated, and the fetal radiation risk is negligible—0.04 mGy—with appropriate shielding (Krishna, 2013). But, because breast tissue is denser in pregnancy, mammography has a false-negative rate of 35 to 40 percent (Woo, 2003). If the decision to biopsy is uncertain, MR imaging may be used.

To better classify imaging findings for breast masses, the American College of Radiology (2013) developed the Breast Imaging-Reporting and Data System—BI-RADS. Suitable for sonography, mammographic, and MR imaging results, the intent is to communicate an individual woman's risk of developing breast cancer (Table 66-1).

Cystic breast lesions are simple, complicated, or complex. Simple cysts do not require special management or monitoring, but they may be aspirated if symptomatic. Complicated cysts

TABLE 66-1. American College of Radiology: Breast Imaging Reporting and Data Systems—BI-RADS[a]

BI-RADS Category	Interpretation	
0	Addition mammography views or sonography required	Focal asymmetry, microcalcifications, or a mass identified on a screening mammogram
1	No abnormalities identified	Normal fat and fibroglandular tissue
2	Not entirely normal, but definitely benign	Fat necrosis from a prior excision, stable biopsy-proven fibroadenoma, stable cyst
3	Probably benign <2% probability of malignancy	Circumscribed mass that has been followed for <2 years
4A	Low suspicion for malignancy (2–9%), but intervention required	Probable fibroadenoma, complicated cyst
4B	Moderate suspicion for malignancy (10–49%), intervention required	Partially indistinctly marginated mass otherwise consistent with a fibroadenoma
4C	High suspicion (50–94%), but not classical for carcinoma	New cluster of fine pleomorphic calcifications, ill-defined irregular solid mass
5	Almost certainly malignant (>95% probability)	Spiculated mass, fine linear and branching calcifications
6	Biopsy-proven carcinoma	Biopsy-proven carcinoma

[a]Mammography, sonography, or magnetic resonance imaging.

show internal echoes during sonography, and they sometimes are indistinguishable from solid masses. These are typically aspirated, and if the sonographic abnormality does not resolve completely, a core-needle biopsy is usually performed. Complex cysts have septa or intracystic masses seen sonographically. Because some breast cancer may form complex cysts, excision is usually recommended.

For solid breast masses, evaluation uses the *triple test*, that is, clinical examination, imaging, and core needle biopsy. If all three suggest a benign lesion or if all three suggest a breast cancer, the test is considered *concordant*. A concordant benign triple test is ≥99-percent accurate, and breast lumps in this category can be followed by clinical examination alone. Most masses in pregnancy have these three reassuring features. In contrast, if any of the three assessments suggests malignancy, the mass should be excised.

Management

With breast cancer, a limited search of the most common metastatic sites is completed. For most, this includes a chest radiograph, liver sonography, and skeletal MR imaging (Becker, 2016; Krishna, 2013). MR imaging can also evaluate the abdomen, pelvis, and brain.

Treatment of breast cancer includes an obstetrician, breast surgeon, and medical oncologist. Initially, desires for pregnancy continuation are addressed, and data indicate that pregnancy interruption does not influence the course or prognosis of breast cancer (Cardonick, 2010). With pregnancy continuation, treatment in general mirrors that for nonpregnant women. Important caveats are that chemotherapy and surgery are postponed to the second trimester, and adjuvant radiotherapy is withheld until after delivery (Brewer, 2011). Delay should be avoided as the risk of metastases increases with every few months by 5 to 10 percent (McCormick, 2018).

Surgical treatment may be definitive. In the absence of metastatic disease, either a wide excision or a modified or total mastectomy—each with axillary node staging—can be performed (Rosenkranz, 2006). Staging by sentinel lymph node biopsy and lymphoscintigraphy with technetium-99m is safe. Breast reconstruction, if desired, is typically delayed until after delivery (Viswanathan, 2011). That said, one small series showed good results in 10 pregnant women who underwent immediate reconstruction after mastectomy (Caragacianu, 2016).

Chemotherapy is usually given with both positive- and negative-node breast cancers. In premenopausal women, survival rates with this approach are improved, even if lymph nodes are cancer free. For node-positive disease, multiagent chemotherapy is begun if delivery is not anticipated within several weeks. Cyclophosphamide, doxorubicin, and cisplatin are currently used (Euhus, 2016). If an anthracycline-based agent such as doxorubicin is used, pretherapy maternal echocardiography is performed because of associated cardiotoxicity (Brewer, 2011). Good maternal and perinatal results have been reported (Freret, 2020; McCormick, 2018).

Immunotherapy for breast cancers is now commonplace. Trastuzumab (*Herceptin*) is a monoclonal antibody to the HER2/neu receptor, which is found in approximately a third of invasive breast cancers (Hudis, 2007). The drug is not recommended in pregnancy. This is because HER2/neu is strongly expressed in fetal renal epithelium, and trastuzumab has been linked with miscarriage, fetal renal failure and related oligohydramnios, and preterm birth (Amant, 2010; Azim, 2010).

The effects of pregnancy on the course of breast cancer and its prognosis are complex. Breast cancer is more aggressive in younger women, but whether it is more aggressive during pregnancy in these same women is debatable (Azim, 2014). Clinically, most studies indicate little difference in overall survival rates with pregnancy-associated breast cancer compared with similarly aged and staged nonpregnant women (Beadle, 2009). Other reports note worse overall survival rates with pregnancy-associated breast cancer (Rodriguez, 2008). These investigators do conclude, however, that later disease stages are more prevalent in pregnant women.

Because breast cancer is usually found at a more advanced stage in pregnant women, the overall prognosis is diminished (Andersson, 2015). The aggregate of studies published after 1990 indicate that up to 60 percent of pregnant women have concomitant axillary node involvement at diagnosis. And although, stage for stage, the 5-year survival rate is comparable in pregnant and nonpregnant women, the more advanced stages that are typical of pregnant women worsen their prognosis (Kuo, 2019; Zemlickis, 1992).

Pregnancy Following Breast Cancer

After breast cancer treatment, chemotherapy will render some women infertile, but childbearing options were noted earlier (p. 1164). For those who become pregnant, long-term maternal survival rates are not adversely affected (Averette, 1999; Lambertini, 2019). One metaanalysis found that for women with early breast cancer, pregnancy that occurs 10 months after diagnosis may, in fact, confer a survival benefit (Valachis, 2010). Breastfeeding does not adversely alter the course.

In women successfully treated for breast cancer, recurrence is a concern. Because recurrences are more common soon after treatment, it seems reasonable to delay conception for 2 to 3 years. Hormonal contraceptive methods are contraindicated, and a copper-containing intrauterine device is an excellent method for many. That said, women with breast cancer who subsequently conceive do not appear to have diminished survival rates (Ives, 2006). Those who developed breast cancer within 10 years of delivery have and increased risk for metastases (Goddard, 2019). Importantly, tamoxifen, which may be used long-term following initial therapy, is a teratogen. Discontinuation 2 months prior to conception is recommended (Zydus Pharmaceuticals, 2020).

BRCA1/2 MUTATIONS

Hereditary breast and ovarian cancer (HBOC) syndrome yields a susceptibility to either one or both of these two cancers in individuals with recognized gene mutations (Table 66-2). *BRCA1* and *BRCA2* mutations are preeminent, but others are associated.

Preventively, cancer screening, chemoprevention, prophylactic surgery, and preimplantation testing are options. First,

TABLE 66-2. Some Genes Associated with Hereditary Cancers

Genes with established association with breast cancer										
BRCA1	*BRCA2*	*STK11*	*CDH1*	*PALB2*	*CHEK2*	*ATM*	*TP53*	*PTEN*	*NF1*	*NBN*
Genes with established association with epithelial ovarian cancer[a]										
BRCA1	*BRCA2*	*BR1P1*	*MSH2*	*MSH6*	*MLH1*	*RAD51C*	*RAD51D*			
Genes with established association with uterine cancer										
			MSH2	*MSH6*	*MLH1*	*PMS2*				

[a]*STK11* mutation is associated with ovarian sex-cord stromal tumors but not epithelial types.

American College of Obstetricians and Gynecologists, 2019d; Amin, 2020; Easton, 2015; Menon, 2018; Peters, 2017; Tamura, 2019.

ovarian cancer screening with TVS or serum CA125 levels is not routinely recommended (Daly, 2021). For breast cancer, surveillance in those aged 25 to 29 years is clinical breast examination (CBE) performed by a provider once or twice yearly plus annual breast MR imaging. For older individuals, yearly MR imaging and mammography are alternated every 6 months.

For women with *BRCA1* and *BRCA2* gene mutation, combination oral contraceptives (COC) are recognized chemoprevention for ovarian cancer (Chen, 2019). COC effects on breast cancer risk are conflicting, and studies show no risk or modest increased risk (Daly, 2021). For breast cancer chemoprevention, tamoxifen can lower cancer risk in those with *BRCA2* defects (King, 2001).

Prophylactic bilateral salpingo-oophorectomy (BSO) is recommended after childbearing in those aged 35 to 40 years with *BRCA1* defects and aged 40 to 45 years in those with *BRCA2* mutations (Chen, 2019). BSO or mastectomy also decreases breast cancer risk in these women (Kotsopoulos, 2016; Li, 2016; Rebbeck, 2009).

BRCA1/2 genes are transmitted in an autosomal dominant fashion. In those planning pregnancy, affected women may elect *preimplantation genetic testing* of blastocysts (Chen, 2019). However, with an established pregnancy, *prenatal testing* poses ethical concerns regarding pregnancy termination for a mutation that may not lead to cancer. Currently, testing for conditions that do not accrue until adulthood are discouraged by the American College of Obstetricians and Gynecologists (2020a,b).

Regarding parity, protective benefits for breast cancer in women with either *BRCA* defect show conflicting data (Kotsopoulos, 2018; Pan 2014; Rieder, 2015; Toss, 2017). For ovarian cancer, parity lowers rates for women with *BRCA1* but not *BRCA2* mutations (Kotsopoulos, 2015). Women with either *BRCA* mutation who undergo induced abortion do not have an elevated breast cancer risk (Friedman, 2006). Breastfeeding conveys a protective effect against breast cancer in those with *BRCA1* defects but not *BRCA2* mutations. It lowers ovarian cancer rates for those with either mutation (Kotsopoulos, 2012; 2020).

Among those with either *BRCA* mutation, a breast cancer diagnosis during pregnancy does not lower survival rates compared with similarly affected but not pregnant women (Valentini, 2013). After breast cancer treatment, women with either *BRCA* defect who pursue pregnancy do not experience increase pregnancy complication rates. Moreover, disease-free or overall survival rates are not worsened (Lambertini, 2020; Valentini, 2013).

THYROID CANCER

Palpable thyroid nodules are detected in 4 to 7 percent of the population, and management is found in Chapter 61 (p. 1098). Approximately 10 percent are malignant (Burman, 2015). In pregnancy, thyroid cancer incidence approximates 10 cases per 100,000 births (Spiegel, 2019; Sullivan, 2019). With this diagnosis, pregnancy termination is not necessary. Primary therapy is partial or subtotal thyroidectomy ideally done during the second trimester. Most lesions are well differentiated, and delayed treatment is acceptable (Angell, 2019). For aggressive tumors, however, prompt surgical treatment is recommended. Postoperatively, replacement thyroxine is given. A higher risk for VTE is reported for these women (Spiegel, 2019).

In some thyroid cancer types, radioiodine is used for primary or postoperative treatment. This is contraindicated in both pregnancy and lactation for several reasons. First, iodine-131 transferred transplacentally is avidly trapped by the fetal thyroid gland to cause hypothyroidism. Second, during lactation, the breast also concentrates a substantial amount of iodide. This may pose neonatal risk due to radioiodine-contaminated milk ingestion and raise maternal cancer risk from significant breast irradiation. To limit maternal exposure, a delay of 3 months between lactation and thyroid ablation will more reliably ensure complete breast involution (Sisson, 2011). In women with thyroid cancer who ultimately receive iodine-131 doses, pregnancy should be avoided for 6 months to 1 year. This time ensures thyroid function stability and permits confirmation of cancer remission (Abalovich, 2007).

LYMPHOMAS

Hodgkin Disease

This lymphoma is probably B-cell derived and is cytologically distinguished from other lymphomas by Reed–Sternberg cells.

TABLE 66-3. Lugano Classification Staging System for Hodgkin and Other Lymphomas

Stage	Findings
I	Involvement in a single lymph node region or lymphoid site—e.g., spleen or thymus
II	Involvement of two or more lymph node groups on the same side of the diaphragm or cancer extends from one node group to a nearby organ
III	Involvement of lymph nodes on both sides of the diaphragm 1. Limited to spleen or splenic hilar, celiac, or portal nodes 2. Includes paraaortic, iliac, or mesenteric nodes plus those in II
IV	Extralymphatic involvement—e.g., liver, bone marrow, or lungs

Substage A = no symptoms; substage B = fever, sweats, or weight loss; substage E = extralymphatic involvement excluding liver and bone marrow; X = bulky disease.

Of cancers in pregnancy, lymphomas are common, and gestational rates are rising because of delayed childbearing (see Fig. 66-1) (Horowitz, 2016). In one review from the Nationwide Inpatient Sample, the incidence of Hodgkin lymphoma approximates 1 case in 12,400 births (El-Messidi, 2015).

In more than 70 percent of these cases, lymph nodes painlessly enlarge at sites above the diaphragm, that is, in the axillary, cervical, or submandibular chains. Approximately one third of patients have fever, night sweats, malaise, weight loss, or pruritus. Diagnosis is by histological examination of involved nodes (McCormick, 2018).

The Lugano staging system is applied to Hodgkin and other lymphomas (Table 66-3). For staging, pregnancy limits the use of some radiographic studies, but at minimum, chest radiography, abdominal imaging with sonography or MR imaging, and bone marrow biopsy are completed (Shah, 2020). MR imaging is excellent for evaluating thoracic and abdominal paraaortic lymph nodes.

The current trend for nonpregnant individuals is to administer chemotherapy for all stages of Hodgkin disease. In pregnancy, for early-stage disease in the first trimester, options include pregnancy termination or observation until after 12 weeks' gestation and then multiagent chemotherapy (Eyre, 2015; McCormick, 2018). For most advanced-stage disease after the first trimester, cycles of doxorubicin, bleomycin, vinblastine, and dacarbazine are given. In general, postponement of therapy until fetal maturity is achieved seems justifiable only when the diagnosis is made late in pregnancy.

Women with Hodgkin lymphoma have a higher incidence of VTE (El-Messidi, 2015; Horowitz, 2016). Also, in our experiences, the gravidas—even after they are "cured"—are inordinately susceptible to infection and sepsis. Active antineoplastic therapy only raises this vulnerability.

The overall prognosis with Hodgkin lymphoma is similar to that for nonpregnant women, and 5-year survival rates exceed 90 percent (Maggen, 2019). Pregnancy does not adversely affect the cancer course of this lymphoma, and pregnancy outcomes are not generally adversely affected. For women with disease in remission, pregnancy does not stimulate relapse (Weibull, 2016).

Non-Hodgkin Lymphomas

Although usually B-cell tumors, non-Hodgkin lymphomas can also be T-cell or natural-killer-cell neoplasms. Their biology, classification, and treatment are complex. They are associated with viral infections, and their incidence has risen sharply at least partly because 5 to 10 percent of persons with HIV infection develop lymphoma. Other associated viruses include Epstein-Barr and hepatitis C viruses and human herpes virus 8. Some of these lymphomas are aggressive, and survival rates vary with the type of cell line involved.

Non-Hodgkin lymphomas are infrequent during pregnancy (Pinnix, 2016). They also are staged according to the Lugano system. If diagnosed in the first trimester, pregnancy termination followed by multiagent chemotherapy is recommended for all but indolent or very early disease. These less aggressive forms may be observed in the first trimester, and then full treatment given in the second. One regimen is rituximab plus the CHOP combination of cyclophosphamide, doxorubicin (hydroxydaunorubicin), vincristine [Oncovin], and prednisone. In a study of 80 pregnant women with this regimen, the 3-year survival rate was 73 to 96 percent (Maggen, 2021).

Burkitt lymphoma is an aggressive B-cell tumor associated with Epstein-Barr virus infection. Prognosis is poor, and treatment is multiagent chemotherapy. In an earlier review of 19 women whose pregnancies were complicated by this lymphoma, 17 died within a year of diagnosis (Barnes, 1998).

Leukemias

These malignancies generally arise either from lymphoid tissues—lymphoblastic or lymphocytic leukemias, or from bone marrow—myeloid leukemias. They can be acute or chronic. Adult leukemias are more prevalent after age 40 but still are among the most common malignancies of young women (see Fig. 66-1). In two large registries, the incidence was 1 case in 40,000 to 50,000 births (Nolan, 2020; Smith, 2003). In a review of 72 pregnancies complicated by leukemia from 1975 until 1988, 44 had acute myelogenous leukemia; 20 had acute lymphocytic leukemia; and eight had one of the chronic leukemias (Caligiuri, 1989). Nolan and colleagues (2020) cite similar proportions.

Acute leukemias almost always cause marked peripheral blood count abnormalities, and often the white blood cell count is elevated with readily recognizable circulating blast cells. The diagnosis is made from bone marrow biopsy.

With current multiagent chemotherapy, remission during pregnancy is common, and termination does not further improve the prognosis. In some cases, pregnancy termination before

viability may simplify management of an acutely ill woman. Abortion is a consideration in early pregnancy to avoid potential chemotherapy teratogens. One is all-*trans*-retinoic acid, also known as *tretinoin*, which causes retinoic acid syndrome (Chap. 8, p. 154) (Li, 2020; Santolaria, 2020). Tyrosine kinase inhibitors are another teratogenic group (p. 1163) (Palani, 2015).

Other than these caveats, treatment of gravidas with leukemia is similar to that for nonpregnant women. Acute myeloid leukemia is treated without delay (Ali, 2015). After induction chemotherapy, postremission maintenance therapy is mandatory to prevent a relapse, which is then usually treated with stem-cell transplantation. If allogeneic stem-cell transplantation is indicated, early delivery is considered. With some chronic leukemias, it may be possible to delay therapy until after delivery (Fey, 2008). As with lymphoma, infection and hemorrhage are significant complications that should be anticipated in women with active disease.

Most descriptions of leukemia treatment in pregnancy are single cases or small series (Routledge, 2018; Sanz, 2015). In one review of 58 cases, 75 percent were diagnosed after the first trimester (Reynoso, 1987). Half were acute myelogenous leukemia, which had a remission rate of 75 percent with chemotherapy. Only 40 percent of these pregnancies resulted in a live birth (Caligiuri, 1989). In a more recent report of 92 pregnant women with acute promyelocytic leukemia, 91 percent had a complete remission (Santolaria, 2020).

MALIGNANT MELANOMA

These most often originate from melanocytes in a preexisting nevus. Lesions most often develop in fair-skinned whites and commonly in childbearing-aged women. Pigmented lesions that change in contour or height or show discoloration, bleeding, or ulceration should prompt biopsy (Richtig, 2017).

In some population studies, melanoma is the most frequent malignancy complicating pregnancy (Andersson, 2015; Bannister-Tyrrell, 2015). The reported incidence ranges from <1 to 3 cases per 1000 births (Cottreau, 2019; Eibye, 2013). Many are treated outpatient and thus not entered into tumor registries.

Staging is clinical. Stage I is a melanoma with no palpable lymph nodes; in stage II, lymph nodes are palpable; and in stage III, distant metastases are identified. For patients with stage I, tumor thickness is the single most important predictor of survival. The Clark classification includes five levels of involvement by depth into the epidermis, dermis, and subcutaneous fat. The Breslow scale measures tumor thickness and size, in addition to invasion depth.

Primary surgical treatment for melanoma is determined by the stage and includes wide local resection, sometimes with extensive regional lymph node dissection. The American Academy of Dermatology recommends sentinel lymph node mapping and biopsy using technetium-99m–sulfur colloid, which has a calculated fetal dose of 0.014 mSv or 0.014 mGy (Swetter, 2019). Routine regional node dissection reportedly improves survival rates in nonpregnant patients with microscopic metastases. For gravidas, an algorithm is proposed that begins with resection of the primary tumor under local anesthesia but postpones sentinel lymph node biopsy until postpartum (Broer, 2012). Although prophylactic chemotherapy or immunotherapy is usually avoided during pregnancy, it may be given if indicated by tumor stage and maternal prognosis. In most cases of distant metastatic melanoma, treatment is at best palliative.

Stage-for-stage, survival is equivalent between pregnant and nonpregnant women (Driscoll, 2016; Johansson, 2014). In two studies, half of pregnant women presented with an advanced stage (de Haan, 2017; Sawyers, 2020). Placentas are submitted for histological evaluation to exclude metastasis (p. 1164). Therapeutic abortion does not improve maternal survival rates. Clinical stage is the strongest determinant of survival, and women with deep cutaneous invasion or regional node involvement have the worst prognosis. Approximately 60 percent of recurrences will manifest within 2 years, and 90 percent by 5 years. Thus, most recommend that pregnancy be avoided for 3 to 5 years after surgical resection. Interim contraception can include combination oral contraceptives, as they do not appear to have adverse cancer effects (Still, 2017).

GASTROINTESTINAL TRACT CANCER

Carcinomas of the colon and rectum are the third most frequent cancer in all women in the United States (American Cancer Society, 2021). Their incidence in pregnancy is rising because of delayed childbearing (Murphy, 2018). Even so, colorectal tumors are uncommon before age 40. An approximate incidence of 1 case in 150,000 deliveries was derived from the California Cancer Registry (Smith, 2003). In another report, however, the incidence approximated 1 case in 13,000 pregnancies (Salani, 2014). Of colorectal carcinomas in pregnant women, 80 percent arise from the rectum. In one review, only 41 cases in pregnancy were colon cancers located above the peritoneal reflection (Chan, 1999).

The most frequent symptoms are abdominal pain, distention, nausea, constipation, and rectal bleeding. If symptoms of colon disease persist, digital rectal examination, stool tests for occult blood, and colonoscopy are done. Some gastrointestinal (GI) tract cancers are found because of metastases to the ovary. These *Krukenberg tumors* are tumor-laden ovaries from another, often GI, primary and carry a bleak prognosis (Kodama, 2016).

Colon cancer treatment in gravidas mirrors that for nonpregnant women. Without evidence of metastatic disease, surgical resection is preferred, but most pregnant women have advanced lesions (Al-Ibrahim, 2014). During the first half of pregnancy, hysterectomy is not necessary to perform colon or rectal resection, and thus, therapeutic abortion is not mandated. During later pregnancy, therapy may be delayed until fetal maturation. However, bowel hemorrhage, obstruction, or perforation may force surgical intervention.

Gastric and esophageal cancers are rare in pregnancy. Despite this, persistent unexplained upper GI symptoms should be prompt upper abdominal sonography and perhaps endoscopy.

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CHAPTER 67

Infectious Diseases

Infections remain a major cause of maternal and fetal morbidity and mortality worldwide. The unique maternal–fetal vascular interface in some cases serves to protect the fetus from infectious agents, but in other instances it provides a conduit for transmission. Maternal serological status, acquisition mode, gestational age at the time of infection, and immunological status of mother and fetus all influence disease outcome.

The TORCH acronym reflects the infections toxoplasmosis, others, rubella, and cytomegalovirus and herpesvirus infections. These can cross the placenta to cause fetal infection and substantial neonatal sequelae. Of members in the "others" category, parvovirus B19 infection is discussed here. Herpesvirus and syphilis infections are described in Chapter 68.

MATERNAL AND FETAL IMMUNOLOGY

Maternal Immunological Changes

Despite significant advances, many of the maternal immunological adaptations to pregnancy remain unclear. Successful pregnancy results from a complex interplay between the innate and adaptive immune systems to establish fetal tolerance (Chap. 5, p. 93) (Liu, 2017). Within the innate system, decidual natural killer (dNK) cells interact with and aid invasion of fetal extravillous trophoblasts via human leukocyte antigen (HLA)-G (Fig. 21-8, p. 404). Also, cytokines produced during viral infection activate dNK cells to induce protective cytotoxicity (Tilburgs, 2015).

Within the adaptive immune system, a CD4+ subset of T helper cells called regulatory T cells (Tregs) express *forkhead box P3 (FOXP3)*. This is an immune-suppressive transcription factor that plays a critical role in inducing maternal immune tolerance to the fetus (Kahn, 2010). However, this same mechanism compromises maternal defense against bacterial pathogens. Noncoding microRNAs, whose roles are incompletely defined, regulate activation and proliferation of both innate and adaptive immune cells (Robertson, 2017).

In describing infections, *horizontal transmission* is the spread of an infectious agent from one individual to another. *Vertical transmission* is passage of an infectious agent from the mother to her fetus through the placenta, during labor or delivery, or by breastfeeding. Thus, preterm rupture of membranes or prolonged labor may enhance the risk of some neonatal infections (American College of Obstetricians and Gynecologists, 2020b). Table 67-1 shows specific infections by mode and acquisition timing. A final term, the *secondary attack rate*, is the probability that infection develops in a susceptible individual following known contact with an infectious person.

Fetal and Newborn Immunology

The active immunological capacity of the fetus and neonate is compromised compared with that of older children and adults. That said, fetal innate and adaptive immunity begin to develop by 9 to 15 weeks' gestation (McGovern, 2017). The primary fetal response to infection is mediated by innate immunity—macrophages and dendritic cells—and to a lesser extent, by adaptive immunity—B and T cells (Chougnet, 2018). Passive immunity

TABLE 67-1. Specific Causes of Some Fetal and Neonatal Infections

Intrauterine
Transplacental
Viruses: varicella-zoster, coxsackie, rubella, CMV, human parvovirus B19, HIV, Zika, SARS-CoV-2
Bacteria: *Listeria*, syphilis, *Borrelia*
Protozoa: toxoplasmosis, malaria
Ascending infection
Bacteria: GBS, coliforms
Viruses: HIV
Intrapartum
Maternal exposure
Bacteria: gonorrhea, chlamydia, GBS, tuberculosis, mycoplasmas
Viruses: HSV, HPV, HIV, hepatitis B, hepatitis C, Zika
External contamination
Bacteria: staphylococcus, coliforms
Viruses: HSV, varicella zoster
Neonatal
Human transmission: staphylococcus, HSV, influenza, SARS-CoV-2
Respirators and catheters: staphylococcus, coliforms

CMV = cytomegalovirus; GBS = group B *Streptococcus*; HIV = human immunodeficiency virus; HPV = human papillomavirus; HSV = herpes simplex virus; SARS-CoV-2 = severe acute respiratory syndrome coronavirus-2.

is provided by maternal immunoglobulin G (IgG) transferred across the placenta. By 16 weeks' gestation, this transfer begins to rise rapidly, and by 26 weeks, fetal concentrations are equivalent to those of the mother. Evidence suggests maternal vaccination also primes the fetal cell-mediated immune response independent of passive immunity (Wilcox, 2018).

Neonatal infection, especially in its early stages, may be difficult to diagnose because these newborns often fail to express classic clinical signs. If the fetus was infected in utero, it may be depressed and acidotic at birth for no apparent reason. The neonate may suck poorly, vomit, or show abdominal distention. Respiratory insufficiency can develop, which may present similarly to idiopathic respiratory distress syndrome. The neonate may be lethargic or jittery. The response to sepsis may be hypothermia rather than hyperthermia, and the total leukocyte and neutrophil counts can be depressed.

VIRAL INFECTIONS

Cytomegalovirus

The most common perinatal infection in the developed world is caused by cytomegalovirus (CMV). It is a ubiquitous DNA herpesvirus that eventually infects most humans, and some evidence of fetal infection is found in 0.2 to 2.2 percent of all neonates (American College of Obstetricians and Gynecologists, 2020a). The virus is secreted into all body fluids, and person-to-person contact with viral-laden saliva, semen, urine, blood, and nasopharyngeal and cervical secretions can transmit infection. The fetus may become infected by transplacental viremia, but amniocentesis does not result in iatrogenic fetal transmission (Revello, 2008). The neonate is infected at delivery or during breastfeeding and acquisition continues to accrue. Day-care centers, for example, are a frequent source.

Up to 85 percent of women from lower socioeconomic backgrounds are seropositive by the time of pregnancy, whereas only half of women in higher income groups have detectable IgG antibodies to CMV. Following primary CMV infection, and behaving similarly to other herpesvirus infections, the virus becomes latent but undergoes periodic reactivation characterized by viral shedding. This occurs despite high serum levels of anti-CMV IgG antibody. These antibodies do not prevent maternal recurrence, reactivation, or reinfection, nor do they totally mitigate fetal or neonatal infection.

Maternal Infection

Pregnancy does not increase the risk or severity of maternal CMV infection. Most primary infections are asymptomatic, but 10 to 15 percent of infected adults have a mononucleosis-like syndrome characterized by fever, pharyngitis, lymphadenopathy, and polyarthritis. Immunocompromised women may develop myocarditis, pneumonitis, hepatitis, retinitis, gastroenteritis, or meningoencephalitis. Most women with primary infection have elevated serum aminotransferase levels or lymphocytosis. Reactivated disease usually is asymptomatic, although viral shedding is common.

Because most primary maternal infections are clinically silent, they are detected by IgG seroconversion. The rate of seroconversion during pregnancy may reach 20 percent. Rates are higher in regions with greater seroprevalence (Mussi-Pinhata, 2018). Women who are seronegative before pregnancy and then acquire primary CMV infection during pregnancy are at highest risk of having a congenitally infected fetus. Vertical transmission rates for primary infection are 30 to 36 percent in the first trimester, 34 to 40 percent in the second, and 40 to 72 percent in the third (American College of Obstetricians and Gynecologists, 2020a**;** Picone, 2017). Approximately 23 percent of congenital CMV infections in the United States are from primary maternal infection (Wang, 2011).

In contrast, recurrent or reactivated maternal infection infects the fetus in only 0.15 to 2 percent of pregnancies. However, up to 90 percent of congenitally infected neonates in high-prevalence areas are born to women with recurrent infection (Mussi-Pinhata, 2018). The diagnosis of recurrent or reactivated maternal CMV infection remains a challenge (Tanimura, 2017).

Congenital Infection

Newborns with apparent sequelae of intrauterine-acquired CMV infection are described as having *symptomatic CMV infection*. Congenital CMV infection is a syndrome that may include growth restriction, microcephaly, intracranial calcifications, chorioretinitis, mental and motor delays, sensorineural deficits, hepatosplenomegaly, jaundice, hemolytic anemia, and thrombocytopenic purpura. An example of periventricular calcifications is shown in Figure 67-1. Of the estimated 40,000

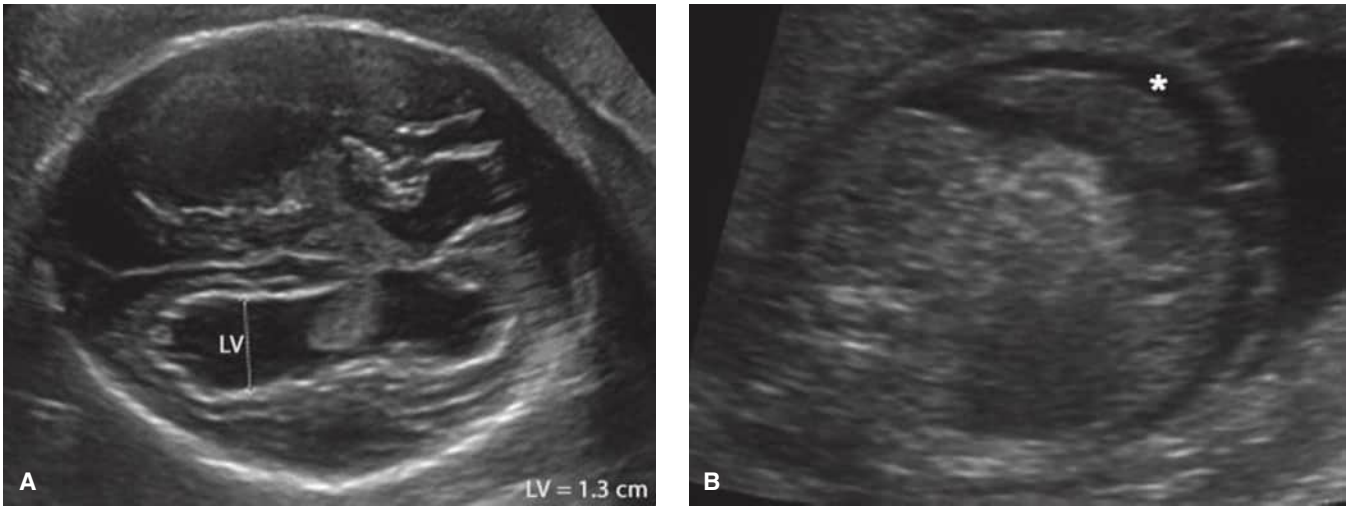


FIGURE 67-1 Congenital cytomegalovirus infection. **A.** Transverse view of the fetal head demonstrates ventriculomegaly (*LV*) and periventricular calcifications. **B.** Transverse image of the fetal abdomen with ascites (*asterisk*) and echogenic bowel.

CMV-infected neonates born each year, only 5 to 10 percent demonstrate this syndrome (Fowler, 1992). Thus, most infected newborns are asymptomatic at birth, but some develop late-onset sequelae. These may include hearing loss, neurological deficits, chorioretinitis, psychomotor delay, and learning disabilities. Infections in dichorionic twins most likely are nonconcordant (Egaña-Ugrinovic, 2016).

Prenatal Diagnosis

Routine prenatal CMV serological screening is not recommended. Pregnant women undergo serological testing for CMV if they present with a mononucleosis-like illness or if congenital infection is suspected based on abnormal sonographic findings (Fig. 67-2) (American College of Obstetricians and Gynecologists, 2020a; Society for Maternal-Fetal Medicine, 2016). If

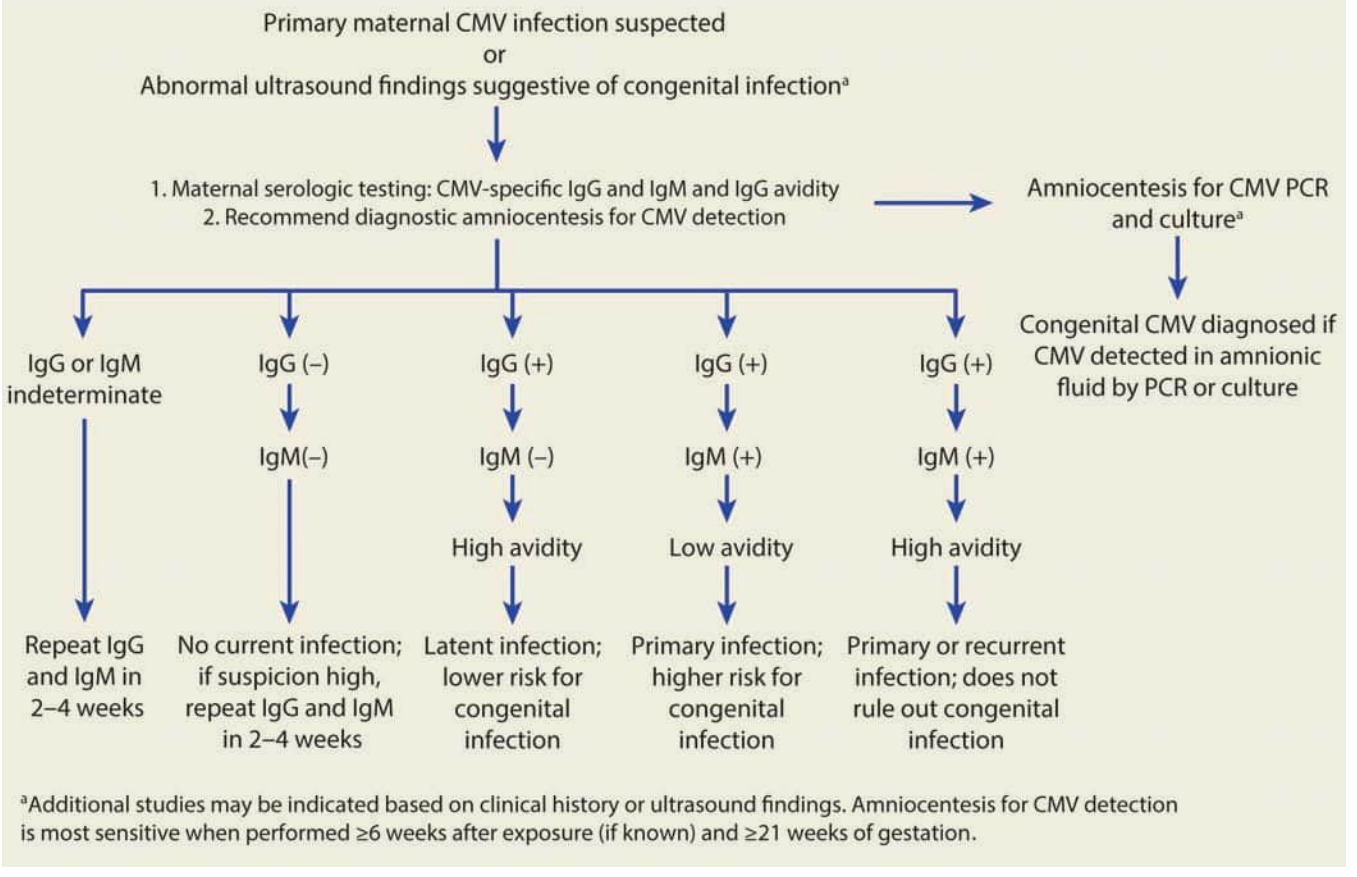


FIGURE 67-2 Diagnostic algorithm for evaluation of cytomegalovirus (CMV) infection in pregnancy. IgG = immunoglobulin G; IgM = immunoglobulin M; PCR = polymerase chain reaction.

either ultrasound or serological results indicate infection, diagnostic amniocentesis is pursued.

Serum levels of CMV IgM alone do not accurately diagnose primary infection because antibodies may persist for more than a year after infection and may rise again following reactivation or reinfection. To help clarify a primary infection from a past one, serological CMV-specific IgG avidity assays measure the "avidity" or binding strength between IgG antibodies and virus. Following primary infection, IgG antibodies have low avidity, which during the next 2 to 4 months matures to high avidity. Low IgG avidity indicates primary CMV infection within the preceding 3 to 4 months, and high IgG avidity excludes primary infection within the previous 3 months. Thus, primary infection during the first trimester may not be excluded if maternal avidity testing is performed in the second or third trimesters (Prince, 2014). In this case, diagnostic amniocentesis is still recommended if ultrasound findings suggest congenital infection. In other cases, early primary infection may be so recent that IgM is not yet detectable. If suspicion is high, serological assays are repeated in 2 to 4 weeks.

More commonly, numerous sonographic fetal findings may prompt CMV testing. Fetal abnormalities associated with CMV infection include microcephaly, ventriculomegaly, and cerebral calcifications; ascites, hepatomegaly, splenomegaly, and hyperechoic bowel; hydrops; early growth restriction; and oligohydramnios. Findings will prompt maternal serological CMV testing and diagnostic amniocentesis (see Fig. 67-2).

CMV polymerase chain reaction (PCR) testing of amnionic fluid is considered the gold standard for the diagnosis of fetal infection. Sensitivities range from 70 to 99 percent and depend on amniocentesis timing. Sensitivity is highest when amniocentesis is performed at least 6 weeks after maternal infection and after 21 weeks' gestation (Guerra, 2000). Abnormal sonographic findings seen in combination with positive findings in amnionic fluid samples are predictive of an approximate 75-percent risk of symptomatic congenital infection (Leruez-Ville, 2016a). A negative result from amnionic fluid PCR testing does not exclude fetal infection and may need to be repeated if suspicion for fetal infection is high. Diagnostic viral culture of amnionic fluid is also suitable although sensitivity is somewhat lower. Isolation of virus from cell culture allows detection of actively replicating virus, and rapid shell vial culture methods enable detection within 24 hours (Saldan, 2017).

Management and Prevention

The management of the immunocompetent pregnant woman with primary, reactivated, or recurrent CMV is limited to symptomatic treatment. If primary CMV infection is diagnosed serologically or if fetal sonographic abnormalities suggest congenital infection, amnionic fluid analysis should be offered (see Fig. 67-2). Counseling regarding fetal outcome depends on the gestational age during which primary infection is documented. Lipitz and associates (2013) reported hearing loss or neurodevelopmental delay in 15 to 25 percent of infants following primary maternal infection in the first trimester compared with 2 to 16 percent after second-trimester infection. Despite the high infection rate with primary infection in the first half of pregnancy, most fetuses develop normally. That said, pregnancy termination may be an option for some.

Currently, no curative treatments are available for CMV infection. One study group reported that treating pregnant women with high-dose oral valacyclovir, 8 g daily, apparently mitigated adverse outcomes for 80 percent of moderately asymptomatic fetuses compared with a historical cohort (Leruez-Ville, 2016b). Kimberlin and colleagues (2015) previously showed that oral valganciclovir administered for 6 weeks to neonates with symptomatic central nervous system (CNS) disease prevented hearing deterioration at 6 months and possibly later. In a recent randomized trial, CMV-specific hyperimmune globulin given to pregnant women with primary infection was ineffective in lowering perinatal CMV infection rates (Hughes, 2021).

For the CMV-affected fetus, a detailed anatomical sonographic evaluation is performed. Referral to a maternal–fetal medicine specialist is warranted, and serial sonography is indicated to identify poor growth, oligohydramnios, or fetal hydrops, which confers a worse prognosis. Antenatal surveillance is typically implemented after a shared discussion about the goals of surveillance in a fetus with known congenital infection. Delivery at term is the goal, although consultation with maternal–fetal medicine and neonatology experts is warranted to determine whether earlier delivery is indicated.

Prevention of congenital infection relies on avoiding maternal primary infection, especially in early pregnancy. Basic hygiene measures such as hand washing and not sharing food or utensils have been promoted, particularly in women with toddlers in day care (Rawlinson, 2017). CMV may be sexually transmitted among infected partners, but no data address the efficacy of preventive strategies. Several clinical trials of a CMV vaccine are underway (Gerna, 2019).

Varicella-Zoster Virus

Maternal Infection

Varicella-zoster virus (VZV) is a double-stranded DNA herpesvirus acquired predominantly during childhood, and 90 percent of adults have serological evidence of immunity. The incidence of varicella infection declined by approximately 95 percent after the introduction of varicella vaccination. Maternal and fetal varicella rates subsequently dropped (Baxter, 2014). In the United States between 2003 and 2010, the incidence of maternal varicella among 7.7 million pregnancy admissions was 1.21 cases in 10,000 (Zhang, 2015).

Primary infection—*varicella* or *chickenpox*—is transmitted by respiratory droplets or through direct contact with an infected individual. The incubation period is 10 to 21 days, and a nonimmune woman has a 70- to 90-percent risk of becoming infected after exposure (Whitley, 2018). Primary varicella has a 1- to 2-day flu-like prodrome, which is followed by pruritic vesicular lesions that crust after 3 to 7 days. Affected patients are contagious from 1 day before the rash onset until all lesions become crusted.

In adults, mortality risk rises with age and is predominantly due to secondary infection or VZV pneumonia (Leung, 2018). Risk factors for severe pneumonitis include immunosuppression and early bacterial co-infection (Mirouse, 2017). Although

the incidence was once thought to be higher in gravidas, only 2.5 percent develops VZV pneumonia (Zhang, 2015).

Symptoms of VZV pneumonia usually appear 3 to 5 days into the illness course. Fever, tachypnea, dry cough, dyspnea, and pleuritic pain are characteristic. Nodular infiltrates are similar to other viral pneumonias. Although resolution of pneumonitis parallels that of skin lesions, fever and compromised pulmonary function may persist for weeks.

If primary varicella is reactivated years later, it causes *herpes zoster* or *shingles*. The associated unilateral dermatomal vesicular eruption often produces severe pain. Zoster does not appear to be more frequent or severe in gravidas. Congenital varicella syndrome rarely develops in cases of maternal herpes zoster (Ahn, 2016). Zoster is contagious if there is direct contact with broken blisters.

Fetal and Neonatal Infection

In women with primary varicella during the first half of pregnancy, the fetus may develop *congenital varicella syndrome*. Some features include chorioretinitis, microphthalmia, cerebral cortical atrophy, growth restriction, hydronephrosis, limb hypoplasia, and cicatricial skin lesions (Ahn, 2016; Auriti, 2009). Among 1373 pregnant women with primary varicella infection in one study, only 0.4 percent with a rash before 13 weeks' gestation had neonates with congenital varicella syndrome (Enders, 1994). The highest risk period for vertical transmission was between 13 and 20 weeks, during which 2 percent of exposed fetuses had evidence of infection. After 20 weeks' gestation, the researchers found no clinical evidence of congenital varicella. Others described similar findings (Ahn, 2016). That said, fetuses that do develop congenital varicella in the third trimester may have CNS abnormalities and skin lesions (Koren, 2005).

If the fetus or neonate is exposed to active infection just before or during delivery, and therefore before maternal antibody has formed, the newborn faces a serious threat. Attack rates range from 25 to 50 percent, and mortality rates approach 30 percent. In some instances, neonates develop disseminated visceral and CNS disease, which is commonly fatal. For this reason, *varicella-zoster immune globulin (VariZIG)* should be administered to neonates born to mothers who have clinical evidence of varicella 5 days before and up to 2 days after delivery (Centers for Disease Control and Prevention, 2013).

Diagnosis

Prior maternal varicella is usually confirmed clinically based on reported history of prior illness or vaccination. Infection is confirmed by PCR-based testing of vesicular fluid or of a crust that is lifted from the skin. Congenital varicella may be diagnosed using PCR-based testing of amnionic fluid, although a positive result does not correlate well with the development of congenital infection (Mendelson, 2006). A detailed anatomical sonographic evaluation performed at least 5 weeks after maternal infection may disclose abnormalities, but the sensitivity is low (Mandelbrot, 2012).

Management and Prevention

Maternal Viral Exposure. *Any patient diagnosed with primary varicella infection or herpes zoster should be isolated from pregnant women.* Several aspects of maternal VZV exposure and infection in pregnancy affect management. Exposed gravidas with a negative clinical history for prior chickenpox or vaccination should undergo VZV serological testing. At least 70 percent of these women will be seropositive and thus immune. Seronegative women should be given intramuscular VariZIG, 125 units per 10 kg body weight, up to a maximum dose of 625 units (5 vials). Although best given within 96 hours of exposure, its use is approved for up to 10 days to prevent or attenuate varicella infection (Centers for Disease Control and Prevention, 2013). This passive immunization appears to be highly effective (Jespersen, 2016). In women with a reported history of chickenpox or varicella vaccination, VariZIG is not indicated.

Maternal and Fetal Infection. For women with primary varicella, a chest radiograph is recommended by many because VZV pneumonia often presents with few symptoms. Most women require only supportive care, but those who require intravenous fluids and especially those with pneumonia are hospitalized. Acyclovir therapy is given to women requiring hospitalization—10 to 15 mg/kg intravenously every 8 hours until afebrile. This is followed by oral acyclovir, 800 mg five times daily to complete 7 days and until lesions have crusted. For uncomplicated primary varicella without hospitalization or for herpes zoster, treatment is oral acyclovir, 800 mg five times daily for 7 days.

For the VZV-affected fetus, greater antenatal surveillance is typically implemented. Serial sonography may help identify poor growth. Delivery at term is the norm unless fetal findings prompt earlier timing.

Vaccination. An attenuated live-virus vaccine is recommended for nonpregnant adolescents and adults with no history of varicella. Two doses are needed and are separated by 4 to 8 weeks. The vaccine is not recommended for gravidas or for those who may become pregnant within one month following each vaccine dose. However, a registry of more than 1000 vaccine-exposed pregnancies reports no cases of congenital varicella syndrome or other associated congenital malformations (Peppa, 2020). The attenuated vaccine virus is not secreted in breast milk. Thus, postpartum vaccination should not be delayed because of breastfeeding (American College of Obstetricians and Gynecologists, 2019e).

■ Influenza Virus

Influenza A and B belong to the Orthomyxoviridae family of RNA viruses, and both cause epidemic human disease (Wright, 2018). Influenza A viruses are subclassified further by hemagglutinin (H) and neuraminidase (N) surface antigens. Influenza outbreaks occur annually, and severity is determined by the number of outpatient visits, hospitalizations, and deaths (Xu, 2019).

Maternal Infection

Fever, dry cough, and systemic symptoms characterize this infection, which usually is not life-threatening in otherwise healthy adults. However, pregnant women in general are more susceptible to serious complications, particularly pulmonary

involvement (Mertz, 2017; Rasmussen, 2012). Severe infection during the 2009 to 2010 pandemic had a maternal mortality rate of 1 percent and caused 12 percent of pregnancy-related deaths (Callaghan, 2015).

No firm evidence links influenza A virus and congenital malformations. Rather, the increased rates of neural-tube defects seen in neonates born to women with influenza may be associated with hyperthermia. Viremia is infrequent, and transplacental passage is rare (Rasmussen, 2012). Stillbirth, preterm delivery, and first-trimester abortion have all been reported, but these usually correlate with maternal infection severity (Fell, 2017; Meijer, 2015; Wang, 2021).

Influenza may be detected by nasopharyngeal swab of symptomatic patients using rapid molecular or viral antigen detection assays known as rapid influenza diagnostic tests (RIDTs). Recently, commercially available multiplex molecular assays have allowed nucleic acid detection and differentiation of both influenza and severe acute respiratory syndrome (SARS)-CoV-2 respiratory viruses. Molecular tests are more sensitive and specific than RIDTs, which have sensitivities of 50 to 70 percent. *Decisions to administer antiviral medications for influenza treatment or chemoprophylaxis should be based on clinical symptoms and epidemiological factors*. Namely, the start of therapy should not be delayed pending testing results.

Management

Of available agents, *neuraminidase inhibitors* are highly effective for the treatment of early influenza A and B. These include *oseltamivir* (Tamiflu), which is taken orally for treatment and for chemoprophylaxis; *zanamivir* (Relenza), which is inhaled for treatment; and *peramivir* (Rapivab), which is administered intravenously. A newer agent, *baloxavir marboxil* (Xofluza), was approved by the U.S. Food and Drug Administration in 2018 for acute uncomplicated influenza, although data in pregnancy are limited.

In pregnancy, experience is most robust with oseltamivir. The American College of Obstetricians and Gynecologists (2019a) and the Infectious Diseases Society of America recommend oral oseltamivir—75 mg twice daily for 5 days—for pregnant women with suspected or confirmed influenza, ideally within 48 hours of symptom onset (Uyeki, 2019). Early administration may reduce length of hospital stays (Oboho, 2016). For prophylaxis following exposure to a contact with confirmed infection, oseltamivir, 75 mg orally once daily for 7 days, is recommended. Antibacterial medications are added when a secondary bacterial pneumonia is suspected (Chap. 54, p. 962).

Vaccination

Effective vaccines against influenza are formulated annually and encouraged for all women who will be pregnant during the influenza season, which extends from October through March. Vaccination throughout the influenza season, but optimally before the end of October, is recommended (American College of Obstetricians and Gynecologists, 2019c; Grohskopf, 2020). This is especially important for those affected by chronic medical disorders such as diabetes, heart disease, asthma, or human immunodeficiency virus (HIV) infection. Influenza vaccination was associated with a 40-percent reduction in influenza-associated hospitalizations in pregnant women (Thompson, 2019).

Importantly, no evidence shows teratogenicity or developmental problems in children exposed to maternal vaccination (Conlin, 2018; Ludvigsson, 2016). Moreover, for mothers vaccinated during pregnancy, their infants are protected from lower respiratory tract infections for the first 3 months of life (Nunes, 2017). All inactivated or recombinant influenza vaccines may be used in gravidas (Grohskopf, 2020). However, a live attenuated influenza virus vaccine available for intranasal use is not recommended for pregnant women. Inactivated or recombinant influenza vaccines may be administered concomitantly or sequentially with other vaccines including COVID-19 and tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis (Tdap) vaccines.

Coronavirus

These single-stranded RNA viruses are named for the "crown" of surface proteins covering the particles. Seven coronaviruses infect humans, four of which cause upper respiratory disease characterized by rhinorrhea, sneezing, and congestion (Cui, 2019). Three newer coronaviruses of zoonotic origin have emerged in the past two decades and may cause serious lower respiratory tract illness in humans. These are SARS-CoV, Middle East respiratory syndrome (MERS-CoV), and the novel coronavirus of 2019 (SARS-CoV-2).

The first SARS-CoV emerged from China in 2003 and infected more than 8000 people. In a cohort of 12 pregnant women with confirmed infection, the predominant symptoms were myalgia, chills, and cough (Wong, 2004). All women had radiographic evidence of atypical pneumonia, 33 percent required mechanical ventilation, and 80 percent of women diagnosed after 24 weeks' gestation delivered preterm. Although no vertical transmission occurred, the maternal fatality rate was 25 percent.

MERS-CoV emerged in the Middle East in 2012 and can cause respiratory illness, acute kidney injury, and gastrointestinal illness (Hui, 2018). Although experience with MERS-CoV in pregnancy is limited, the mortality rate in a small series was 40 percent (Assiri, 2016).

SARS-CoV-2

This virus causes the clinical illness known as coronavirus disease 2019 (COVID-19). The SARS-CoV-2 pandemic began in China in late 2019, and by mid-2021 it had caused respiratory illness in more than 151 million people and 3 million deaths globally (World Health Organization, 2021). The mortality rate is between 1 and 2 percent in adults, and it increases sharply with age (Verity, 2020). Compared with MERS-CoV and SARS-CoV, SARS-CoV-2 is more infectious but less deadly. Variants with increased transmissibility are emerging, and the Delta (B.1.617.2) variant has recently predominated (Centers for Disease Control and Prevention, 2020a). Evidence suggests increased disease severity in gravidas who acquire this variant (Adhikari, 2021).

SARS-CoV-2 is predominantly transmitted via respiratory droplets. Asymptomatic or presymptomatic individuals account for 40 to 50 percent of transmissions (He, 2020; Kimball, 2020). The immune response to natural infection appears to require both humoral and cell-mediated immunity (Hartley, 2020). Because of the potential for asymptomatic transmission,

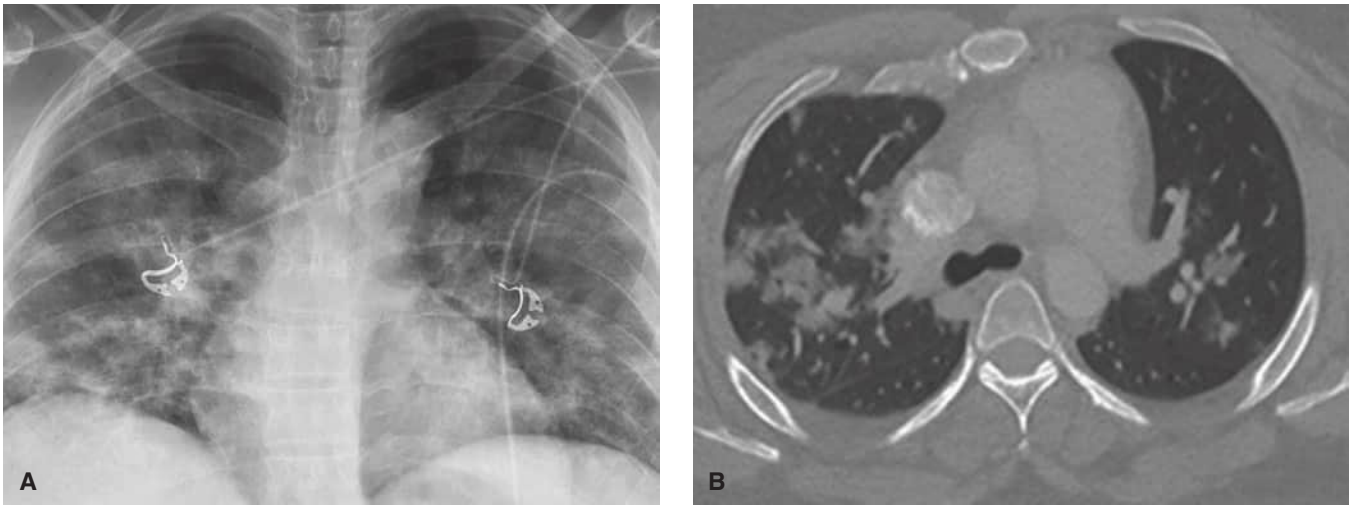


FIGURE 67-3 **A.** Chest radiograph of a critically ill pregnant woman at 26 weeks' gestation demonstrating diffuse bilateral pulmonary opacities with peripheral predominance. **B.** Axial image of the chest from a computed tomographic scan demonstrates advanced COVID-19 disease with multiple peripheral lobular consolidations and ground glass opacities.

interventions such as masking and social distancing are recommended (Centers for Disease Control and Prevention, 2021b).

Maternal Infection

COVID-19 symptoms in gravidas do not differ from those in nonpregnant individuals. An incubation period of approximately 5 to 14 days is followed by fever, cough, and myalgia. Loss of smell (anosmia) and taste (ageusia) are reported in more than half of patients (Patel, 2020). Diarrhea, nausea, and vomiting are somewhat less common. Lower respiratory involvement develops in some individuals approximately 8 days after symptom onset (Huang, 2020). Signs of worsening of disease include dyspnea, tachypnea, decreased oxygen saturation, and rarely, acute respiratory distress syndrome. Imaging indicative of moderate to severe viral pneumonia reveals multifocal opacities in a predominantly peripheral distribution and ground glass opacities on computed tomography (Fig. 67-3). Pregnant women may be at higher risk for intensive care unit admission, invasive ventilation, and death (Zambrano, 2020). A study from Parkland Hospital demonstrated that 5 percent of infected gravidas developed severe or critical illness, and diabetes may be a risk factor (Adhikari, 2020). Although COVID-19 was not associated with adverse pregnancy outcomes, women with severe illness experienced a higher rate of preterm birth. In a surveillance program of COVID-19 in pregnant women, the rate of preterm birth was higher than the general population—13 percent compared with 10 percent (Woodworth, 2020).

Fetal Infection

Infection of the placenta by SARS-CoV-2 has been demonstrated, but transmission to the fetus is rare (Schwartz, 2020). Microscopic examination of the placenta may demonstrate inflammation and syncytiotrophoblast necrosis (Fig. 67-4). Standardized criteria have been proposed for determining definite, probable,

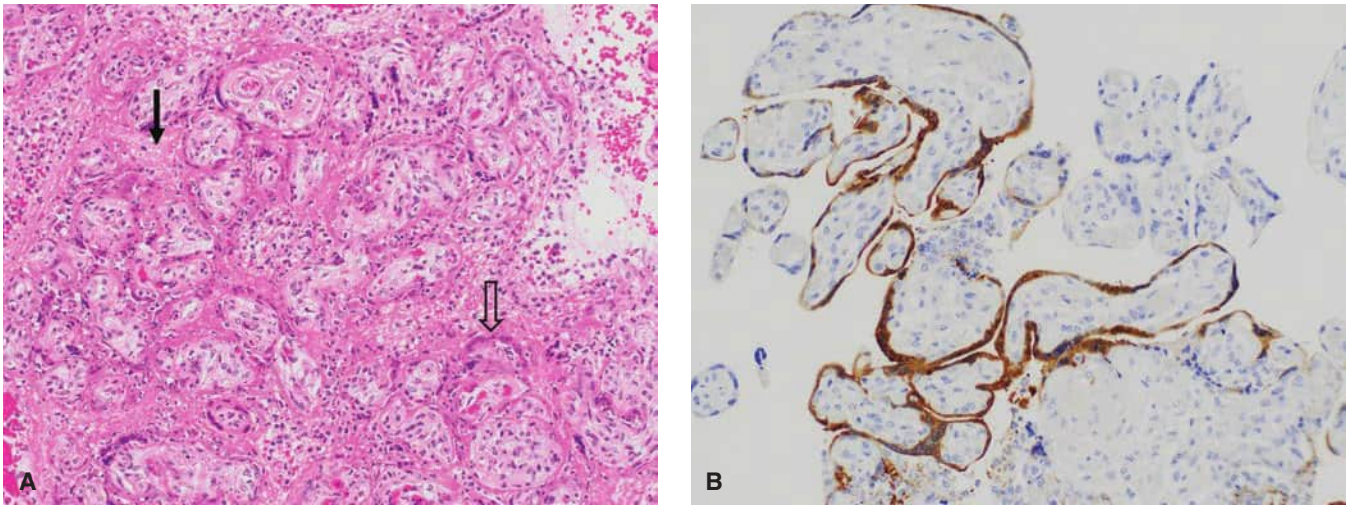


FIGURE 67-4 Placental SARS-CoV-2 infection. **A.** Histologic slide of a placenta with known maternal SARS-CoV-2 infection. Large, discrete areas of the placenta showed increased perivillous fibrin (*solid arrow*), focal trophoblast necrosis (*open arrow*), and marked histiocytic inflammation. **B.** Anti-SARS-CoV-2 viral nucleocapsid antibody is positive in villous trophoblast (*brown immunostaining*), confirming placental infection. (Reproduced with permission from Dr. Rebecca Collins.)

or possible placental infection by SARS-CoV-2 (Roberts, 2021). When vertical transmission does occur, infected neonates may have asymptomatic, mild, or severe illness (Raschetti, 2020; Sisman, 2020). Adhikari and associates (2020) demonstrated infection in 3 percent of neonates tested at 24 and 48 hours after birth. Mechanisms of vertical transmission are poorly understood. No evidence suggests transmission of SARS-CoV-2 through breastmilk (Centeno-Tablante, 2021). Newborns with SARS-CoV-2 do not need to be separated from their mothers but are isolated from the general newborn nursery population.

Diagnosis

Active maternal infection can be diagnosed from nasopharyngeal, nasal, or saliva specimens. Reverse transcriptase–polymerase chain reaction (RT-PCR) testing identifies viral RNA, whereas rapid antigen testing detects viral antigen. Several commercial tests are available and listed on the Centers for Disease Control and Prevention (CDC) (2021a) website. Rapid antigen tests are inexpensive but less sensitive in asymptomatic individuals. Thus, test result interpretation depends on pretest probability, epidemiological risk factors, and intended use for diagnostic or screening purposes in health-care or congregate settings. The latter include dormitories, correctional facilities, nursing homes, and housing shelters providing social services. Serological screening for IgG is used for epidemiological and seroprevalence studies rather than diagnosis of acute infection.

Management

For mild to moderate illness, supportive care is indicated and delivery is reserved for obstetric indications. For those with mild illness at high risk for clinical progression, anti-SARS-CoV-2 monoclonal antibodies may be administered within 10 days of symptom onset and according to variant predominance (National Institutes of Health, 2021). Pregnancy is considered a high-risk criterion, and use of monoclonal antibodies can be considered in consultation with specialists. Inpatient observation may be considered for moderate illness, as up to 40 percent may worsen (Adhikari, 2020). For pregnant women with severe to critical illness, inpatient management includes supporting respiratory function, managing comorbid conditions, and, when indicated, coordinating safe delivery with subspecialists (Society for Maternal-Fetal Medicine, 2021). The goal of respiratory support is to maintain oxygen saturation ≥95 percent and reduce dyspnea and tachypnea (Pacheco, 2020). Prone positioning of gravidas to improve oxygenation in severe cases of COVID-19 pneumonia has been described (Tolcher, 2020).

With severe infection, a dysregulated inflammatory response contributes to lung injury and hypoxia. A United Kingdom trial found decreased mortality rates at 28 days with intravenous or oral dexamethasone, 6 mg daily for up to 10 days in patients requiring supplemental oxygen or mechanical ventilation, compared with usual care (RECOVERY Collaborative Group, 2021). In the ACTT-1 trial, intravenous remdesivir, a broad-spectrum antiviral agent, was associated with shortened time to recovery among patients requiring low-flow supplemental oxygen (Beigel, 2020). Remdesivir is approved by the Food and Drug Administration for treatment of COVID-19 in hospitalized adults. Data on efficacy and safety of antiviral and biological agents for COVID-19 in pregnancy are limited. In a study of remdesivir in hospitalized gravidas with COVID-19, no serious adverse events were reported, but elevated serum aminotransaminase levels were common (Burwick, 2020). Decisions to use currently available therapeutic agents under Emergency Use Authorization are made in consultation with experts and should balance potential benefits and theoretical risks (National Institutes of Health, 2021). Antibiotics for respiratory illness are rarely necessary unless bacterial co-infection is suspected.

Prevention

Non-pharmaceutical interventions are mainstays for reducing the spread of SARS-COV-2. These include universal masking, maintaining physical distance of at least 6 feet, and hand hygiene. In healthcare settings, airborne and contact isolation precautions are used, particularly when invasive procedures are planned (Centers for Disease Control and Prevention, 2021c).

Currently available vaccines are highly protective against viral transmission and clinical disease in nonpregnant adults (Baden, 2021; Polack, 2020). In one study, the BNT162b2 mRNA vaccine was associated with a reduction in COVID-19 diagnosed in pregnancy (Goldshtein, 2021). The American College of Obstetricians and Gynecologists and the Society for Maternal-Fetal Medicine (2021) recommend that pregnant and lactating women receive the COVID-19 vaccine. Individuals who accept vaccination are counseled to anticipate common reactions such as injection-site pain, headache, fatigue, myalgia, and low-grade fever (Shimabukuro, 2021). Recent evidence from national experts suggests no greater miscarriage rate in gravidas receiving the vaccine (Zauche, 2021).

■ Mumps Virus

This is an RNA paramyxovirus that primarily infects the salivary glands but also may involve the gonads, meninges, pancreas, and other organs. It is transmitted by direct contact with respiratory secretions, saliva, or fomites. Most transmission occurs before and within 5 days of parotitis onset, and droplet isolation is recommended during this time (Kutty, 2010). Treatment is symptomatic, and mumps during pregnancy is no more severe than in nonpregnant adults.

An increased risk of spontaneous abortion has been observed in women who acquire mumps in the first trimester. Infection is not associated with congenital malformations, and fetal infection is rare (McLean, 2013).

Recent outbreaks in previously vaccinated young adults prompted the recommendation of a third dose of measles-mumps-rubella (MMR) vaccine for at-risk nonpregnant individuals during any outbreak (Marin, 2018). The MMR vaccine is a live-virus vaccine. Thus, it is contraindicated in pregnancy, although fetal risk from inadvertent administration is theoretical (McLean, 2013). Pregnancy should be avoided for 30 days after vaccination. The vaccine is encouraged for susceptible postpartum women, and breastfeeding is not contraindicated.

■ Measles Virus (Rubeola)

This is a highly contagious RNA virus of the family Paramyxoviridae that infects only humans. In endemic areas, annual

outbreaks of measles occur in late winter and early spring, with larger epidemic cycles every 2 to 5 years. Although once declared eliminated in the United States, recent outbreaks raise concerns regarding waning population immunity (Patel, 2019; Strebel, 2019). Transmission is by respiratory droplets, and the secondary attack rate among susceptible contacts exceeds 90 percent (Rainwater-Lovett, 2018).

Typical symptoms include fever, coryza, conjunctivitis, and cough. *Koplik spots*, small white lesions with surrounding erythema, appear on the buccal mucosa. A characteristic erythematous maculopapular rash develops on the face and neck and then spreads to the back, trunk, and extremities. Diagnosis of acute infection is made by detection of measles-specific IgM antibodies in serum. Additionally, measles RNA may be detected by RT-PCR testing of a throat swab, nasopharyngeal swab, or urine specimen. Treatment of measles is supportive, and evaluation for secondary infections may be necessary.

For pregnant women without evidence of measles immunity, postexposure prophylaxis is intravenous immune globulin (IVIG), and a 400-mg/kg dose is ideally given within 6 days of exposure (Centers for Disease Control and Prevention, 2020d). Human immune globulin (IG) is a blood product used to provide antibodies for short-term prevention of infectious diseases and is prepared from plasma pools derived from thousands of donors.

Measles in pregnancy is associated with increased risk for pregnancy loss, pneumonia, and death (Eberhart-Phillips, 1993; Ogbuanu, 2014). If a woman develops measles shortly before delivery, risk of serious infection developing in the neonate is considerable, and neonatal chemoprophylaxis is warranted.

As a live-virus vaccine, MMR vaccine is not provided during pregnancy as prevention. However, MMR vaccination is not an indication for pregnancy termination. Susceptible women are vaccinated routinely postpartum, and breastfeeding is not contraindicated.

Rubella Virus

Also called German measles, rubella is caused by an RNA togavirus and is of minor importance in the absence of pregnancy. Transmission is via nasopharyngeal secretions, and the transmission rate is 80 percent to nonimmune individuals. The peak incidence is late winter and spring in endemic areas (Lambert, 2015).

In 2018, more than 26,000 cases of rubella virus were reported worldwide (Grant, 2019). In the United States, ongoing or sustained transmission was eliminated in 2004, and large epidemics of rubella have virtually disappeared here because of immunization. However, up to 10 percent of women are susceptible, and cases are also imported each year from countries with incomplete vaccine coverage (Al Hammoud, 2018).

Maternal rubella is usually a mild febrile illness that follows an incubation of 12 to 23 days. A generalized maculopapular rash begins on the face and spreads to the trunk and extremities. Other symptoms may include arthralgias or arthritis, head and neck lymphadenopathy, and conjunctivitis. However, 25 to 50 percent of infections are asymptomatic. Viremia usually precedes clinical signs by approximately a week, and adults are infectious during viremia and through 7 days after the rash appears. Up to half of maternal infections are subclinical despite viremia that may cause spontaneous abortion or devastating fetal infection, described subsequently.

Diagnosis

Rubella virus may be isolated from the urine, blood, nasopharynx, and cerebrospinal fluid for up to 2 weeks after rash onset. However, the diagnosis is usually made with serological analysis. Specific IgM antibody can be detected using enzyme-linked immunoassay for 4 to 5 days after onset of clinical disease, but antibody can persist for up to 6 weeks after appearance of the rash. Importantly, rubella virus reinfection can give rise to transient low levels of IgM. With this, no adverse fetal effects have been described. A false-positive IgM result is also possible in populations with low prevalence of disease.

Serum IgG antibody titers peak 1 to 2 weeks after rash onset. These may fail to distinguish between recent infection and preexisting immunity if the specimen is obtained more than a week after symptoms. IgG avidity testing aids differentiation, and high-avidity IgG antibodies indicate an infection at least 2 months prior.

Fetal Effects

Rubella virus is one of the most complete teratogens, and its effects are worst during organogenesis. Up to 90 percent of pregnant women with rubella and a rash during the first 12 weeks of gestation have an affected fetus (Miller, 1982). At 13 to 14 weeks' gestation, this incidence is 50 percent, and by the end of the second trimester, it is 25 percent. Defects are rare after 20 weeks' gestation.

Features of congenital rubella syndrome are cardiac septal defects, pulmonary stenosis, microcephaly, cataracts, microphthalmia, and hepatosplenomegaly (Yazigi, 2017). Other abnormalities include sensorineural deafness, intellectual disability, neonatal purpura, and radiolucent bone disease. *Neonates born with congenital rubella may shed the virus for many months and thus be a threat to other infants and to susceptible adults who contact them.*

Management and Prevention

Rubella has no specific treatment. Droplet precautions for 7 days after the onset of the rash are recommended. Postexposure passive immunization with IVIG may be of benefit if given within 5 days of exposure (Young, 2015).

When rubella infection is diagnosed in the mother, targeted sonographic examination is performed to evaluate for fetal structural anomalies described in the last section. Referral to and counseling by a maternal–fetal medicine specialist is warranted. If ultrasound findings suggest congenital infection or growth delay, diagnostic amniocentesis is recommended to detect rubella virus by PCR and to test for other congenital infections.

As prevention, MMR vaccine should be offered to nonpregnant women of childbearing age who lack evidence of immunity. Vaccination of all susceptible hospital personnel who might be exposed to patients with rubella or who might have contact with pregnant women is important. Rubella

vaccination is avoided 1 month before or during pregnancy because the vaccine contains attenuated live virus, although the fetal malformation risk is theoretical. MMR vaccination is not an indication for pregnancy termination. Prenatal serological screening for rubella is indicated for all pregnant women. Women found to be nonimmune are offered the MMR vaccine postpartum.

■ Parvovirus B19

This virus causes *erythema infectiosum* or *fifth disease*. It is a small, single-stranded DNA virus that replicates in rapidly proliferating cells such as erythroblast precursors. This can lead to anemia, which is its primary fetal effect. In individuals with increased red cell turnover, such as with sickle-cell disease, parvovirus infection may cause an aplastic crisis.

The primary mode of parvovirus transmission is respiratory secretions, although infection through blood transfusion or organ donation has been reported. Most infections occur in late winter to early spring. The maternal infection rate is highest in women with school-aged children and in day-care workers. Viremia develops 4 to 14 days after exposure, and a rash follows several days later. An otherwise immunocompetent individual is no longer infectious at the onset of the rash. By adulthood, only 40 percent of women are susceptible. The annual seroconversion rate is 1 to 2 percent, and the secondary attack rate approaches 50 percent.

Maternal Infection

In 20 to 30 percent of adults, infection is asymptomatic. In others, fever, headache, and flu-like symptoms may begin in the last few days of the viremic phase. Several days later, a bright red rash with erythroderma affects the face and gives a slapped-cheek appearance. The rash becomes lacelike and spreads to the trunk and extremities. Adults often have milder rashes and develop symmetrical polyarthralgia that may persist for several weeks. No evidence suggests that parvovirus infection is altered by pregnancy. With recovery, IgM antibody is generated 7 to 10 days postinfection, and production persists for 3 to 4 months. Several days after IgM is produced, IgG antibody is detectable and persists for life with natural immunity (American College of Obstetricians and Gynecologists, 2020a).

Fetal Infection

There is vertical transmission to the fetus in up to a third of maternal parvovirus infections (de Jong, 2011; Lamont, 2011). Fetal infection is associated with abortion, nonimmune hydrops, and stillbirth (Fig. 67-5). The fetal loss rate with serologically proven parvovirus infection is 8 to 17 percent before 20 weeks' gestation, and 2 to 6 percent after midpregnancy (American College of Obstetricians and Gynecologists, 2020a). Currently, no data support screening asymptomatic mothers or evaluating stillborn fetuses for parvovirus infection.

Fetal hydrops develops in approximately 4 percent of gravidas infected with parvovirus (Enders, 2004). Still, it is the most frequent infectious cause of nonimmune hydrops in autopsied fetuses (Rogers, 1999). Hydrops usually stems from infection in the first half of gestation. In one report, more than 80 percent of cases of fetal infection developed within 10 weeks of maternal infection. The mean interval was 6 to 7 weeks (Yaegashi, 2000). The critical period for maternal infection leading to fetal hydrops is estimated to be between 13 and 16 weeks' gestation, which coincides with the period in which fetal hepatic hemopoiesis is greatest (Chap. 7, p. 128).

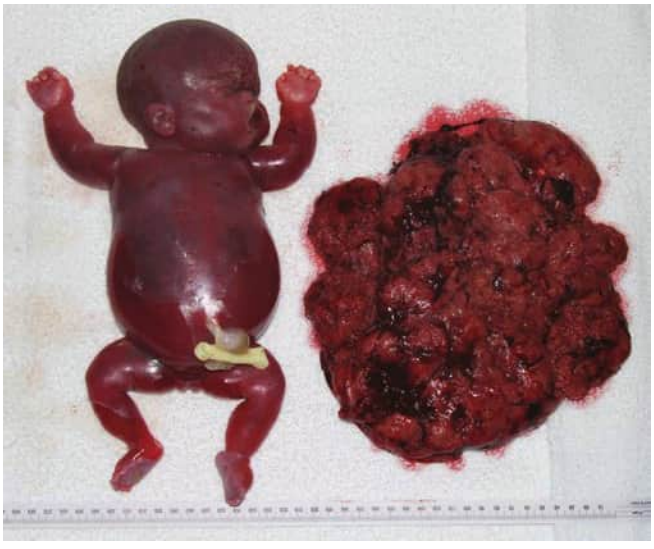


FIGURE 67-5 Stillborn, hydropic fetus and characteristically large placenta resulting from intrauterine parvovirus B19 infection. (Reproduced with permission from Dr. April Bleich.)

Diagnosis and Management

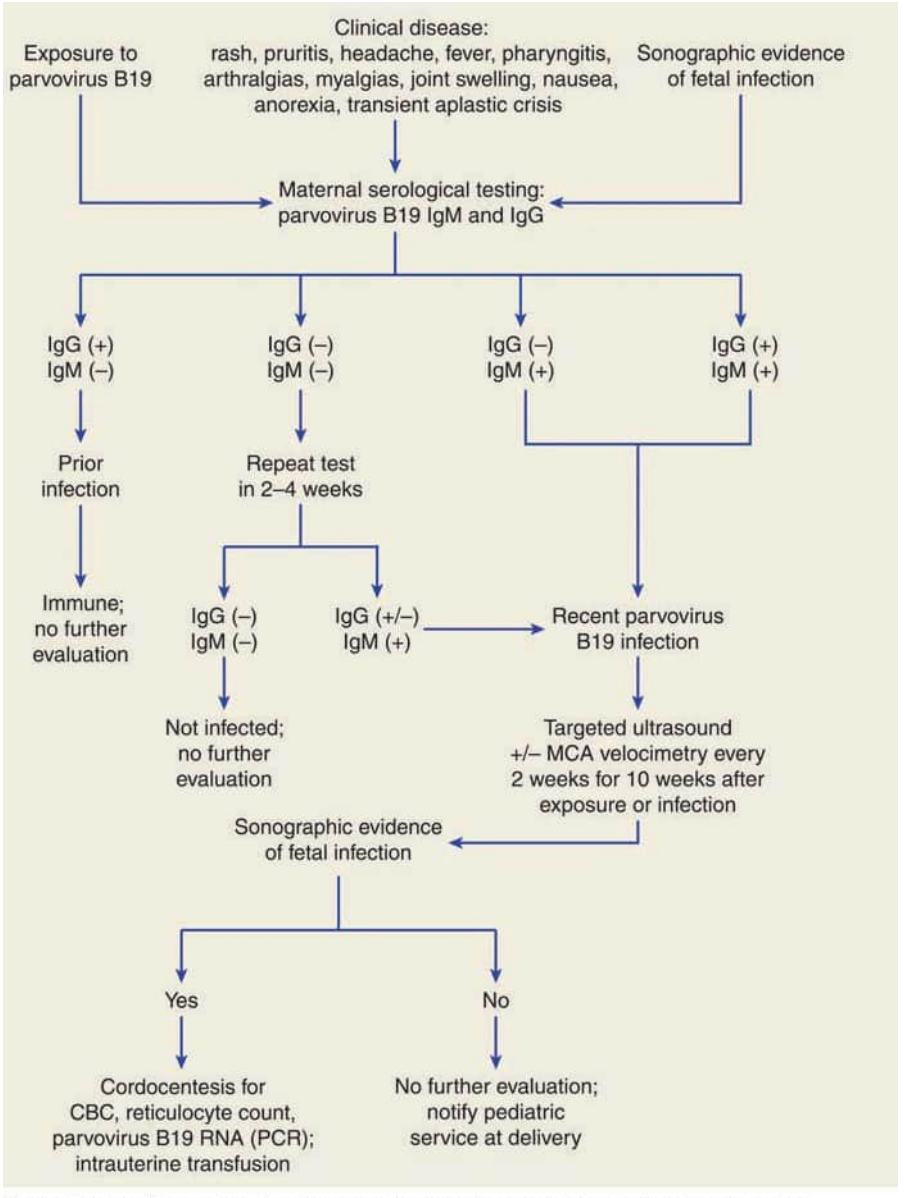
An algorithm for diagnosis of maternal parvoviral infection is illustrated in Figure 67-6. Diagnosis is generally made by maternal serological testing for specific IgG and IgM antibodies. Viral DNA may be detectable by PCR testing in maternal serum during the prodrome and persist for months to years after infection. Fetal infection is diagnosed by detection of B19 viral DNA in amnionic fluid (American College of Obstetricians and Gynecologists, 2020a). Fetal and maternal viral loads do not predict fetal morbidity and mortality (de Haan, 2007).

Most cases of parvovirus-associated hydrops develop in the first 10 weeks after infection. Thus, sonography should be performed every 2 weeks in women with recent infection. As discussed in Chapter 14 (p. 262), middle cerebral artery (MCA) Doppler interrogation is used to predict fetal anemia. MCA Doppler findings that suggest anemia may warrant fetal blood sampling followed by transfusion.

In hydropic fetuses without transfusion, mortality rates up to 30 percent have been reported. With transfusion, 94 percent of hydrops cases resolve within 6 to 12 weeks, and the overall mortality rate is <10 percent. Most fetuses require only one transfusion because hemopoiesis resumes as infection resolves.

Long-term Prognosis

Neurodevelopmental outcomes in fetuses transfused for B19 infection-induced anemia have varied. In one review of 24 transfused hydropic fetuses, abnormal neurodevelopment was noted in 5 of 16 survivors—32 percent—at 6 months to 8 years (Nagel, 2007). Outcomes were not related to severity of fetal anemia or acidemia, and these investigators hypothesized that the infection



[a]Hydrops fetalis, hepatomegaly, splenomegaly, placentomegaly, elevated MCA peak systolic velocity

FIGURE 67-6 Algorithm for evaluation and management of human parvovirus B19 infection in pregnancy. CBC = complete blood count; IgG = immunoglobulin G; IgM = immunoglobulin M; MCA = middle cerebral artery; PCR = polymerase chain reaction; RNA = ribonucleic acid.

itself induced cerebral damage. In another study of 28 children treated with intrauterine transfusion, 11 percent had neurodevelopmental impairment during evaluation at a median age of 5 years (de Jong, 2012). Conversely, Dembinski (2003) found no significant neurodevelopmental delay despite severe fetal anemia.

Prevention

Currently, no parvovirus vaccine is available, and no antiviral agent is recommended for prevention or treatment of maternal or fetal infection. Decisions to avoid higher-risk work settings are complex and require assessment of exposure risks. Pregnant women should be counseled that risks for infection approximate 5 percent for casual, infrequent contact; 20 percent for intense, prolonged work exposure such as for teachers; and 50 percent for close, frequent interaction such as in the home. Workers at day-care centers and schools need not avoid infected children because infectivity is greatest before clinical illness. Last, infected children do not require isolation.

Other Respiratory Viruses

More than 200 antigenically distinct respiratory viruses cause the common cold, pharyngitis, laryngitis, bronchitis, and pneumonia. The DNA-containing adenovirus is more likely to produce cough and lower respiratory tract involvement, including pneumonia. The RNA-containing rhinovirus, respiratory enterovirus, and nonpandemic common coronavirus usually produce a trivial illness characterized by rhinorrhea, sneezing, and congestion. An enterovirus named EV-D68 caused large outbreaks of respiratory illness in several countries and was linked to clusters of polio-like illness in children, known as *acute flaccid myelitis* (Sejvar, 2016).

The teratogenic risks of respiratory viruses are low. In one study, amnionic fluid viral PCR testing was done on samples from 1191 women undergoing amniocentesis for fetal karyotyping (Adams, 2012). Viral PCR was positive in 6.5 percent, and adenovirus was the virus most frequently identified. There was an association with fetal-growth restriction, nonimmune hydrops, foot/hand abnormalities, and neural-tube defects. Adenoviral infection is a known cause of childhood myocarditis and has been reported in cases of fetal myocarditis and nonimmune hydrops (Towbin, 1994).

Other Enteroviruses

Characterized by a clinical phenotype distinct from that of respiratory enteroviruses, these viruses are a major subgroup of RNA picornaviruses that include nonrespiratory enterovirus species, coxsackievirus, poliovirus, and echovirus. They are trophic for intestinal epithelium but can also cause widespread maternal, fetal, and neonatal infections that may include the CNS, skin, heart, and lungs. Most maternal infections are subclinical yet can be fatal to the fetus-neonate (Tassin, 2014). Hepatitis A is an enterovirus discussed in Chapter 58 (p. 1036).

Coxsackievirus infections with group A and B are usually asymptomatic. Symptomatic infections—usually with group B—include aseptic meningitis; polio-like illness; hand, foot, and mouth disease; rashes; respiratory disease; pleuritis; pericarditis;

and myocarditis. No treatment or vaccination is available (Cohen, 2018). Coxsackievirus may be transmitted by maternal secretions to the fetus at delivery in up to half of mothers who seroconverted during pregnancy (Modlin, 1988). Transplacental passage also has been reported, which may cause neonatal skin lesions, myocarditis, pneumonia, or encephalitis (Ornoy, 2006). Some have reported higher rates of cardiac anomalies and of low-birthweight, preterm, and growth-restricted newborns (Chen, 2010).

Polioviruses are highly contagious and cause subclinical or mild infections. The virus is trophic for the brain, and it can cause paralytic poliomyelitis (Cohen, 2018). Siegel (1955) demonstrated that pregnant women not only were more susceptible to polio but also had a higher death rate. Perinatal transmission has been observed, especially when maternal infection developed in the third trimester (Bates, 1955). Inactivated subcutaneous polio vaccine is recommended for susceptible pregnant women who must travel to endemic areas or are placed in other high-risk situations. Live oral polio vaccine has been used for mass vaccination during pregnancy without harmful fetal effects (Harjulehto, 1989).

■ Mosquito-borne Viruses

West Nile Virus

This mosquito-borne RNA flavivirus is a human neuropathogen. It is the most common cause of arthropod-borne disease in the United States (McDonald, 2019). West Nile viral infection is typically acquired through mosquito bites and is rarely transmitted through donated blood or organs. The incubation period is 2 to 14 days, and most persons have mild or no symptoms. Less than 1 percent of infected adults develop meningoencephalitis or acute flaccid paralysis. With these, presenting symptoms may include fever, mental status changes, muscle weakness, and coma (Stewart, 2013).

West Nile infection is diagnosed based on clinical symptoms and detection of viral IgG and IgM in serum and IgM in cerebrospinal fluid (Centers for Disease Control and Prevention, 2018). Management is supportive, and no effective antiviral treatment is available. The primary strategy for preventing exposure in pregnancy is use of insect repellant containing *N*,*N*-diethyl-*m*-toluamide (DEET), which is considered safe (Wylie, 2016). Avoiding outdoor activity and stagnant water and wearing protective clothing also are recommended.

Adverse effects of West Nile viremia on pregnancy are unclear. Animal data suggest that embryos are susceptible, and one case report of human fetal infection at 27 weeks' gestation described chorioretinitis and severe cerebral leukomalacia (Alpert, 2003; Julander, 2006). However, data from the West Nile Virus Pregnancy Registry show no increased risk for miscarriage, preterm birth, or major malformations (O'Leary, 2006; Pridjian, 2016). No evidence suggests that maternal West Nile virus infection is harmful to a breastfeeding infant.

Zika Virus

This RNA flavivirus is the first major mosquito-borne teratogen recognized (Rasmussen, 2016). Zika virus is primarily transmitted by mosquito bite, but sexual transmission is possible. The virus may be detected in body fluids for months following acute infection (Joguet, 2017; Paz-Bailey, 2017). It was first introduced to a nonimmune Brazilian population in 2014, but as of 2020, no countries had reported active Zika transmission.

Maternal-Fetal Infection. Zika infection is asymptomatic in approximately 80 percent of adults. It may cause mild rash, fever, headache, arthralgia, and conjunctivitis lasting a few days. The fetus can be severely infected whether or not the mother is symptomatic. In one report of 134 women with positive RT-PCR results, the fetal mortality rate was 7 percent (Brasil, 2016). Among live births with first-trimester exposure, the rate of fetal birth defects ranges from 5 to 15 percent (Reynolds, 2017). In the most severely affected fetuses, a *congenital Zika syndrome* has been described that includes microcephaly, lissencephaly, ventriculomegaly, intracranial calcifications, ocular abnormalities, and congenital contractures (Honein, 2017).

Diagnosis and Management. Zika virus is typically detectable in blood around the time of symptom onset and may persist days to months in pregnant women (Meaney-Delman, 2016). Serum IgM antibodies typically become detectable within the first 2 weeks and may persist for months. IgG antibodies develop shortly after IgM ones and confer long-lived immunity (Centers for Disease Control and Prevention, 2019).

Laboratory testing for Zika infection is recommended only in *symptomatic* gravidas with residence in or recent travel to areas with active dengue transmission and risk for Zika transmission (Centers for Disease Control and Prevention, 2019). For a pregnant woman within 12 weeks of symptom onset, PCR testing of serum and urine specimens for both dengue and Zika virus RNA is recommended. For women with prenatal ultrasound findings suggesting congenital Zika syndrome, Zika virus PCR and IgM are initially performed on serum and urine. Amnionic fluid PCR may be performed, although less is known about its diagnostic accuracy for congenital infection.

Currently, no specific treatment or vaccine is available for Zika infection, although several vaccines are in development (Shan, 2018). Prophylaxis includes protective netting, insect spray to control the vector mosquito, personal DEET spray use, and avoidance of sexual contact with partners recently exposed.

■ Ebola Virus

A member of the RNA Filoviridae family, the Ebola virus is transmitted by direct person-to-person contact (Kuhn, 2018). Infection produces a severe hemorrhagic fever with pronounced immunosuppression and disseminated intravascular coagulopathy. Treatment is supportive. Data are few concerning Ebola viral infection in gravidas (Money, 2015; Oduyebo, 2015). Henwood and associates (2017) described an approximate 50-percent risk of death among pregnant and nonpregnant women with Ebola virus disease, and universally poor fetal and neonatal outcomes. That said, no evidence suggests that pregnant women are more susceptible to Ebola virus infection. In survivors, persistent Ebola virus has been detected months after recovery in "sanctuary sites" such as the eyes and gonads.

A live-attenuated Ebola virus vaccine, rVSV-ZEBOV, was approved in 2019 in the United States for individuals studying or treating Ebola virus. Among 84 health-care workers

who inadvertently received vaccination in early pregnancy or who became pregnant soon after vaccination, pregnancy loss or congenital anomalies were not associated with the vaccine (Legardy-Williams, 2020).

BACTERIAL INFECTIONS

Group A Streptococcus

Streptococcus pyogenes is the most frequent bacterial cause of acute pharyngitis. In most cases, streptococcal pharyngitis, scarlet fever, and erysipelas are not life threatening. Treatment, usually with penicillin, is equivalent for pregnant and nonpregnant women. *S pyogenes* produces numerous toxins and enzymes responsible for its local and systemic toxicity. Pyrogenic exotoxin-producing strains are usually associated with severe disease (Wessels, 2018). In the United States, *S pyogenes* infrequently causes puerperal infection. Still, it remains the most common cause of severe maternal postpartum infection and death worldwide, and their incidence is rising (Hamilton, 2013; Wessels, 2018). Puerperal infections are discussed in detail in Chapter 37 (p. 649).

Group B Streptococcus

Streptococcus agalactiae colonizes the gastrointestinal and genitourinary tract in 10 to 25 percent of gravidas (Kwatra, 2016). Group B *Streptococcus* (GBS) is isolated in a transient, intermittent, or chronic fashion during pregnancy. Although the organism is more likely always present in these same women, its isolation is not always consistent.

Maternal and Perinatal Infection

Maternal and fetal GBS effects range from asymptomatic colonization to septicemia. *S agalactiae* can cause maternal bacteriuria, pyelonephritis, osteomyelitis, postpartum mastitis, and puerperal infections. GBS may also have the ability to overcome normally protective cervical mucus barriers during pregnancy to cause ascending antenatal infection (Vornhagen, 2018). As such, GBS has also been implicated in preterm labor, prelabor rupture of membranes, chorioamnionitis, fetal infections, and stillbirth (Randis, 2014; Seale, 2017).

Among newborns in the United States, GBS remains the leading infectious cause of morbidity and mortality (Nanduri, 2019). Infection <7 days after birth is defined as *early-onset disease*, although many investigators recognize a threshold of <72 hours of life as most compatible with intrapartum acquisition of disease (Stoll, 2011). Tudela and associates (2012) reported that newborns with early-onset GBS infection often had clinical evidence of fetal infection during labor or at delivery.

In many neonates, septicemia involves signs of serious illness that usually develop within 6 to 12 hours of birth. These include respiratory distress, apnea, and hypotension. At the outset, therefore, neonatal infection must be differentiated from respiratory distress syndrome caused by insufficient surfactant production (Chap. 34, p. 615). The mortality rate with early-onset disease has declined to approximately 4 percent, and preterm newborns are disparately affected.

Late-onset disease caused by GBS is noted in 0.28 per 1000 live births and usually manifests as meningitis 1 week to 3 months after birth (Centers for Disease Control and Prevention, 2020a). The mortality rate, although appreciable, is lower for late-onset meningitis than for early-onset sepsis. Unfortunately, it is not uncommon for surviving infants of both early- and late-onset disease to exhibit devastating neurological sequelae.

Prophylaxis for Perinatal Infections

Maternal intrapartum antibiotic administration is the main prevention of early-onset GBS disease. In the United States, rates of early-onset neonatal sepsis decreased from 3 cases per 1000 live births in the early 1990s to 0.25 cases in the years following widespread prophylaxis (Centers for Disease Control and Prevention, 2020a). Both culture- and risk-based criteria to identify candidates for intrapartum prophylaxis have been proposed and debated (Table 67-2) (Braye, 2019; Hughes, 2017).

TABLE 67-2. Indications for Intrapartum Group B Streptococcal Infection Prophylaxis[a]

Intrapartum Prophylaxis Indicated	Intrapartum Prophylaxis Not Indicated
GBS bacteriuria	Negative vaginal–rectal culture obtained at ≥36 weeks' gestation during current pregnancy
Previous infant with invasive GBS disease	Cesarean delivery before labor onset or membrane rupture, regardless of GBS status or gestational age
Positive GBS screening culture during current pregnancy (unless cesarean delivery is performed before labor onset and with intact membranes)	Negative vaginal–rectal GBS culture in late gestation during the current pregnancy, regardless of intrapartum risk factors
Unknown GBS status at labor onset and any of the following:	Unknown GBS status and intrapartum NAAT result negative and no intrapartum risk factors present
Birth at <$37^{0/7}$ weeks' gestation	
Membrane rupture ≥18 hr	
Intrapartum temperature ≥100.4° F (38.0°C)	
Intrapartum NAAT result positive for GBS	
Positive GBS status in prior pregnancy	

[a]Perform vaginal and rectal GBS culture at 36–38 weeks' gestation for all pregnant women, unless intrapartum antibiotic prophylaxis indicated for current pregnancy based on bacteriuria or prior infant with invasive GBS disease.
GBS = group B *Streptococcus*; NAAT = nucleic acid amplification test.

Culture-based Prevention. The American College of Obstetricians and Gynecologists (2020b) recommends universal vaginal-rectal culture screening for GBS at 36 to 38 weeks' gestation. This is followed by intrapartum antibiotic prophylaxis for women identified to be carriers. Selective enrichment of the vaginal-rectal culture to favor GBS growth and then subculture improves detection. GBS isolates can also be tested for inducible clindamycin resistance in women with reported penicillin allergy. Updated guidance also recommends consideration of antenatal maternal penicillin-allergy testing in GBS-colonized women at high risk for anaphylaxis or IgE-mediated hypersensitivity (American College of Obstetricians and Gynecologists, 2020b). In a recent surveillance study of neonates with early-onset sepsis, 53 percent of those diagnosed with GBS disease were born to mothers with negative antenatal screening results (Stoll, 2020).

In women with heavy colonization, GBS may be specifically identified in a routine prenatal urine culture obtained to exclude asymptomatic bacteriuria (ASB). Cultures with $\geq 10^5$ colony-forming units (cfu) should prompt treatment of ASB to reduce the risk of acute pyelonephritis in pregnancy. Values $<10^5$ do not require acute antepartum antibiotics for ASB. However, women are given GBS prophylaxis in labor (see Table 67-2). As a surrogate, we also consider a urine culture result that identifies gram-positive cocci, without further speciation, to be a presumptive positive result for GBS.

Risk-based Prevention. This approach is recommended for women in labor and whose GBS culture results are not known. It relies on risk factors associated with intrapartum GBS transmission. Intrapartum chemoprophylaxis is then given to candidates with criteria listed in Table 67-2.

At Parkland Hospital we use the risk-based approach for intrapartum prophylaxis. Additionally, all term neonates who were not given intrapartum prophylaxis are treated in the delivery room with aqueous penicillin G, 50,000 to 60,000 units intramuscularly. With this strategy, early-onset neonatal sepsis rates in our predominantly minority population decreased to levels similar to those reported by national surveillance data (Stafford, 2012; Wendel, 2002).

Nucleic Acid–based Testing. Approximately 20 percent of laboratories now offer PCR testing for maternal GBS screening (Fay, 2019). Additionally, a rapid point-of-care PCR test has been evaluated for intrapartum identification of maternal GBS (El Helali, 2019). One major limitation is cost, which is currently several times greater than that of culture-based techniques. A second is the inability to determine antibiotic sensitivities using current PCR techniques.

GBS Vaccine

Serotype-specific capsular antibody concentrations clinically correlate with reduced rates of GBS neonatal disease. However, vaccine development is challenged by the diversity of GBS serotypes. Another hurdle is the bacterium's ability to undergo serotype switching by altering its capsular polysaccharide (Dangor, 2016). No vaccines are clinically available at this time.

Intrapartum Antimicrobial Prophylaxis

Penicillin remains the first-line agent for prophylaxis, and ampicillin is an acceptable alternative (Table 67-3) (American College of Obstetricians and Gynecologists, 2020b). Women with a penicillin allergy and at low risk for anaphylaxis are given cefazolin (Briody, 2016). Those at high risk for anaphylaxis or other life-threatening reaction, such as Stevens-Johnson syndrome, should have antimicrobial susceptibility testing for erythromycin and clindamycin performed on GBS isolates. Clindamycin-sensitive but erythromycin-resistant isolates should undergo inducible clindamycin resistance testing. If clindamycin resistance is confirmed, vancomycin should be administered. *Erythromycin is no longer used for penicillin-allergic patients*.

Management of spontaneous preterm labor, threatened preterm delivery, or preterm prelabor rupture of membranes includes obtaining a GBS culture. Intrapartum chemoprophylaxis is initiated until the culture results. Women undergoing cesarean delivery before labor onset with intact membranes do not need GBS chemoprophylaxis, regardless of colonization status or gestational age.

TABLE 67-3. Regimens for Intrapartum Antimicrobial Prophylaxis for Perinatal GBS Disease

Regimen	Treatment[a]
Recommended	Penicillin G, 5 million units IV initial dose, then 2.5 to 3.0 million units IV every 4 hr
Alternative	Ampicillin, 2 g IV initial dose, then 1 g IV every 4 hr or 2 g every 6 hr
Penicillin allergic	
Patients not at high risk for anaphylaxis	Cefazolin, 2 g IV initial dose, then 1 g IV every 8 hr
Patients at high risk for anaphylaxis and with GBS resistant to clindamycin or susceptibility unknown	Vancomycin, 1 g IV every 12 hr *or* 20 mg/kg IV every 8 hr with a maximum of 2 g per single dose
Patients at high risk for anaphylaxis and with GBS susceptible to clindamycin	Clindamycin, 900 mg IV every 8 hr until delivery

[a]Following initial dose, subsequent doses are continued until delivery.
GBS = group B *Streptococcus*; IV = intravenous.
Data from the American College of Obstetricians and Gynecologists, 2020; Verani, 2010.

Methicillin-resistant *Staphylococcus Aureus* (MRSA)

Staphylococcus aureus is a pyogenic gram-positive organism and is considered the most virulent staphylococcal species. It primarily colonizes the nares, skin, genital tissues, and oropharynx. Although approximately 30 percent of adults carry *S aureus*, MRSA colonizes 2 percent of adults (Gorwitz, 2008). MRSA colonization is considered the greatest risk factor for subsequent infection (Marzec, 2016).

MRSA infection may be hospital- or community-acquired MRSA (CA-MRSA). CA-MRSA is diagnosed in an outpatient setting or within 48 hours of hospitalization in a person without health-care exposures in the past year. Exposures include prior hospitalization, dialysis or surgery, or indwelling catheters or devices (Dantes, 2013). In pregnant women, most cases are CA-MRSA, which disproportionately affects persons in lower socioeconomical strata (See, 2017).

MRSA and Pregnancy

Skin and soft tissue infections are the most common presentation of MRSA in pregnant women. Mastitis and breast abscesses have been reported in up to a fourth of MRSA cases in pregnancy (Laibl, 2005; Lee, 2010). Perineal or episiotomy abscess, abdominal surgical site infection, and rare placental abscess and chorioamnionitis have been associated with MRSA (Maeda, 2018; Pimentel, 2009). Last, osteomyelitis and spinal-epidural abscess have been topics of case reports (Tanamai, 2016; Vakili, 2017).

Vertical transmission of MRSA is rare. Postnatal colonization and infection in the newborn are associated with maternal and health-care worker colonization or infection near the time of delivery (Jimenez-Truque, 2012; Reich, 2016).

Management

Uncomplicated superficial infections are primarily managed by drainage and local wound care. Although historically de-emphasized, evidence suggests benefit from antibiotic therapy added to incision and drainage of smaller abscesses (Daum, 2017; Forcade, 2012). Severe superficial infections, especially those that fail to respond to local care or those in patients with medical comorbidities, are treated with MRSA-appropriate antibiotics. Purulent cellulitis should be treated empirically for MRSA until culture and sensitivity results are available.

Most CA-MRSA strains are sensitive to trimethoprim-sulfamethoxazole or clindamycin (Miller, 2015; Talan, 2016). Rifampin rapidly develops resistance and should not be used as monotherapy. Linezolid, although effective against MRSA, is expensive, and little information guides its use in pregnancy. Although effective for MRSA infections, doxycycline, minocycline, and other tetracyclines should not be used in pregnancy. Vancomycin remains a first-line therapy for inpatient treatment of serious MRSA infections.

The control and prevention of MRSA infection relies on appropriate hand hygiene and prevention of skin-to-skin contact. Routine screening of obstetrical patients for MRSA colonization is not recommended (American College of Obstetricians and Gynecologists, 2020c. That said, for women with culture-proven MRSA colonization or infection, we add a single dose of vancomycin to routine beta-lactam perioperative prophylaxis for cesarean deliveries and deep perineal lacerations. Decolonization is not effective in the general obstetrical population (Huang, 2019). Breastfeeding in women colonized with MRSA is not prohibited, but optimal hygiene and attention to minor skin breaks is encouraged.

Listeriosis

Listeria monocytogenes is a facultative intracellular gram-positive bacillus that causes 100 to 200 infections requiring hospitalization each year in the United States (Tack, 2020). Nearly all cases are thought to be foodborne. Outbreaks have been caused by contaminated dairy products, fruits and vegetables, and undercooked or processed meats and deli foods.

Invasive listerial infections are more common in pregnant women, immunocompromised patients, and the very old or young. For unclear reasons, infection during pregnancy is 10 to 20 times more common than in the general population (Craig, 2019). Although pregnancy losses linked to listeriosis are more likely to be reported, another hypothesis is that pregnant women are more susceptible because of decreased cell-mediated immunity (Baud, 2011).

Maternal and Fetal Infection

Infections with *Listeria* may result in noninvasive, febrile gastroenteritis, sepsis, or CNS infection after a 2- to 4-week incubation. Listeriosis during pregnancy may be asymptomatic or may cause a febrile illness that is confused with influenza, pyelonephritis, or meningitis. The diagnosis usually is not apparent until blood cultures are reported as positive. Occult or clinical infection also may stimulate labor. Transplacental bacterial invasion leads to fetal infection, which can result in stillbirth or clinical illness similar to early-onset GBS sepsis. A classic description of overwhelming fetal infection is that of disseminated microabscesses and granulomas known as *granulomatosis infantiseptica*. Chorioamnionitis is common, and placental macroabscesses may be seen. Late-onset neonatal infection can also follow exposure at delivery. In a review of 222 cases, infection with *Listeria* resulted in abortion or stillbirth in 20 percent, and neonatal sepsis developed in 68 percent of surviving newborns (Mylonakis, 2002). In one prospective cohort study, 24 percent of mothers experienced fetal loss, but none after 29 weeks' gestation (Charlier, 2017). However, a neonatal case fatality rate of 21 percent has been reported (Sapuan, 2017).

Treatment with ampicillin plus gentamicin is usually recommended because of its synergism against *Listeria* species (Rouse, 2016). Trimethoprim-sulfamethoxazole can be given to penicillin-allergic women. Maternal treatment in most cases is also effective for fetal infection. No vaccine is available. Prevention is by washing raw vegetables, cooking all raw food, and avoiding the implicated foods listed previously (American College of Obstetricians and Gynecologists, 2019d).

Salmonellosis

Infections from *Salmonella* species continue to be a major cause of foodborne illness. Six serotypes, including *Salmonella* subtypes *typhimurium* and *enteritidis*, account for most cases in the

United States. Nontyphoid *Salmonella* gastroenteritis is contracted through contaminated food. Symptoms that include nonbloody diarrhea, abdominal pain, fever, chills, nausea, and vomiting begin 6 to 48 hours after exposure. Diagnosis is made by stool studies (Chap. 57, p. 1018).

Treatment is with intravenous crystalloid solutions given for rehydration. Antimicrobials are not given in uncomplicated infections because they do not commonly shorten illness and may prolong the convalescent carrier state. If gastroenteritis is complicated by high fever or bacteremia, antimicrobials are given (Angelo, 2016). Rare case reports have linked *Salmonella enteritidis* bacteremia with septic abortion (Delcourt, 2019).

Typhoid fever caused by *Salmonella typhi* remains a global health problem. Infection is spread by oral ingestion of contaminated food, water, or milk. Although uncommon in the United States, an outbreak in Central America in 2017 involved almost 300 cases (Pan American Health Organization, 2018). Severe complications among patients requiring hospitalization include gastrointestinal bleeding—11 percent; intestinal perforation—9 percent; encephalopathy—8 percent; renal failure—6 percent; and cardiovascular collapse—7 percent (Bano-Zaidi, 2018). In pregnant women, the disease is more likely to be encountered during epidemics and in those with recent travel (Engsbro, 2019). Septic abortion is rare but reported (Jena, 2017).

Fluroquinolones and third-generation cephalosporins are the preferred empirical treatment for enteric (typhoid) fever and invasive nontyphoidal *Salmonella* infection (Shane, 2017). Antimicrobial susceptibility testing is important to tailor the course of therapy, which typically lasts 1 to 2 weeks. Two licensed vaccines for prevention of typhoid fever are available in the United States (Milligan, 2018). From limited evidence, typhoid vaccine administration to pregnant women before travel is not linked to adverse outcomes.

■ Shigellosis

Transmitted via the fecal–oral route, shigellosis is a common cause of diarrheal outbreaks in children attending day-care centers and in adults following international travel. Bacillary dysentery caused by *Shigella* species can range from mild diarrhea to severe dysentery with fever, bloody stools, abdominal cramping, and tenesmus. In immunosuppressed individuals, severe infection may lead to toxic megacolon, seizures or meningitis, or hemolytic uremic syndrome (Kotloff, 2018).

Although mild infection is typically self-limited, treatment of dehydration is essential. Antimotility drugs are avoided, and meticulous hygiene is recommended to avoid transmission. Antimicrobial therapy during pregnancy includes fluoroquinolones, ceftriaxone, or azithromycin. Resistance is rapidly emerging, and antibiotic susceptibility testing can help guide appropriate therapy (Centers for Disease Control and Prevention, 2020e). Shigellosis can stimulate uterine contractions and cause preterm birth (Parisot, 2016).

■ Lyme Disease

Caused by the spirochete *Borrelia burgdorferi*, Lyme disease is the most commonly reported vector-borne illness in the United States (Centers for Disease Control and Prevention, 2021g). Lyme borreliosis results from tick bites of the genus *Ixodes*. There are three stages (Steere, 2018). Early infection—stage 1—causes a distinctive local skin lesion, *erythema migrans*, which may be accompanied by a flu-like syndrome and regional adenopathy. If untreated, early disseminated infection—stage 2—follows in days to weeks. Multisystem involvement is frequent, but skin lesions, neuropathies, myalgia, carditis, and meningitis predominate. If still untreated after months, late or persistent infection—stage 3—manifests in perhaps half of patients as a migratory arthritis. Native immunity is acquired, and the disease enters a chronic phase in approximately 10 percent. Some patients remain asymptomatic, but others in the chronic phase develop various skin, joint, or neurological manifestations.

Clinical diagnosis is important because serological and PCR testing have many pitfalls (Steere, 2016). IgM and IgG serological testing is recommended in early infection and is followed by a second test—either a second immunoassay or western blot—for confirmation (Mead, 2019). Ideally, acute and convalescent serological evaluation is completed if possible, however, rates of false-positive and -negative results are high.

Treatment is recommended by the Infectious Diseases Society of America (Lantos, 2021). For erythema migrans, doxycycline for 10 days or amoxicillin or cefuroxime axetil for 14 days is recommended. However, doxycycline is usually avoided in pregnancy. Azithromycin for 7 days is a second-line regimen. For other manifestations, a 14- to 28-day oral or intravenous course of the same first-line drugs is recommended. No vaccine is commercially available. Avoiding areas with endemic Lyme disease and improving tick control in those areas is the most effective prevention. Self-examination with removal of unengorged ticks within 36 hours of attachment reduces infection risk. For tick bites recognized within 72 hours, a single 200-mg oral dose of doxycycline may reduce infection development (Lantos, 2021).

Several reports describe Lyme disease in pregnancy, although large series are lacking. Transplacental transmission has been confirmed, but no congenital effects of maternal borreliosis have been conclusively identified (Shapiro, 2014). Prompt treatment of early maternal infection should prevent most adverse pregnancy outcomes. In the northeast United States, between 2 and 40 percent of women with early Lyme disease may be co-infected with *Babesia microti*, which is another parasite transmitted by same tick. *Babesiosis* has been reported to cause congenital infection (Saetre, 2018).

■ Tuberculosis

Diagnosis and management of tuberculosis during pregnancy is discussed in Chapter 54 (p. 965).

PROTOZOAL INFECTIONS

■ Toxoplasmosis

The obligate intracellular parasite *Toxoplasma gondii* has a life cycle with two distinct stages (Kim, 2018). The *feline* stage takes place in cats—the definitive host—and their prey. Unsporulated oocysts are excreted in feces. In the *nonfeline* stage, tissue cysts containing bradyzoites or oocysts are ingested by

the intermediate host, including humans. Gastric acid digests the cysts to release bradyzoites, which infect small-intestinal epithelium. Here, they are transformed into rapidly dividing tachyzoites, which can infect all cells within the host mammal. Humoral and cell-mediated immune defenses eliminate most of these, but tissue cysts develop. Their lifelong persistence is the chronic form of toxoplasmosis.

Human infection is acquired by eating raw or undercooked meat infected with tissue cysts or by ingesting soil or water contaminated with oocysts from cat feces. Prior infection is confirmed by serological testing, and its prevalence depends on geographical locale and parasite genotype. The incidence of congenital toxoplasmosis in the United States has declined and now approximates 0.23 cases in 10,000 live births (Maldonado, 2017).

Maternal and Fetal Infection

Most acute maternal infections are subclinical and are detected only by prenatal or newborn serological screening. In some cases, maternal symptoms may include a flu-like illness with lymphadenopathy. In immunocompetent adults, initial infection confers immunity, and prepregnancy infection nearly eliminates any risk of vertical transmission. Infection in immunocompromised women, however, may be severe, and reactivation may cause encephalitis, chorioretinitis, or mass lesions.

Vertical transmission can cause fetal infection and then congenital toxoplasmosis. The latter is a fetopathy characterized by ocular or intracranial lesions and growth delay. Congenital toxoplasmosis is also associated with an increased risk for preterm delivery (Freeman, 2005).

The estimated rate of vertical transmission rises with gestational age. In one metaanalysis, the rate was 15 percent at 13 weeks, 44 percent at 26 weeks, and 71 percent at 36 weeks (SYROCOT Study Group, 2007). Although transmission risk is lower in early pregnancy, sequelae of congenital toxoplasmosis are more likely to be severe (American College of Obstetricians and Gynecologists, 2020a).

Notably, most infected fetuses are born without obvious toxoplasmosis stigmata. Clinically affected neonates usually have generalized disease expressed as low birthweight, hepatosplenomegaly, jaundice, and anemia. Some primarily have neurological disease with intracranial calcifications, hydrocephaly, or microcephaly (Dhombres, 2017). Many eventually develop chorioretinitis and exhibit learning disabilities. This classic triad—chorioretinitis, intracranial calcifications, and hydrocephalus—is often accompanied by convulsions. Infected neonates with clinical signs are at risk for long-term complications (Abdoli, 2014).

Screening and Diagnosis

With IgG antibody confirmed before pregnancy, there is no risk for fetal infection in immunocompetent hosts. The American College of Obstetricians and Gynecologists (2020a) does not recommend prenatal screening for toxoplasmosis in low-prevalence areas, including the United States. Screening IgG serology tests should be performed in immunocompromised gravidas, including those with HIV infection.

Pregnant women with suspected toxoplasmosis also should be tested. The parasite is rarely detected in tissue or body fluids. IgG antibodies against *Toxoplasma* develop within 2 to 3 weeks after infection, peak at 1 to 2 months, and usually persist for life—sometimes in high titers. Although IgM antibodies appear by 10 days after infection and usually become negative within 3 to 4 months, they may remain detectable for years. Thus, IgM antibodies are not used alone to diagnose acute toxoplasmosis. Best results are obtained with the Toxoplasma Serologic Profile performed at the Dr. Jack S. Remington Laboratory for Specialty Diagnostics (www.sutterhealth.org). Toxoplasma IgG avidity increases with time. Thus, if a high-avidity IgG result is found, infection in the preceding 3 to 5 months is excluded. Multiple tests are available that allow high-avidity results to confirm latent infection with a 100-percent positive predictive value (Villard, 2013).

Congenital toxoplasmosis is suspected when sonography reveals findings such as hydrocephaly, intracranial or hepatic calcifications, ascites, placental thickening, hyperechoic bowel, and growth restriction. These are similar to abnormalities that may be seen with congenital CMV. If these are found incidentally, diagnostic amniocentesis with PCR testing for toxoplasma as well as cytomegalovirus DNA is recommended, along with maternal serologic testing for both infections. The sensitivity of PCR for detection of toxoplasma DNA varies with gestational age and is lowest before 18 weeks' gestation (Filisetti, 2015; Yamamoto, 2017).

Management

Prenatal treatment of acute maternal toxoplasmosis is based on two regimens. Spiramycin may be given alone, or a pyrimethamine plus sulfonamide combination is taken with folinic acid (American College of Obstetricians and Gynecologists, 2020a). These two regimens have also been used consecutively. Most experts will use spiramycin in women with acute infection early in pregnancy to reduce the risk of vertical transmission. Because it does not cross the placenta, spiramycin may not be used to treat fetal infection. Pyrimethamine plus sulfadiazine with folinic acid is selected for maternal infection after 18 weeks' gestation or if fetal infection is suspected. The SYROCOT study group (2007) reviewed data from 1438 treated pregnancies and found weak evidence for early treatment to reduce congenital toxoplasmosis risks. Treatment has been associated with a reduced rate of serious neurological sequelae and neonatal demise (Cortina-Borja, 2010).

Prevention

No vaccine is available to prevent toxoplasmosis. Strategies to avoid infection include: (1) cooking meat to safe temperatures; (2) peeling or thoroughly washing fruits and vegetables; (3) cleaning all food preparation surfaces and utensils that have contacted raw meat or unwashed fruits and vegetables; (4) wearing gloves when changing cat litter or delegating this duty; and (5) avoiding feeding cats raw or undercooked meat and keeping cats indoors. Although these preventive steps are recommended, no robust data support their effectiveness (American College of Obstetricians and Gynecologists, 2020a; Di Mario, 2015).

■ Malaria

This protozoan infection remains a global health crisis. In 2018, it caused 260,000 deaths, and most occurred among children

younger than 5 years (World Health Organization, 2019). Sub-Saharan Africa and India carry the largest burden of cases. Malaria had been effectively eradicated in Europe and in most of North America, but some cases are imported in returning military personnel or recent immigrants from endemic areas (Mace, 2017). Transmitted by infected *Anopheles* mosquitoes, six species of *Plasmodium* cause human disease.

Pregnant women have increased susceptibility (Kourtis, 2014). After infection, antibodies to the parasite surface antigen VAR2CSA help mediate placental accumulation of infected erythrocytes and lead to the harmful effects of malaria (Mayor, 2015). Through this mechanism, some immunity accrues with parity and is termed *pregnancy-specific antimalarial immunity*. Ironically, malaria treatment dampens this immunity.

Maternal and Fetal Infection

Clinical manifestations are fever, chills, and flu-like symptoms, which may occur episodically. Symptoms are less severe with recurrences. Malaria may be associated with anemia and jaundice, and infections with *Plasmodium falciparum* may cause kidney failure, coma, and death. That said, many otherwise healthy but infected adults in endemic areas are asymptomatic because of partial immunity. Pregnant women, although often asymptomatic, are said to be more likely to develop traditional symptoms.

Malarial infections in pregnancy—either symptomatic or asymptomatic—are associated with higher rates of perinatal morbidity and mortality (Rogerson, 2018). Adverse outcomes include stillbirth, preterm birth, low birthweight, and maternal anemia. These correlate with high levels of placental parasitemia. The maternal anemia and low birthweight are documented most frequently (Machado Filho, 2014; McClure, 2013). Approximately 16 percent of low-birthweight neonates born to women in Africa are attributable to maternal malaria infection (World Health Organization, 2019). Effects stem from parasitized erythrocytes, monocytes, and macrophages that accumulate in the vascular areas of the placenta (Fig. 67-7). Infections with *P falciparum* are the worst, and early infection raises the risk for abortion. The incidence of malaria increases significantly in the latter two trimesters and postpartum (Diagne, 2000). Despite this, congenital malaria develops in <5 percent of neonates born to infected mothers.

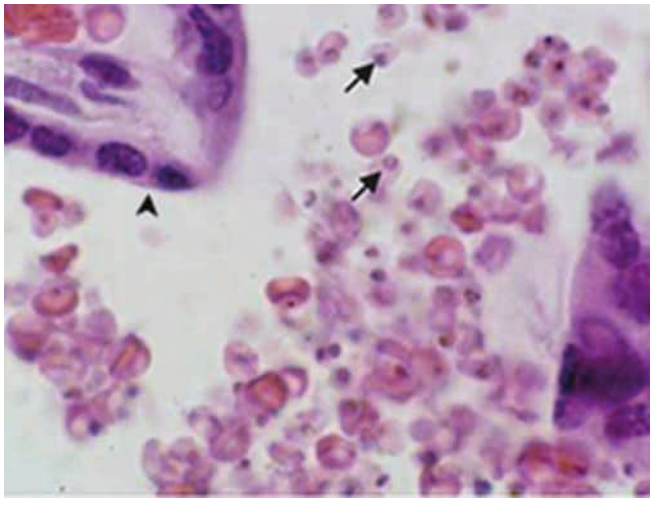


FIGURE 67-7 Photomicrograph of placental malaria. Multiple infected erythrocytes are seen, and two are identified (*arrows*). Cross section of nearby chorionic villus is shown (*arrowhead*).

Diagnosis and Management

Identification of parasites by microscopic evaluation of a blood smear remains the diagnostic gold standard. In women with low parasite densities, however, the sensitivity of microscopy is poor. Malaria-specific antigens are now being used for rapid testing, which has become the diagnostic standard (Cunningham, 2019).

For treatment, the most frequently used antimalarial drugs are not contraindicated in pregnancy. The World Health Organization recommends that all infected patients living in or traveling from endemic areas be treated with an artemisinin-based regimen for uncomplicated falciparum malaria (Tarning, 2016). The CDC (2020c) recommends that initial treatment be determined by where the infection was acquired.

Pregnant women diagnosed with uncomplicated malaria caused by *P vivax*, *P malariae*, *P ovale*, and chloroquine-sensitive *P falciparum* should be treated with hydroxychloroquine or chloroquine (Centers for Disease Control and Prevention, 2020c). For women infected with multidrug-resistant *P falciparum*, the first-line agent for gravidas in the second and third trimesters is a drug containing both artemether and lumefantrine. The PREGACT Study Group (2016) compared four artemisinin-based drugs in 3428 pregnant women with falciparum malaria and reported no serious maternal or perinatal adverse effects. Chloroquine-resistant *P vivax* should be treated with mefloquine. Chloroquine-sensitive *P vivax* or *P ovale* should be treated with chloroquine throughout pregnancy and then primaquine postpartum. Resistance to all the antimalarial drugs has been reported, including the recently added artemisinin-based compounds.

Treatment regimens for uncomplicated and severe malarial infections in pregnancy are detailed at: www.cdc.gov/malaria/diagnosis_treatment. The CDC also maintains a malaria hotline for treatment recommendations (855-856-4713).

Prevention and Chemoprophylaxis

Malaria control and prevention relies on chemoprophylaxis when traveling to or living in endemic areas. Vector control also is important. Insecticide-treated netting, pyrethroid insecticides, and DEET-based insect repellent lower malarial rates in endemic areas. These are well tolerated in pregnancy. If travel is necessary, chemoprophylaxis is recommended.

Chloroquine or hydroxychloroquine prophylaxis is safe and well tolerated in pregnancy. One evaluation compared prophylaxis during pregnancy with either sulfadoxine-pyrimethamine or dihydroartemisinin-piperaquine and found the latter to be more effective in preventing placental infection (Kakuru, 2016). Atovaquone/proguanil use is approved for gravidas, however, primaquine and doxycycline are contraindicated (Briggs, 2022). The latest chemoprophylaxis regimens for pregnancy can be obtained from the CDC *Travelers' Health* website at: www.cdc.gov/malaria/travelers/. The CDC also publishes *Health Information for International Travel* (The Yellow Book) at: www.cdc.gov/yellowbook. For women living in endemic areas, intermittent preventive treatment with sulfadoxine-pyrimethamine

is superior to intermittent screening plus indicated treatment, although resistance is a growing concern (Desai, 2018).

Amebiasis

Approximately 10 percent of the world population is infected with *Entamoeba histolytica*, and most are asymptomatic (Andrade, 2018). Amebic dysentery, however, may take a fulminant course during pregnancy. Symptoms are fever, abdominal pain, and bloody stools. Prognosis is worse if complicated by a hepatic abscess. Identifying *E histolytica* cysts or trophozoites within a stool sample is diagnostic. Therapy is similar to that for nonpregnant woman. For amebic colitis and invasive disease, tinidazole may be preferred over metronidazole, (Gonzales, 2019).

MYCOTIC INFECTIONS

Disseminated fungal infection—usually pneumonitis—during pregnancy is uncommon with coccidiomycosis, blastomycosis, cryptococcosis, or histoplasmosis. Their identification and management are considered in Chapter 54 (p. 965). Vulvovaginal candidiasis is described in Chapter 68 (p. 1218).

TRAVEL PRECAUTIONS DURING PREGNANCY

Pregnant travelers face general medical, obstetrical, and potentially hazardous destination risks. Several sources provide travel information (Freedman, 2016). The International Federation for Tropical Medicine has comprehensive information available at www.iftm-hp.org, and the International Society of Travel Medicine publishes information at www.istm.org. Also, *The Yellow Book* from the CDC has extensive travel information regarding pregnancy and breastfeeding.

BIOTERRORISM

The concept of bioterrorism involves the deliberate release of bacteria, viruses, or other infectious agents to cause illness or death. These natural agents are often altered to raise their infectivity or their resistance to medical therapy. Health-care providers should be alert for significant increases in the number of persons with febrile illnesses accompanied by respiratory symptoms or with rashes not easily associated with common illnesses. Clinicians are urged to contact their state health department or the CDC for current information and recommendations. In their Committee Opinion, the American College of Obstetricians and Gynecologists (2019b) has addressed disaster preparedness for obstetricians.

Smallpox

The variola virus causes smallpox and is considered a serious weapon. The virus is highly transmissible and carries an overall 30-percent case fatality rate. The last case of smallpox in the United States was reported in 1949, and worldwide it was reported in Somalia in 1977. Nishiura (2006) has reviewed the severe perinatal and maternal morbidity and mortality caused by smallpox. The case fatality rate of smallpox is 61 percent if the pregnant woman is unvaccinated. Rates of stillbirth, abortion, preterm delivery, and neonatal demise rise significantly in pregnancies complicated by this infection. The smallpox vaccine is made with live virus. Thus, pregnancy should be delayed for 4 weeks after vaccination.

Anthrax

Bacillus anthracis is a gram-positive, spore-forming, aerobic bacterium. It can cause three main types of clinical anthrax: inhalational, cutaneous, and gastrointestinal (Centers for Disease Control and Prevention, 2020b). Anthrax meningitis may accompany any of the clinical anthrax forms and is fatal in most cases. When inhaled, anthrax spores are deposited in the alveoli. They are engulfed by macrophages and germinate in mediastinal lymph nodes. The incubational period is usually less than 1 week but may be as long as 2 months. Within 1 to 5 days of symptom onset, the second stage is heralded by the abrupt onset of severe respiratory distress and high fevers. Mediastinitis and hemorrhagic thoracic lymphadenitis are common. Chest radiographs show a widened mediastinum. Case-fatality rates with inhalational anthrax are high, even with aggressive antibiotic and supportive therapy.

Other Bioterrorism Agents

Other category A bioterrorism agents include *Francisella tularensis*—tularemia, *Clostridium botulinum*—botulism, *Yersinia pestis*—plague, and Ebola, Marburg, Lassa, or Machupo viruses—hemorrhagic fever. The guidelines for these biological agents are evolving and are detailed at the CDC Bioterrorism website: emergency.cdc.gov/bioterrorism.

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CHAPTER 68

Sexually Transmitted Infections

Sexually transmitted infections (STIs) include syphilis, gonorrhea, chlamydial and trichomonal infections, and infections caused by human immunodeficiency virus (HIV), herpes simplex virus (HSV), human papillomavirus (HPV), and hepatitis B and C viruses. In describing their pathogenesis, *horizontal transmission* is transfer to a contemporary. Instead, *vertical transmission* refers to passage of an infectious agent from the mother to her fetus through the placenta, during labor or delivery, or by breastfeeding. Many STIs can harm the mother or fetus. Thus, these are sought through both asymptomatic screening and symptomatic diagnostic testing and then treated. For this, the Centers for Disease Control and Prevention (CDC) provides guidelines, which are described throughout this chapter.

For STI screening and diagnosis, *serological testing* is recommended in some cases and identifies antibodies formed by the patient against the pathogen. In others, *direct detection* of an infectious agent by culture or by a nucleic acid amplification test (NAAT) of body fluids or lesions is suitable. NAATs include any molecular method used to detect the presence of DNA or RNA of a pathogen. NAATs may be polymerase chain reaction (PCR) tests (most common), transcription-mediated amplification (TMA) tests, or others. NAATs may be qualitative (detecting presence or absence only) or quantitative depending on the specific test. The terms NAAT and PCR may be used interchangeably in some cases when appropriate.

If one STI is identified, patients are offered screening for all STIs, because these infections are commonly comorbid. Treatment of most STIs is associated with improved pregnancy outcome and prevention of perinatal morbidity. Logically, education, screening, treatment, and prevention are essential components of prenatal care.

SYPHILIS

This infection remains a major threat for both mother and fetus. Since 2001, the combined rate of primary and secondary syphilis has risen almost yearly, and among women in 2019, the rate was 4 cases per 100,000 persons (Centers for Disease Control and Prevention, 2021b). For congenital syphilis, the rate in 2019 was 48 cases per 100,000 live births. This is a nearly 300 percent rise since 2015. Of risks, higher congenital syphilis rates are linked to inadequate prenatal care, substance use during pregnancy, African American race, and lack of screening and treatment (Smullin, 2021). The CDC also includes sex work, multiple or new sexual partners, incarceration, or homelessness (Workowski, 2021). Syphilis remains a significant global health problem (Korenromp, 2019).

Pathogenesis

Syphilis is caused by the spirochetal bacterium *Treponema pallidum.* With horizontal transmission, minute abrasions on the vaginal mucosa provide entry, and cervical eversion, hyperemia, and friability raise this risk. Spirochetes replicate and

disseminate through lymphatic channels and then hematogenously if untreated.

During vertical transmission, spirochetes readily cross the placenta. This is the most common route, but neonatal infection may result from contact with spirochetes from lesions at delivery or across the placental membranes. Fetal infection develops in >50 percent of untreated early maternal syphilis cases and in up to 10 percent of late latent disease (Fiumara, 1975; Hollier, 2001).

Clinical Manifestations

Maternal Syphilis and Definitions

This is staged according to clinical features and disease duration.

- *Primary syphilis* is diagnosed by its characteristic chancre, which develops at the inoculation site. Typically, a solitary, painless lesion has a raised, firm border and a red, smooth ulcerated base without significant pus (Fig. 68-1). Nonsuppurative lymphadenopathy may develop. A chancre usually resolves spontaneously in 2 to 8 weeks, even if untreated. Multiple lesions, if found, are predominantly in women with HIV co-infection.
- *Secondary syphilis* stems from spirochete dissemination to multiple organ systems. Manifestations develop 4 to 10 weeks after the chancre appears and include dermatological abnormalities in up to 90 percent. A diffuse macular rash, plantar and palmar circular lesions, patchy alopecia, and mucous patches may be seen (Fig. 68-2). *Condylomata lata* are flesh-colored flat nodules found on the perineum and perianus. Mucosal lesions teem with spirochetes and are highly infectious. Women may have constitutional symptoms such as fever, headache, and myalgias. Hepatitis, nephropathy, ocular changes, anterior uveitis, and periostitis are less common findings. Manifestations of secondary syphilis resolve without treatment after 1 to 6 months, despite incomplete clearance of organisms by the immune system.
- With *latent syphilis*, clinical manifestations of primary or secondary syphilis either have resolved or were never recognized, but infection persists and is identified by serological testing. *Early latent syphilis* is subclinical disease acquired within the preceding 12 months. Timing of infection is determined by laboratory seroconversion results, clearly described symptoms consistent with primary or secondary syphilis within the prior 12 months, or exposure to a sexual partner in the previous 12 months with primary, secondary, or early latent syphilis. If the duration of infection is either unclear or beyond 12 months, the term is *latent syphilis, unknown duration or late*.
- *Tertiary syphilis* is a slowly progressive disease that affects any organ system but is rarely seen in reproductive-aged women.

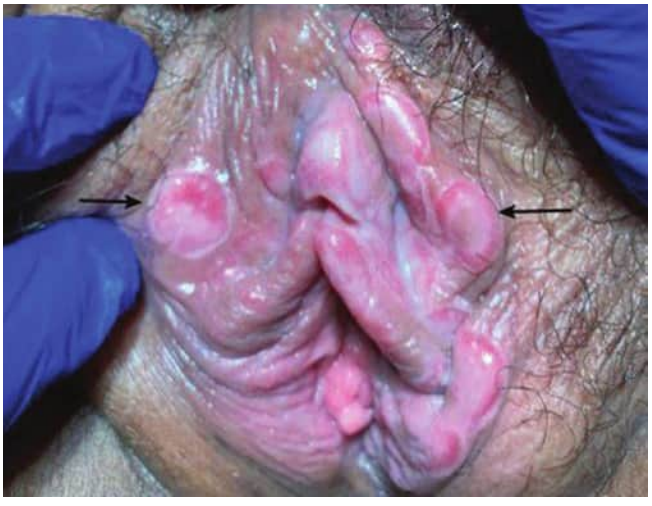

FIGURE 68-1 Primary syphilis. Chancres show a raised, firm border and smooth base and may be singular or multiple, as seen here. Arrows point to two reciprocal or "kissing" lesions, which develop as infection on one side spreads to the other when tissues are apposed. (Reproduced with permission from Dr. Allison J. Tracy, MD.)

Early-stage syphilis includes primary, secondary, and early latent syphilis. These are associated with high spirochete loads, and partner transmission rates range from 30 to 60 percent (Garnett, 1997; Singh, 1999). *Late-stage syphilis* includes latent syphilis, unknown duration or late and tertiary syphilis. In these, transmission rates decline because of smaller inoculum sizes.

Congenital Syphilis

Without screening and treatment, approximately 70 percent of infected women will have an adverse pregnancy outcome

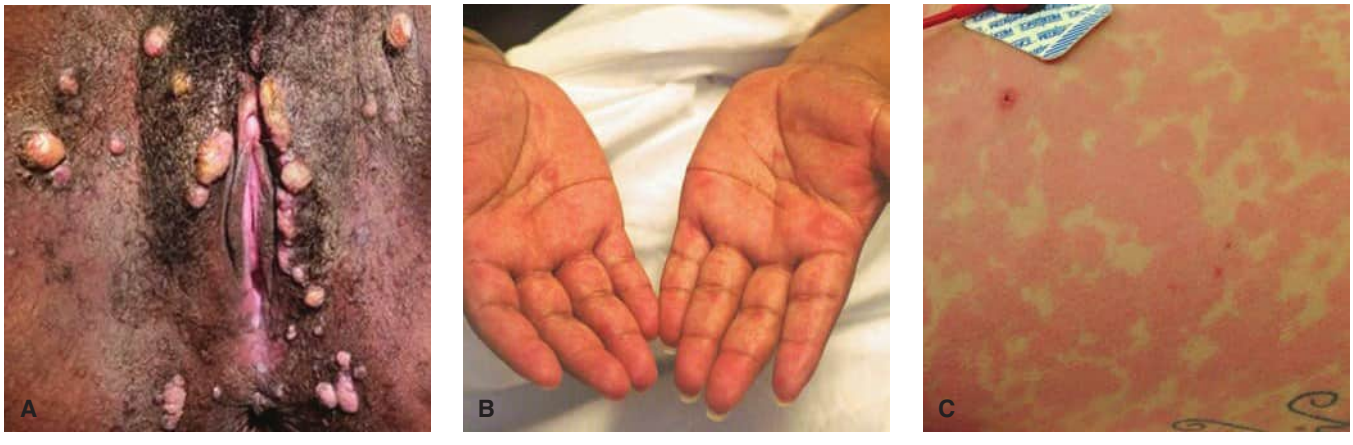

FIGURE 68-2 Secondary syphilis. **A.** Condyloma lata. (Reproduced with permission from Dr. Ralynn Brann.) **B.** Target lesions on the palms. **C.** Diffuse maculopapular rash.

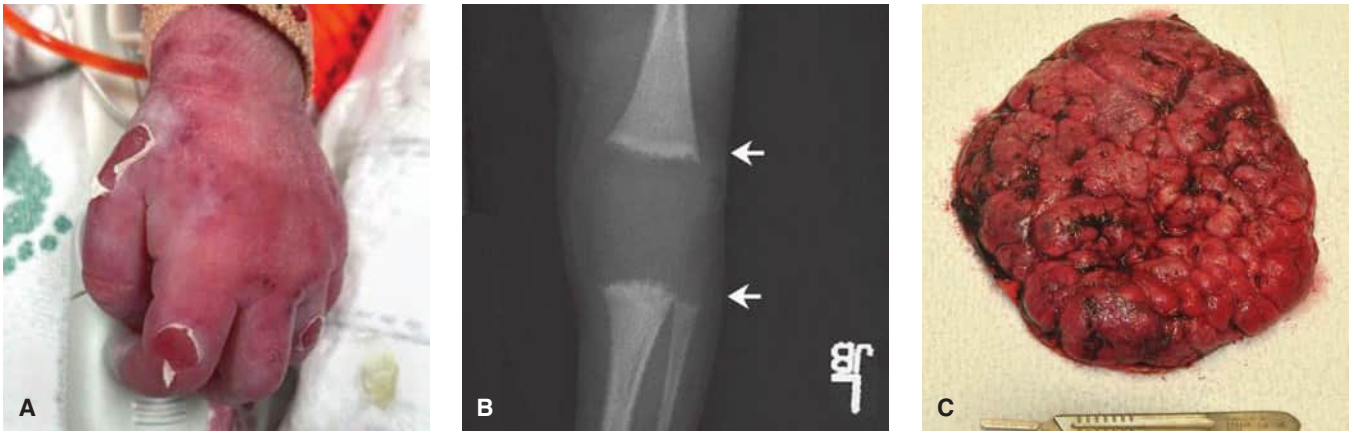

FIGURE 68-3 Congenital syphilis. **A.** A desquamating skin rash known as *pemphigus syphiliticus* may be seen. **B.** Neonatal lower-extremity long-bone radiographs show a "moth-eaten" appearance (*arrows*). **C.** Enlarged hydropic placenta of a syphilis-infected pregnancy.

(Hawkes, 2011). Maternal infection can lead to congenital infection, preterm labor, low birthweight, and fetal or neonatal death (Qin, 2014). Because of its immune incompetence prior to mid-pregnancy, the fetus is less likely to manifest the immunological inflammatory response characteristic of congenital infection before this time (Silverstein, 1962). However, congenital infection is still presumed in all cases, and thus treatment is imperative.

When vertical transmission occurs, severe congenital syphilis progresses along a continuum. Hepatic abnormalities are followed by anemia, thrombocytopenia, and then ascites and hydrops. Stillbirth remains a major complication (Centers for Disease Control and Prevention, 2021b). The newborn may have jaundice with petechiae or purpuric skin lesions, lymphadenopathy, rhinitis, pneumonia, myocarditis, nephrosis, or long-bone involvement (Fig. 68-3).

With syphilitic infection, the placenta becomes large and pale. Microscopically, villi lose their characteristic arborization, and blood vessels diminish or are obliterated as a result of endarteritis and stromal cell proliferation. Sheffield and colleagues (2002c) described these villi in more than 60 percent of placentas from women with untreated syphilis at delivery. Examination of the umbilical cord may reveal necrotizing funisitis, and spirochetes may be microscopically seen after immunohistochemical staining (Adhikari, 2020).

Diagnosis

In their 2018 guidance, the United States Preventive Services Task Force (USPSTF) recommends screening for syphilis in all pregnant women to prevent congenital infection. Testing is performed at the first prenatal visit. In populations with a high prevalence of syphilis or in persons with the risk factors noted earlier, serological testing is repeated at 28 weeks' gestation and again at delivery (Workowski, 2021).

Treponema pallidum cannot be cultured from clinical specimens. However, direct diagnosis of early-stage disease can be completed by dark-field microscopic examination, NAAT, or immunostaining of lesion exudate, tissue, or body fluid. These methods are not widely available and are less sensitive for blood specimens (Pillay, 2018). In practice, a diagnosis is made with serological testing coupled with clinical findings.

Two types of serological tests are employed to diagnose and screen, and sequential use of both reduces false-positive diagnoses. If the first is positive, the second type is then performed. This combination identifies infection but by itself does not determine disease stage. Instead, disease stage is assigned based on initial serological titer levels, patient history of potential exposures and prior treatment, and clinical-stage definitions, described earlier.

Traditionally, the first type is *nontreponemal testing,* and either the Venereal Disease Research Laboratory (VDRL) or the rapid plasma reagin (RPR) is selected. Both tests measure patient immunoglobulin M and G (IgM and IgG) antibodies formed against cardiolipin that is released from damaged host cells and possibly also from treponemes. Notably, these same antibodies can also be produced in response to other acute events that include recent vaccination, febrile illness, and pregnancy itself. They can be produced in response to chronic conditions such as intravenous (IV) drug abuse, systemic lupus erythematosus, aging, leprosy, or cancer. As such, these all serve as potential sources of false-positive results (Larsen, 1995). Conversely, early infection may be characterized by very high levels of antibody or antigen, which prevent immune complex formation and lead to false-negative test results. This is the prozone effect. Alternatively, seroconversion occurs at around the third week of infection but can take up to 6 weeks (Peeling, 2004). Thus, women with very early primary syphilis can have initially false-negative serological test results.

With positive nontreponemal test results, findings are quantified and expressed as titers. Because titers reflect disease activity, they rise during early syphilis and often exceed levels of 1:32 in secondary syphilis. A nontreponemal titer is usually measured on the day of treatment initiation. Subsequent titer declines are considered relative to this day-of-treatment titer.

The second type of serological test is used to confirm the presence of *T pallidum*–specific antibodies. These tests include fluorescent treponemal-antibody absorption tests (FTA-ABS), *T pallidum* passive particle agglutination (TP-PA) tests, and various immunoassays (Association of Public Health Laboratories, 2020). *Of note, these treponemal-specific tests generally remain positive throughout life, even after treatment.* Antibodies may be detected by treponemal assays up to a few weeks earlier than those detected by nontreponemal tests (Levett, 2015).

TABLE 68-1. Interpretation of Serologic Tests Using Reverse Sequence Syphilis Screening

Treponemal Test	VDRL or RPR	TP-PA	Possible Interpretations
Nonreactive[a]			1. Absence of syphilis 2. Very early syphilis before seroconversion
Reactive[b]	Nonreactive	Reactive	1. Prior treated syphilis[c]
		Reactive	2. Untreated syphilis[c]
		Nonreactive	3. False-positive treponemal test[d]
Reactive	Reactive		1. Active syphilis[c] 2. Recently treated syphilis with nontreponemal titers that have not yet become nonreactive[c] 3. Treated syphilis with persistent titers (serofast)[e]
Nonreactive[a]	Reactive		1. False-positive nontreponemal test

[a]No further testing performed if the initial treponemal test is negative and if there is no clinical suspicion for early syphilis.
[b]Verified using a second, different treponemal test (TP-PA) if the nontreponemal test is nonreactive.
[c]If prior treatment received, verify treatment adequacy for clinical stage and assess for reexposure. If inadequate, unverified, or no treatment received, perform full clinical staging evaluation and begin treatment course.
[d]May be seen in pregnancy or among immigrants with previous exposure to endemic treponematoses.
[e]Successful treatment is usually considered verification of adequate treatment with a fourfold decline in titers (e.g., from 1:32 to 1:8).
RPR = rapid plasma reagin; TP-PA = *T pallidum* particle agglutination assay; VDRL = Venereal Disease Research Laboratory.
From Centers for Disease Control and Prevention, 2011.

Traditionally, nontreponemal tests are used first for screening, and results are then confirmed by a treponemal-specific test. In a newer *reverse sequence* strategy, screening begins *first* with a treponemal-specific test. Each of the serological tests has limitations, including false-positive and -negative results. Management of discordant finding with this latter sequence is shown in Table 68-1. Notably, both approaches are suitable if a screening, follow-up, and treatment program is in place.

In contrast to these laboratory tests, rapid "point-of-care" (POC) syphilis screening of blood or serum samples is available. Most tests are treponemal-specific, and positive POC results can then be confirmed by laboratory-based tests. In hard-to-reach populations, immediate treatment of women with positive POC results is associated with lower rates of stillbirth, neonatal death, and congenital syphilis (Brandenburger, 2021). This practice, however, risks overtreating previously cured women who still have residual persistent treponemal antibodies. This limitation may be overcome by newer POC dual tests, which simultaneously assess nontreponemal and treponemal antibodies (Satyaputra, 2021).

Following maternal diagnosis, sonographic evaluation is performed for fetuses >20 weeks' gestation to search for signs of congenital syphilis. Rac and associates (2014) noted that 31 percent of infected women diagnosed at ≥18 weeks' gestation had fetuses with abnormal sonographic findings. Hepatomegaly, placental thickening, hydramnios, ascites, hydrops fetalis, and elevated middle cerebral artery Doppler velocimetry measurements suggest fetal infection. Before 20 weeks, treatment is highly successful, and abnormal sonographic findings are rare (Nathan, 1997).

With maternal infection and with a fetus of viable age that shows sonographic findings, antepartum fetal heart rate (FHR) monitoring prior to antibiotic treatment is recommended. If the FHR tracing is reassuring, antibiotic therapy can proceed. In contrast, spontaneous late decelerations or a nonreactive FHR tracing likely reflects an extremely ill fetus that may poorly tolerate a Jarisch-Herxheimer reaction, described subsequently. In this extreme case, consultation with a neonatologist regarding a plan of delaying treatment, pursuing delivery, and then treating in the nursery is a consideration (Wendel, 2002).

After antibiotic treatment, further sonographic surveillance or antenatal testing of fetal well-being is determined in consultation with specialists. Following adequate treatment, sonographic signs of congenital infection resolve over weeks to months, and delivery is reserved for usual obstetrical indications (Rac, 2014). In fetuses *without* initial signs of congenital syphilis, subsequent sonographic evaluations are reserved for other fetal indications.

Treatment

Syphilis therapy during pregnancy aims to eradicate maternal infection and to prevent or treat congenital syphilis. Parenteral penicillin G benzathine remains the preferred treatment for all stages of syphilis during pregnancy (Table 68-2). A second dose of benzathine penicillin G may be given 1 week after the initial dose in patients with early-stage syphilis or sonographic signs of congenital infection. This aims to reduce the risk of fetal treatment failure and is our current practice at Parkland Hospital. High maternal serological titers, preterm delivery, and delivery shortly after antepartum therapy are all risks for failure of maternal treatment to prevent neonatal infection (Sheffield, 2002b). Women should abstain from sexual contact for 7 days, until all skin/mucous membrane lesions heal, and until sexual partners are treated.

TABLE 68-2. Recommended Treatment for Pregnant Women with Syphilis

Category	Treatment
Early syphilis[a]	Benzathine penicillin G (Bicillin L-A)[b], 2.4 million units as a single intramuscular injection; some recommend a second dose 1 week later to help prevent congenital syphilis
>1-yr duration[c]	Benzathine penicillin G (Bicillin L-A)[b], 2.4 million units intramuscularly weekly for 3 doses[d]

[a]Primary, secondary, and early latent syphilis of less than 1-year duration.
[b]Bicillin C-R is not a suitable option.
[c]Latent syphilis of unknown or more than 1-year duration; tertiary syphilis. Missed doses are not acceptable for pregnant women, and those who miss any dose of therapy must repeat the full course of therapy.
[d]Optimal treatment interval is 7 days. If >9 days pass between doses, the entire treatment course is repeated.
Data from Workowski, 2021.

There are no proven alternatives to penicillin therapy during pregnancy. Some data support a 1-g daily IV dose of ceftriaxone for 10 days (Cao, 2017; Liang, 2016). Tetracyclines are effective but not recommended during pregnancy, because of the risk for offspring teeth discoloration.

Following treatment of syphilis before 24 weeks' gestation, nontreponemal tests are repeated in either the third trimester or no sooner than 8 weeks after treatment unless reinfection is suspected (Workowski, 2021). Following treatment after 24 weeks, nontreponemal titers may be repeated in the third trimester in some cases and are repeated at delivery. Adequate serological response to treatment is suggested by a fourfold decline in nontreponemal titer and resolution of any clinical symptoms. A fourfold decline in titer is more likely to occur following treatment of early-stage syphilis, which typically has high nontreponemal titers. Absence of a fourfold decline does not itself determine treatment failure, particularly when the initial nontreponemal titer is <1:8. Titers are best interpreted in conjunction with clinical history and by those experienced with treatment of syphilis in pregnancy. Because VDRL titers do not correspond directly to RPR titers, consistent use of the same test for surveillance is recommended.

Some successfully treated patients may still exhibit persistently low-level positive titers, which are referred to as "serofast." This state is more likely in older individuals, those with lower initial nontreponemal antibody titers, and those with later stages of syphilis (Seña, 2015).

In some instances, a woman may present without symptoms but describes recent sexual contact with a person who has been diagnosed with syphilis. She should be evaluated clinically and serologically. If their sexual contact occurred within the preceding 90 days, the gravida is treated presumptively for early syphilis, even if serological test results are negative. This accounts for early infection but before seroconversion. If contact was more than 90 days ago, treatment is based on serological results.

Penicillin Reactions

Women with a history of penicillin allergy should have either an oral stepwise penicillin-dose challenge or skin testing performed to confirm the risk of IgE-mediated anaphylaxis. If confirmed, penicillin desensitization is recommended and followed by benzathine penicillin G treatment (Table 68-3) (Wendel, 1985).

Distinct from allergy, the *Jarisch-Herxheimer reaction* can develop following penicillin treatment in most women with primary syphilis and approximately half with secondary infection. Uterine contractions, mild maternal temperature elevation, decreased fetal movement, and FHR decelerations are findings. Treatment is supportive with antipyretics as needed, hydration, and oxygen supplementation (Klein, 1990). In a study of 50 gravidas who received benzathine penicillin G for syphilis, the incidence of Jarisch-Herxheimer reactions was 40 percent (Myles, 1998). Of the 31 women monitored electronically, 42 percent developed regular uterine contractions, and 39 percent developed variable decelerations. All contractions resolved within 24 hours. Thus, for fetuses of viable gestational age,

TABLE 68-3. Penicillin Allergy—Oral Desensitization Protocol for Patients with a Positive Skin Test

Penicillin V Suspension Dose[a]	Amount[b] (units/mL)	mL	Units	Cumulative Dose (units)
1	1000	0.1	100	100
2	1000	0.2	200	300
3	1000	0.4	400	700
4	1000	0.8	800	1500
5	1000	1.6	1600	3100
6	1000	3.2	3200	6300
7	1000	6.4	6400	12,700
8	10,000	1.2	12,000	24,700
9	10,000	2.4	24,000	48,700
10	10,000	4.8	48,000	96,700
11	80,000	1.0	80,000	176,700
12	80,000	2.0	160,000	336,700
13	80,000	4.0	320,000	656,700
14	80,000	8.0	640,000	1,296,700

[a]Interval between doses: 15 minutes. Elapsed time: 3 hours and 45 minutes. Cumulative dose: 1.3 million units. Observation period: 30 minutes before parenteral administration of penicillin.
[b]The specific amount of drug was diluted in approximately 30 mL of water and administered orally.
Reproduced with permission from Wendel GD Jr, Stark BJ, Jamison RB, et al: Penicillin allergy and desensitization in serious infections during pregnancy. N Engl J Med 312:1229, 1985.

consideration is given to administering the first dose of antibiotic in labor and delivery to permit continuous fetal monitoring for at least 24 hours when the fetus has sonographic signs of syphilis (Adhikari, 2020; Wendel, 2002). With or without sonographic signs of fetal infection, patients are counseled on symptoms of the Jarisch-Herxheimer reaction prior to syphilis treatment and are encouraged to seek evaluation if they develop.

GONORRHEA

Infection Rates and Effects

Of reportable bacterial STIs, those caused by *Neisseria gonorrhoeae* are the second most common. The incidence in women in the United States has continued to rise since 2015, and the highest rates are in those aged 15 to 24 years (Centers for Disease Control and Prevention, 2021b). Among women giving birth in 2018, the rate was 310 cases per 100,000 live births (Gregory, 2020). In most gravidas, infection is limited to the cervix, urethra, and periurethral and greater vestibular (Bartholin) glands. Acute salpingitis is rare in pregnancy. However, pregnant women account for a disproportionate number of disseminated gonococcal infections (Bleich, 2012).

Gonococcal infection can have adverse effects in any trimester. In affected women, associated rates of preterm delivery, preterm prelabor ruptured membranes (PPROM), low birthweight, and perinatal mortality are slightly higher than in those without infection (Vallely, 2021). Miscarriage rates are not increased. However, untreated gonococcal cervicitis is associated with septic abortion and with uterine infection after surgical abortion (Burkman, 1976) (Chap. 11, p. 203).

Vertical transmission of gonorrhea mainly occurs through fetal contact with cervical infection during birth. The predominant sequela is *gonococcal ophthalmia neonatorum*, which can lead to corneal scarring, ocular perforation, and blindness. Transmission rates are high and approximate 40 percent (Laga, 1986). Outlined in Chapter 32 (p. 593), ocular prophylaxis is provided to all newborns (U.S. Preventive Services Task Force, 2019a).

Screening and Treatment

Pregnant women who live in high-prevalence areas or who are at risk for gonorrhea should undergo first-trimester screening. Risk factors include age ≤25 years, prior or current STI, sex work, a new or nonmonogamous partner, a partner with an STI, multiple sexual partners, and inconsistent condom use if not monogamous (Workowski, 2021). Gonococcal infection is a marker for concomitant chlamydial infection. Thus, if chlamydial testing is unavailable, presumptive chlamydial therapy is given to women treated for gonorrhea.

Screening for gonorrhea in women is by culture or NAAT. NAATs have replaced culture in most laboratories, and kits are available for specific collection from the vagina, endocervix, or urine. Of these, vaginal or cervical samples are preferred, as urine collection may detect up to 10 percent fewer infections (Papp, 2014). If used, the initial urine stream, not midstream, is collected. In women with vaginal symptoms and who practice anal intercourse, rectal screening can be considered. One study of nonpregnant women at urban STI clinics found that approximately 20 percent of rectal chlamydia and gonorrhea infections would be missed if only cervical, vaginal, or urine samples were obtained (Llata, 2018). NAATs are also suitable for diagnosis of rectal or pharyngeal disease (Food and Drug Administration, 2019).

An ultrarapid NAAT for gonorrhea and chlamydia has been approved by the Food and Drug Administration (FDA) for point-of-care use. It performs similarly to laboratory-based testing, and results are available in approximately 30 minutes (Food and Drug Administration, 2021; Van Der Pol, 2020). This test has not been rigorously studied in pregnant women but may reduce barriers to prompt treatment in patients with limited access to care.

Gonorrhea treatment continues to evolve due to the ability of *N gonorrhoeae* to develop antimicrobial resistance (Table 68-4) (St Cyr, 2020). In gravidas, if chlamydia has not been excluded, a 1-g oral dose of azithromycin is added. Patients abstain from intercourse for 7 days after they and their sexual partner(s) have completed treatment.

For those with pharyngeal infection, non-ceftriaxone-based regimens have higher failure rates. Thus, those with contraindications to ceftriaxone merit infectious disease specialist consultation. With pharyngeal infection, a test-of-cure 1 to 2 weeks after treatment is recommend. This is unnecessary after treatment of urogenital or rectal gonorrhea.

To exclude reinfection, repeat testing is recommended 3 months after treatment of any gonorrhea infection. For any

TABLE 68-4. Treatment of Gonorrhea in Pregnancy[a,b]

Regimen	Drug and Dosage
Preferred	Weight <150 kg (<300 lb): ceftriaxone, single 500-mg IM injection[c] Weight ≥150 kg (≥300 lb): ceftriaxone, two simultaneous 500-mg IM injections[c]
Alternative	Cefixime, 800-mg single oral dose Gentamicin, single 240-mg IM dose *plus* azithromycin, 2-g single oral dose

[a]If *Chlamydia trachomatis* co-infection not excluded, then a 1-g oral azithromycin dose is added to regimens not already including azithromycin.
[b]Retesting is recommended at 3 months to exclude reinfection.
[c]1 mL of 1% lidocaine may be added to reduce injection site pain.
IM = intramuscular.
Data from St Cyr, 2020.

woman treated for gonorrhea in the first trimester and for any uninfected woman who is at high risk for gonococcal infection, testing is repeated in the third trimester (American Academy of Pediatrics, 2017; Workowski, 2021).

Sexual contacts are treated. Expedited therapy, discussed with chlamydial infection, is a less-desirable option due to the now-preferred injectable regimen. If elected, a single, oral, 800-mg dose of cefixime is provided. If chlamydia is not excluded, oral doxycycline, 100 mg twice daily for 7 days, is added.

Disseminated Gonococcal Infections

Gonococcal bacteremia may cause disseminated infections that manifest as petechial or pustular skin lesions, arthralgias, or septic arthritis. Antimicrobial susceptibility testing is requested for isolates cultured from infection sites. For treatment, ceftriaxone, 1 g IV or intramuscularly, is given every 24 hours and continued for 24 to 48 hours after clinical improvement (Workowski, 2021). An oral agent that is selected based on susceptibility testing is then provided to complete 1 week of therapy. Prompt recognition and antimicrobial treatment will usually yield favorable outcomes in pregnancy (Bleich, 2012). Meningitis and endocarditis are rare in pregnancy, but they may be fatal. For gonococcal *endocarditis*, ceftriaxone 1 to 2 g IV every 12 hours should be continued for at least 4 weeks, and for *meningitis*, 10 to 14 days. In all these cases, a single, 1-g, oral dose of azithromycin is provided to treat potential chlamydial co-infection (Workowski, 2021).

CHLAMYDIAL INFECTION

Infection Rates and Effects

Chlamydia trachomatis is an obligate intracellular bacterium that attaches to columnar or transitional-cell epithelium to cause urogenital infection. It is the most common reportable STI in the United States. The chlamydial infection rate was 694 cases per 100,000 women in 2019, and the highest rate is in those aged 15 to 24 years (Centers for Disease Control and Prevention, 2021b). Among women giving birth in 2018, the rate was 1844 cases per 100,000 live births (Gregory, 2020). Most infected pregnant women are asymptomatic, but a third have urethral syndrome, urethritis, or greater vestibular (Bartholin) gland infection (Peipert, 2003). Mucopurulent cervicitis may result from chlamydial or gonococcal infection or both. Uncommon manifestations during pregnancy are endometritis, salpingitis, reactive arthritis, and Reiter syndrome.

The role of chlamydial infection in pregnancy complications remains controversial. It is disputed whether untreated cervical infection raises rates of preterm delivery, PPROM, low birthweight, or perinatal mortality (Andrews, 2000; Reekie, 2018; Silva, 2011). Chlamydial infection is not associated with a greater risk of chorioamnionitis or with peripartum pelvic infection (Berman, 1987; Gibbs, 1987). However, delayed postpartum uterine infection has been described by Hoyme and associates (1986). The syndrome, which develops 2 to 3 weeks postpartum, is distinct from early postpartum metritis. It is characterized by vaginal bleeding or discharge, low-grade fever, and uterine tenderness.

Infection at delivery poses a higher risk to the newborn than to the mother. Vertical transmission leads to infection in 8 to 44 percent of neonates delivered vaginally from affected women (Rosenman, 2003). Of neonatal infections, conjunctivitis is the most common (Chap. 32, p. 593). Perinatal transmission to newborns can also cause pneumonia.

Screening and Treatment

Currently, the USPSTF and the American Academy of Pediatrics and American College of Obstetricians and Gynecologists (2017) recommend chlamydia screening for all women at the first prenatal visit (LeFevre, 2014). The College further suggests testing in the third trimester for those treated in the first trimester, all women aged ≤25 years, and those aged >25 years with behavioral factors, which mirror those for gonorrhea. Dionne-Odom and associates (2020) reported a reinfection rate of 10 percent in pregnant women successfully treated before delivery.

Diagnosis is made predominantly by NAAT rather than culture. Of samples for NAAT, vaginal or cervical samples are preferred, because urine collection may detect up to 10 percent fewer infections (Papp, 2014; Wiesenfeld, 2017). However, Roberts and associates (2011) evaluated NAAT of urine specimens compared with cervical secretions in more than 2000 pregnant women and found them to be equivalent. As with gonorrhea, the first portion of the urine stream is collected.

Currently recommended treatment regimens for chlamydial infections are shown in Table 68-5. Azithromycin is first-line treatment in pregnancy. The fluoroquinolones and doxycycline are usually avoided in pregnancy, and erythromycin estolate is contraindicated because of drug-related hepatotoxicity.

A test of cure is repeated 4 weeks after therapy completion in pregnancy. Earlier NAAT may resample dead but treated organisms (Lazenby, 2017). A positive result can reflect a reinfection, a false-positive case from dead organisms, or treatment failure or noncompliance. Fortunately, drug resistance is rare for *C trachomatis* (Deguchi, 2018). Our practice is to re-treat women with positive test-of-cure results. Additionally, repeat screening 3 months after treatment is recommended to exclude reinfection (Workowski, 2021).

Expedited Partner Therapy

To prevent STI transmission, guidelines for expedited partner therapy (EPT) have been created by the Centers for Disease Control and Prevention (2006a) and are endorsed by the American College of Obstetricians and Gynecologists (2020a).

TABLE 68-5. Oral Treatment of *Chlamydia trachomatis* Infection in Pregnancy[a]

Regimen	Drug and Dosage
Preferred	Azithromycin, 1 g as a single dose
Alternative	Amoxicillin, 500 mg three times daily for 7 d

[a]Test of cure is recommended at 1 month. Retesting is performed at 3 months to exclude reinfection.
Data from Workowski, 2021.

With EPT, treatment is provided to persons who were sexual contacts of the patient within the prior 60 days. Partner therapy may be a prescription slip for the partner, direct medication administration to the partner and patient simultaneously, or a medication packet delivered to the partner(s) by the patient. Ideally, EPT does not replace traditional partner referral to allow their medical assessment, counseling, and screening for other STIs.

EPT is acceptable for treatment of sexual contacts with chlamydial infection. Because of new guidelines that recommend injectable ceftriaxone alone, EPT for gonorrhea is less desirable unless the partner(s) will be unable or unwilling to seek treatment (Centers for Disease Control and Prevention, 2021a). Fewer data are available to assess this strategy for trichomoniasis (Kissinger, 2006; Schwebke, 2010). EPT is not recommended for syphilis.

EPT is legally permissible or potentially allowable in all states. Links to specific state laws are found at: www.cdc.gov/std/ept/legal/default.htm. Notably, the risk of litigation following an adverse outcome may be elevated when a practice has uncertain legal status or is outside formally accepted community practice standards (Centers for Disease Control and Prevention, 2006a) Medication-related adverse reactions among treated partners is rare (Jamison, 2019).

The goal of EPT in pregnancy is to lower reinfection rates and adverse maternal and neonatal effects. A recent study at Parkland Hospital showed that EPT did not lower the chlamydia reinfection rate prior to delivery (Zofkie, 2021). Partner compliance, cost, and education may be factors (McCool-Myers, 2020; Slutsker, 2020).

HERPES SIMPLEX VIRUS

Adult Disease

Orogenital HSV infection manifests as shallow ulcers on affected mucosa. Infection stems from either of two different HSV viruses that are distinguished based on immunological differences. Yet, the two viruses have significant DNA homology, and thus prior infection with one type attenuates a primary infection with the other. Type 2 HSV is recovered almost exclusively from the genital tract and is usually transmitted sexually. Type 1 is responsible for most nongenital infections and typically is acquired in childhood. However, more than half of the new cases of genital herpes in adolescents and young adults are now caused by HSV-1 infection (Bernstein, 2013). This rise in the prevalence of HSV-1 genital disease may stem from an increase in rates of oral-genital sexual practices. Another explanation is that HSV-1 acquisition has declined in childhood as a result of improved living conditions and hygiene (Chemaitelly, 2019). Without prior exposure, young people without HSV-1 antibodies are rendered susceptible to *genital* acquisition of HSV-1 or -2.

Genital herpes simplex virus affects an estimated 19 million adolescents and adults in the United States (Spicknall, 2021). In pregnant women, the HSV-2 seroprevalence was 21 percent, and for HSV-1, it was 59 percent from 2007 to 2014. However, from 1999 to 2014, pregnant women with fewer sex partners were increasingly seronegative for both virus types (Patton, 2018). Seronegative pregnant women have a 4 to 5 percent risk to acquire either serotype during pregnancy (Brown, 1997; Kulhanjian, 1992). For those who are already HSV-1 seropositive, acquisition risk for HSV-2 approximates 2 percent (Brown, 1997).

Once transmitted by contact, viruses replicate at the entry site. Following mucocutaneous infection, the virus moves retrograde along sensory nerves. It remains latent in cranial nerves or dorsal spinal ganglia, but recurrences are common. HSV infections may be categorized into three groups.

First-episode primary infection describes the case in which HSV-1 or 2 is isolated from a lesion in the absence of HSV-1 or -2 serological antibodies. The typical incubation period of 6 to 8 days may be followed by a papular eruption with itching or tingling that then becomes painful and vesicular. Multiple vulvar and perineal lesions may or may not coalesce but then ulcerate (Fig. 68-4). Associated inguinal adenopathy can be severe. Many women do not present with typical lesions, and abraded or knife-cut lesions instead may be found. Cervical involvement is common, although it may be unapparent clinically. Transient systemic influenza-like symptoms or isolated high fevers with or without painful lesions are frequent and attributed to viremia. Uncommonly, women require hospitalization for febrile syndrome or for pain control of widespread ulceration. Hepatitis, encephalitis, or pneumonia infrequently develop, and disseminated disease is rare. After 2 to 4 weeks, all signs and symptoms of infection disappear. In contrast to these classic symptoms, the percentage of asymptomatic primary HSV-2 genital infections may reach 90 percent (Fanfair, 2013).

First-episode nonprimary infection is diagnosed when one HSV type is isolated from a lesion in a woman who has only antibodies to the other HSV serotype. For example, prior childhood HSV-1 infection likely provides cross-reacting antibodies to blunt the effects of new HSV-2 acquisition. Compared with primary infection, nonprimary infections produce fewer systemic manifestations or lesions, less pain, and briefer duration of lesions and viral shedding.

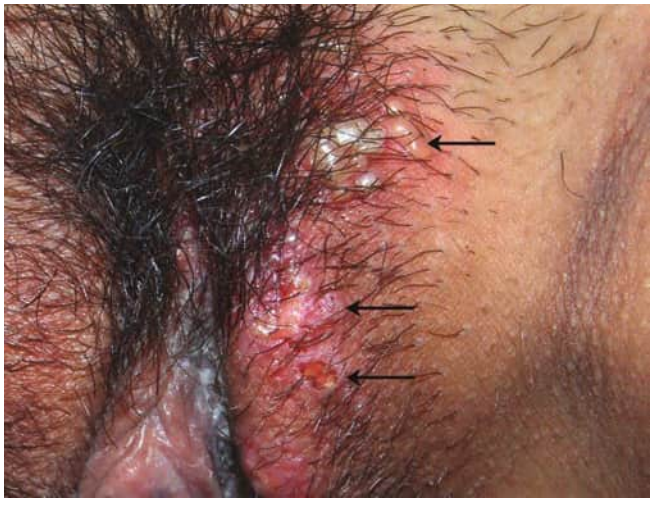

FIGURE 68-4 First-episode primary genital herpes simplex virus infection. As shown by the arrows, lesions may be vesicular, may be crusted, or may be shallow ulcers.

Recurrent disease is characterized by isolation of HSV-1 or -2 from the genital tract in women who carry antibodies to the same serotype. During the latency period, in which viral particles reside in nerve ganglia, reactivation is common and mediated through poorly understood stimuli. In general, lesions are fewer in number, are less tender, and shed virus for a shorter period than those of primary infection. Typically, they recur at the same sites. Recurrences are most frequent in the first year after initial infection, and rates slowly decline subsequently (Benedetti, 1999). Gravidas with a known prior history of genital HSV often experience recurrences (Sheffield, 2006).

Asymptomatic viral shedding is defined by the absence of clinical findings. Most infected women shed virus intermittently over time, and most HSV transmission to a partner occurs during these periods of asymptomatic viral shedding.

Vertical Transmission

HSV poses a higher risk to the newborn than to the mother. Thus, strategies aim to curb rates of vertical transmission, which may occur by three routes: (1) peripartum in 85 percent, (2) postnatal in 10 percent, or (3) intrauterine in 5 percent (James, 2015). Evidence does not suggest an obvious link between HSV infection and miscarriage (Zhou, 2015).

Peripartum transmission is by far the more frequent route of infection, and the fetus is exposed to virus shed from the lower genital tract. HSV-1 or -2 invades the uterus following membrane rupture or is transmitted by contact at delivery. The newborn is mainly infected, but rare cases of maternal endometritis have been described (Hollier, 1997; McGill, 2012). Of neonatal manifestations, infection may localize to the skin, eye, or mouth—*SEM disease*—in approximately 40 percent of cases. Instead, central nervous system (CNS) disease with encephalitis is seen in 30 percent. Last, disseminated disease that involves multiple major organs is found in 32 percent. Localized infection is usually associated with a good outcome. Conversely, even with acyclovir treatment, disseminated infection has a mortality rate of nearly 30 percent (Corey, 2009; Kimberlin, 2011). Of disseminated or cerebral infection survivors, serious developmental and CNS morbidity is seen in 20 to 50 percent.

In the United States, the neonatal infection rate ranges from 1 to 5 cases in 10,000 births (Donda, 2019; Mahant, 2019). Most infected newborns are born to mothers with no reported history of HSV infection (Gardella, 2010). The risk of neonatal infection correlates with the presence of HSV in the genital tract, HSV type, invasive obstetrical procedures, and stage of maternal infection (Brown, 2005, 2007). Neonates born to women who acquire genital HSV near the time of delivery have a 30- to 50-percent risk of infection. This is attributed to higher viral loads and the lack of transplacental protective antibodies (Brown, 1997, 2000). With recurrent HSV, the neonatal infection rate is <1 percent (Pasternak, 2010; Prober, 1987).

Postpartum transmission is uncommon and passed to the newborn by contact with an infected mother, family member, or health-care worker. The clinical presentation mirrors that with peripartum transmission.

In-utero transmission of HSV-1 or HSV-2 is rare and is part of the TORCH (toxoplasmosis, other, rubella, cytomegalovirus, herpes virus) group of infections. Intrauterine HSV infection classically leads to disease involving the skin (blisters, scarring), the CNS (hydranencephaly, microcephaly, intracranial calcification), or the eyes (chorioretinitis, microphthalmia). Bone and viscera can be involved (Marquez, 2011). Congenital infection with HSV or another TORCH infection is considered in a fetus with early or severe growth restriction, microcephaly, intracranial anomalies or calcifications, or hepatomegaly. If sonographic findings are identified, amniocentesis is recommended, and maternal HSV serological testing is done. Analysis of amnionic fluid for HSV-1 and HSV-2 serotypes is by NAAT (PCR) and culture (Curtin, 2013).

Diagnosis

The American College of Obstetricians and Gynecologists (2020d) and USPSTF (2016) recommend against routine serological HSV screening in asymptomatic gravidas. However, for a woman with a reported history of genital or oral lesions, a serological HSV diagnosis is sought. For women with either suspicious ulcers or sonographic findings suggestive of congenital infection, direct virological testing, described next, is performed along with serological testing for HSV. Testing for syphilis and other STIs is also considered for women with genital ulcers.

Direct virological tests, which are either PCR or culture, are performed on a specimen from a mucocutaneous lesion or from amniocentesis. For mucocutaneous lesions, PCR assays are more sensitive, the results generally are available in 1 to 2 days, and specimen handling is easier. The sensitivity of culture for detecting HSV is relatively low as vesicular lesions begin to ulcerate and then crust. Also, results sometimes are not available for 7 to 14 days (Strick, 2006). Regardless of the test performed, HSV viral types should be differentiated (LeGoff, 2014). Importantly, a negative culture or PCR result does not exclude infection. In contrast, false-positive results are rare. For amnionic fluid assessment, both culture and PCR are recommended (Curtin, 2013).

Serological assays detect antibodies produced against the specific HSV glycoproteins, G1 and G2. These proteins evoke type-specific antibody responses to HSV-1 and HSV-2 infection, respectively, and they reliably differentiate the two serotypes. Antibody detection confirms clinical infection and may reflect a carrier state in an asymptomatic patient. IgG antibodies develop 1 to 2 weeks after a primary infection and then persist. Serological testing may be falsely negative in the case of early infection but may also establish a nonprimary infection. For this reason, direct detection of the virus in a lesion with concomitant type-specific serological testing is helpful for clinical interpretation and counseling. Sensitivity and specificity of glycoprotein-based IgG tests approach 90 to 100 percent (Wald, 2002). IgM antibody detection is not a useful test, and antibodies may be detected with recurrent episodes.

Management

In nonpregnant patients, antiviral therapy with acyclovir, valacyclovir, or famciclovir is used to treat first-episode orogenital

TABLE 68-6. Oral Antiviral Medications for Herpesvirus Infection in Pregnancy[a]

Indication	Pregnancy Recommendation
Primary or first episode infection	Acyclovir, 400 mg three times daily for 7–10 d ***or*** Valacyclovir, 1 g twice daily for 7–10 d
Symptomatic recurrent infection (episodic therapy)	Acyclovir, 800 mg twice daily for 5 d ***or*** Acyclovir, 800 mg three times daily for 2 d ***or*** Valacyclovir, 500 mg twice daily for 3 d ***or*** Valacyclovir, 1 g once daily for 5 d
Daily suppression	Acyclovir, 400 mg three times daily from 36 weeks until delivery ***or*** Valacyclovir, 500 mg twice daily from 36 weeks until delivery

[a]Famciclovir not preferred during pregnancy due to fewer safety data.
Data from Workowski, 2021.

herpes. Oral or parenteral preparations attenuate clinical infection and viral shedding duration. Chronic suppressive therapy also is an option to limit recurrences and to reduce heterosexual transmission (Corey, 2004).

In pregnant women, acyclovir and valacyclovir are safe (Briggs, 2022; Stone, 2004). Data are limited regarding fetal effects with famciclovir.

For a primary outbreak during pregnancy, women may be given antiviral therapy to attenuate and decrease the duration of symptoms and viral shedding (Table 68-6). Women with HIV co-infection may require a longer duration of treatment. Those with severe or disseminated HSV are given IV acyclovir, 5 to 10 mg/kg every 8 hours for 2 to 7 days until clinically improved. This is followed by oral antiviral drugs to complete at least 10 days of total therapy (Workowski, 2021). For intense discomfort, oral analgesics and topical lidocaine ointment may provide some relief. Comorbid urinary retention is rare but can be treated briefly with an indwelling bladder catheter.

For recurrent HSV infections during pregnancy, antiviral treatment is provided mainly for symptom relief (see Table 68-6). Although uncommon, acyclovir resistance has been reported, predominantly in immunocompromised patients (Piret, 2016).

Of precautions during pregnancy, amniocentesis, percutaneous cord blood sampling, or transabdominal chorionic villus sampling may be performed even with active genital lesions. Transcervical procedures may best be delayed until lesions have resolved (American College of Obstetricians and Gynecologists, 2020d).

■ Peripartum Shedding Prophylaxis

To diminish vertical transmission risks, cesarean delivery is indicated for women with active genital lesions or prodromal symptoms. Several studies have shown that acyclovir or valacyclovir suppression initiated at 36 weeks' gestation for gravidas with recurrences during pregnancy lowers the number of HSV outbreaks at term. The goal is to decrease the need for cesarean delivery (Hollier, 2008). This suppressive therapy will also decrease viral shedding (Scott, 2002; Sheffield, 2006; Watts, 2003). One systematic review evaluated acyclovir prophylaxis given from 36 weeks to delivery to women with HSV recurrence during pregnancy. Sheffield and colleagues (2003) found that suppressive therapy was associated with significantly lower rates of clinical HSV recurrence, cesarean delivery for HSV recurrences, total HSV detection, and asymptomatic shedding. Subsequent studies using valacyclovir suppression showed similar results (Andrews, 2006; Sheffield, 2006). Because of these studies, the American College of Obstetricians and Gynecologists (2020d) recommends viral suppressive therapy to begin at ≥36 weeks' gestation for women with a clinical history of genital herpes. Suppression continues until delivery. Notably, despite maternal antiviral suppression, several cases of atypical neonatal herpes infection have been reported (Pinninti, 2012).

On presentation for delivery, a woman with a history of HSV should be questioned regarding current prodromal symptoms. A careful examination of the vulva, vagina, and cervix is performed for all, and women without genital lesions may proceed with labor and delivery. Usual obstetrical management, including invasive fetal monitoring, is supported in the absence of active lesions or prodromal symptoms (American College of Obstetricians and Gynecologists, 2020d).

Suspicious lesions should be swabbed for culture or NAAT evaluation. Cesarean delivery is indicated for women with suspicious genital lesions or prodromal symptoms. Moreover, for women with a clinical recurrence at delivery, there is no absolute duration of membrane rupture beyond which the fetus would not benefit from cesarean delivery (American College of Obstetricians and Gynecologists, 2020e).

Cesarean delivery is not recommended for women with a history of HSV infection but no active genital disease at the time of delivery. Moreover, an active lesion in a nongenital area can be covered by an occlusive dressing, and vaginal delivery is allowed.

With PPROM, no evidence suggests that external lesions cause ascending fetal infection. However, antiviral treatment during expectant care is recommended. Major and associates (2003) described expectant management in 29 such women at gestational ages <31 weeks. No cases of neonatal HSV developed, and the maximum infection risk was calculated to be 10 percent.

Women with active HSV lesions may breastfeed if the breast skin has no lesions. Strict hand washing is essential. Valacyclovir and acyclovir may be used for symptomatic maternal lesions during breastfeeding, as drug concentrations in breast milk are low (Sheffield, 2002a).

HUMAN PAPILLOMAVIRUS

Maternal Infection and Prevention

This is a common STI, and numerous serotypes infect the lower genital tract. In the United States from 2005 to 2006, the overall HPV prevalence was 40 percent in females aged 14 to 59 years (Liu, 2016). Prevalence is highest in younger women, and some of this seroprevalence now reflects HPV vaccination in this age group (Brouwer, 2015). Reproductive-aged women often become infected within a few years of sexual activity onset, and most infections are asymptomatic and transient. High-risk types are those with the most oncogenic potential. Of these, HPV types 16 and 18 are often associated with lower reproductive tract dysplasia (Chap. 66, p. 1165). Mucocutaneous genital warts termed *condyloma acuminata* are usually caused by types 6 and 11.

The clear link between HPV infection and cervical neoplasia led to development of vaccines that reduce cervical cancer risk (Lei, 2020). Although three vaccines are licensed, only one vaccine is currently available in the United States. Gardasil 9 is a nonavalent HPV vaccine against serotypes 6, 11, 16, 18, 31, 35, 45, 52, and 58. This vaccine is not recommended for gravidas. However, inadvertent exposures do occur, and no adverse pregnancy outcomes are associated (Kharbanda, 2021; Moreira, 2016; Scheller, 2017). If a woman is found to be pregnant after starting the vaccination series, remaining doses are delayed and given after delivery. Women who are breastfeeding may be vaccinated. Gardasil is licensed for females aged 9 to 45 years, and the target age is 11 to 12 years. It is recommended for those aged 9 to 26 years. It is suitable for those aged 27 to 45 years, after shared decision-making regarding age-related benefits and risks (American College of Obstetricians and Gynecologists, 2020b). The three-dose series is given on a schedule of 0, 2, and 6 months for those aged older than 15 (Table 10-7, p. 189). A two-dose regimen is used for younger individuals.

Condyloma Acuminata Treatment

Genital warts frequently grow in number and size with pregnancy. They commonly undergo apoptosis and resolution postpartum. Rarely, lesions may fill the vagina or cover the perineum and make vaginal delivery or episiotomy difficult. Genital wart eradication during pregnancy is usually unnecessary unless they are symptomatic. Therapy is directed toward debulking symptomatic warts yet minimizing treatment toxicity to the mother and fetus.

Trichloroacetic or *bichloracetic acid* in an 80- to 90-percent solution applied topically weekly is an effective regimen for external warts. Some prefer *cryotherapy, laser ablation*, or *surgical excision*. Agents that have limited safety data and thus are not recommended in pregnancy include podophyllin resin, podofilox solution or gel, imiquimod cream, and sinecatechins.

Neonatal Infection

Vertical transmission rates of HPV to the newborn are minimal. Juvenile-onset recurrent respiratory papillomatosis (JoRRP) is a rare, benign neoplasm of the larynx. It can cause hoarseness and respiratory distress in children and is most often caused by HPV 6 or 11. Risks for infection are maternal genital HPV infection and longer labors (Niyibizi, 2014). Although many newborns are likely exposed to HPV, few develop JoRRP (Smith, 2004). The incidence in 2013 in the United States was 5 cases in 10,000 births, and dropping rates are attributed to HPV vaccination (Meites, 2021). The benefit of cesarean delivery for prevention is unknown, and it is not recommended to avert HPV transmission.

VAGINITIS

Pregnant women frequently develop increased vaginal discharge. This may be a physiological discharge, described in Chapter 4 (p. 54), but should be differentiated from symptomatic vaginitis, which is also common in pregnancy. Fortunately, normal vaginal flora serve to prevent vaginitis. To better understand this, normal vaginal microflora composition and function are currently being studied in the Vaginal Human Microbiome Project (Huang, 2014).

Bacterial Vaginosis

Diagnosis

Bacterial vaginosis (BV) is a maldistribution of normal vaginal flora. With BV, numbers of lactobacilli are decreased, and anaerobic bacterial species are overrepresented. These anaerobes include *Gardnerella*, *Prevotella*, *Mobiluncus*, and *Bacteroides* species; *Atopobium vaginae*; and BV-associated bacteria, provisionally named BVAB1, BVAB2, and BVAB3. These last three are relatively newly recognized bacteria (Fredricks, 2005).

Ribosomal RNA gene-sequencing techniques have identified composite communities of vaginal flora, also called the *vaginal microbiota*. Five types of these composite communities exist and are referred to as *community state types (CSTs)*. A woman can be categorized to one of these five CSTs based on her vaginal microbiota composition (Ravel, 2011). Researchers have begun to quantify the risk of BV associated with these CST groups. Specifically, CSTs I, II, III, and V are rich in lactobacilli. CST IV is a heterogeneous microbiota of strict anaerobes and is associated with BV. CSTs vary racially, and CST IV is the most common in asymptomatic, healthy black women (Fettweis, 2014). Pregnancy-related changes in vaginal microbiota also are being defined and may hold keys to adverse BV-related pregnancy outcomes, discussed subsequently (Romero, 2014).

Of childbearing-aged women in the United States, nearly 30 percent have BV. In black women, the prevalence approximates 50 percent (Allsworth, 2007). Most women are asymptomatic. In those with symptoms, a foul, thin vaginal discharge is a typical complaint. Associated risk factors are douching, multiple partners, smoking, and altered host immunity (Desseauve, 2012; Koumans, 2007; Murphy, 2016).

For clinical diagnosis of BV, three of the four following *Amsel criteria* are present: (1) vaginal pH >4.5; (2) a thin, milky, noninflammatory vaginal discharge; (3) >20 percent clue cells seen microscopically; and (4) a fishy odor after addition of 10-percent potassium hydroxide to a vaginal secretion sample (Amsel, 1983). The last is described as a positive "whiff test" result. Likewise, alkalinity of seminal fluid and blood are responsible for complaints of foul odor after intercourse and with menses in affected women. Initially, a vaginal fluid sample is mixed with saline on a glass slide for microscopic evaluation, and this is often called a wet preparation or "wet prep." Clue cells are vaginal epithelial cells containing many attached bacteria, which create a poorly defined stippled cellular border (Fig. 68-5). Microscopically, leukocyte numbers are not increased. The higher vaginal pH stems from the diminished acid production due to a diminished lactobacilli population. Notably, *Trichomonas vaginalis* infection also is associated with anaerobic overgrowth and elaborated amines. Thus, women diagnosed with BV should have no microscopic evidence of trichomoniasis.

The *Nugent score*, used primarily in research rather than clinical practice, is a system employed for diagnosing BV (Nugent, 1991). During microscopic examination of a gram-stained vaginal discharge smear, scores are calculated by assessing bacteria staining and morphology.

NAATs to detect the bacterial types found in women with BV have suitable accuracy and may be used for symptomatic women (Coleman, 2018). However, these tests assess for bacteria that may also be part of normal flora in asymptomatic women. Moreover, compared with traditional methods, molecular tests have yet to show superior health outcomes but do add substantial cost.

Treatment

Adverse pregnancy-related health outcomes associated with BV are preterm birth, PPROM, and postpartum endometritis (Hillier, 1995; Watts, 1990). It also increases susceptibility to STIs, including HIV (Atashili, 2008; Brotman, 2010). For women at low risk for preterm birth, however, treatment of BV does not reduce preterm birth rates (Brocklehurst, 2013; Carey, 2000). The American College of Obstetricians and Gynecologists (2021) and USPSTF (2020) do not recommend routine BV screening of asymptomatic gravidas at low risk for preterm delivery. For women with prior preterm birth, evidence of screening and treatment benefits are conflicting (Kahwati, 2020). At Parkland Hospital, we do not routinely screen for BV among women with prior preterm birth.

Treatment is reserved for symptomatic women (Table 68-7). Agents not listed are best avoided due to insufficient data regarding their use in pregnancy (Workowski, 2021). It is still debated whether BV is a sexually transmitted infection, and treatment of a male partner does not lower recurrence rates (Amaya-Guio, 2016; Schwebke, 2021).

Trichomoniasis

Diagnosis

Vaginitis caused by *Trichomonas vaginalis* is common, and its prevalence in the United States approximates 2 percent in women (Patel, 2018). The prevalence is higher in those older than 30 years compared with younger women. Risks include black race, douching, and greater number of lifetime sexual partners (Sutton, 2007). Among women, frequent sites of infection include the urethra, endocervix, and vagina. Those with symptomatic vaginitis often have a purulent discharge, pruritus, vulvovaginal erythema, and colpitis macularis. The last is often termed a "strawberry cervix" and displays a patchy, maculoerythematous ectocervix.

Trichomonads are flagellated, pear-shaped, motile organisms that are somewhat larger than leukocytes. These parasites can readily be seen microscopically moving briskly in wet

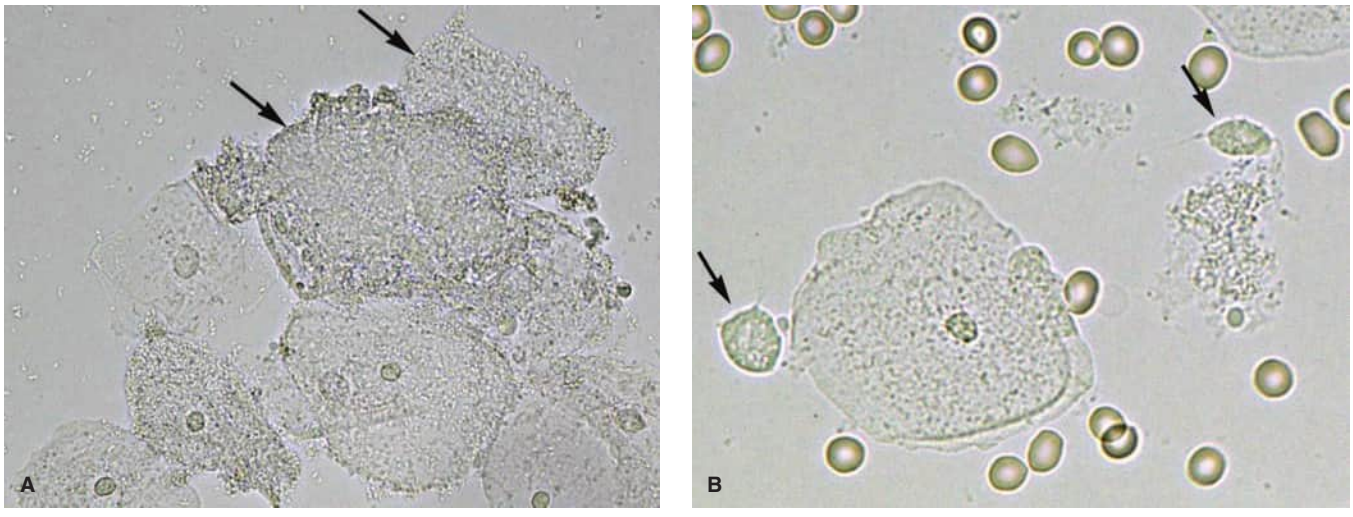

FIGURE 68-5 A. Bacterial vaginosis. Microscopy reveals several squamous cells heavily studded with bacteria. Clue cells are covered to the extent that cell borders are blurred and nuclei are not visible (*arrows*). **B.** Trichomonads (*arrows*).

TABLE 68-7. Treatment of Bacterial Vaginosis in Pregnancy[a]

Regimen	Drug and Dosage
Preferred	Metronidazole, 500 mg orally twice daily for 7 d ***or*** Metronidazole 0.75-percent gel, one applicator intravaginally, daily for 5 d
Alternative	Clindamycin, 300 mg orally twice daily for 7 d ***or*** Clindamycin ovules, 100 mg intravaginally nightly for 3 d

[a]Other agents not listed here are ideally avoided due to insufficient pregnancy data.
Data from Workowski, 2021.

preparation. Prompt inspection of vaginal secretions is advantageous because trichomonads slow with cooling. At times, *T vaginalis* may be found incidentally on a Pap test slide. Both of these microscopic approaches have low diagnostic sensitivity that approximates 60 percent (Krieger, 1988; Wiese, 2000). Pap tests can also yield false-positive results. Thus, Pap test trichomonad findings warrant confirmation with either a wet prep or NAAT.

Of other direct detection methods, culture is expensive, lengthy, and only 75 to 95 percent sensitive (Association of Public Health Laboratories, 2016; Huppert, 2007). Laboratory NAAT-based evaluation of a vaginal, endocervical, or urine sample is available, is completed in minutes to hours, and offers superior sensitivity of 95 to 100 percent (Van Der Pol, 2016). Although more costly than wet-preparation microscopy, a NAAT may be a useful, second-line diagnostic test for microscopy-negative samples. An optimal approach in pregnancy has not been established. Rapid POC testing is also available but may sacrifice sensitivity for speed. The OSOM Trichomonas Rapid Test provides results in 10 minutes, is suitable for office use, and has sensitivities of 88 to 98 percent (Herbst de Cortina, 2016).

Treatment

Treatment is reserved for symptomatic women (Table 68-8). Previously, a one-time, 2-g dose of oral metronidazole was used to eradicate *T vaginalis*. In nonpregnant women, a large randomized trial compared this traditional therapy against metronidazole, 500 mg orally twice daily for 7 days. The longer course provided improved efficacy (Kissinger, 2018). New guidelines from the American College of Obstetricians and Gynecologists (2020g) now recommend this change in nonpregnant women. The CDC recognizes this regimen for pregnancy.

Reinfection rates among women treated for trichomoniasis are high (Kim, 2020). Thus, retesting for *T vaginalis* is recommended for all sexually active women within 3 months following initial therapy (Workowski, 2021). Some authors recommend retesting 3 weeks after treatment in pregnancy (Lazenby, 2019).

TABLE 68-8. Oral Treatment of Trichomoniasis in Pregnancy[a,b]

Regimen	Drug and Dosage
Preferred	Metronidazole, 500 mg orally twice daily for 7 d

[a]Retesting is encouraged at 3 months to exclude reinfection.
[b]Tinidazole is not recommended in pregnancy.
Data from Workowski, 2021.

Metronidazole is not teratogenic or fetotoxic, and it may be used in all pregnancy stages (Briggs, 2022; Czeizel, 1998; Workowski, 2021). The manufacturer recommends against its use during the first trimester (Pfizer, 2021). Fewer data are available for tinidazole, and thus metronidazole is preferred. For allergic patients, metronidazole desensitization is effective (Helms, 2008). With breastfeeding, the longer, lower-dose metronidazole regimen is not associated with adverse infant outcomes (LactMed, 2021).

Perinatal transmission of trichomoniasis by direct contact in the birth canal is rare but may lead to neonatal respiratory or genital infection (Bruins, 2013; Trintis, 2010). Some studies have linked trichomonal infection with preterm birth (Van Gerwen, 2021). A few other studies implicate this infection with PPROM and small-for-gestational age newborns (Silver, 2014). However, treatment in two randomized studies did not lower preterm birth rates (Klebanoff, 2001; Stringer, 2010).

In sum, treating symptomatic women is reasonable. For most asymptomatic women during pregnancy, screening is not done. However, screening at the first prenatal visit and prompt treatment are encouraged for gravidas with comorbid HIV infection. In this group, *T vaginalis* infection may be a risk factor for vertical HIV transmission (Gumbo, 2010).

Candidiasis

Candida albicans or other candidal species can be identified by culture from the vagina during pregnancy in approximately 20 percent of women. A link between candidiasis and preterm birth is not robust (Cotch, 1998; Roberts, 2015). Thus, asymptomatic colonization requires no treatment. The organism, however, can create a profuse, irritating discharge.

For symptoms, effective treatment is listed in Table 68-9. In pregnancy, the CDC recommends 7-day regimens and suggests topical rather than oral azoles (Workowski, 2021). In some women, infection is likely to recur and require repeat treatment. In these cases, symptomatic infection usually subsides after pregnancy (Sobel, 2007). Although not preferred treatment, a single, 150-mg oral fluconazole dose is generally not considered teratogenic. Data showing a small association with cardiac anomalies are conflicting, but more recent evidence is

TABLE 68-9. Daily, Intravaginal Agents in 7-Day Regimens for Vulvovaginal Candidiasis Treatment in Pregnancy

Brand Name	Formulation
Clotrimazole	
Clotrimazole	1% cream, 1 applicator
Miconazole	
Miconazole Monistat 7, Miconazole 7	100-mg, 1 suppository 2% cream, 1 applicator
Terconazole	
Terazol[a]	0.4% cream, 1 applicator

[a]Prescription required.

reassuring (Mølgaard-Nielsen, 2013; Zhu, 2020). In 2019, the FDA noted that reviewed data do not provide conclusive evidence for an increased miscarriage or stillbirth risk.

HUMAN IMMUNODEFICIENCY VIRUS

Pathogenesis

For *human immunodeficiency viruses*, which are *HIV-1* and *HIV-2,* sexual intercourse is the main mode of transmission. The virus can be passed by blood, and infected mothers may infect their fetuses during labor and delivery or by breast milk. The primary determinant of transmission is the maternal plasma viral load.

For sexual transmission, the viral HIV envelope binds to mucosal dendritic cells. These cells then present the viral particle to specific T lymphocytes. These lymphocytes are defined phenotypically by their *cluster of differentiation 4 (CD4)* glycoprotein surface antigens. The CD4 site serves as a receptor for the virus. Once infected, CD4 T lymphocytes are gradually depleted, which creates an immunodeficiency that is characterized by low serum CD4 counts. In some infected with HIV, *acquired immunodeficiency syndrome (AIDS)* reflects profound immunodeficiency that gives rise to various opportunistic infections and neoplasms.

The incubation period from exposure to clinical disease averages 3 to 6 weeks. Acute HIV infection is similar to many other viral syndromes and usually lasts less than 10 days. Common symptoms, if any, include fever, fatigue, rash, headache, lymphadenopathy, pharyngitis, myalgias, nausea, and diarrhea. After symptoms abate, the level of viremia usually declines to a set point, and patients with the highest viral burden at this time progress more rapidly to AIDS and death. According to the CDC, AIDS is defined by a CD4 T-cell count <200 cells/μL, by CD4 T cells constituting <14 percent of all lymphocytes, or by one of several AIDS-defining illnesses (Selik, 2014). Route of infection, viral strain's pathogenicity, initial viral inoculum, and the host's immunological status all affect progression.

Prenatal HIV Screening

In the United States, approximately 5000 women with HIV give birth annually (Nesheim, 2018). However, the estimated number of perinatally acquired HIV cases has dropped, and the rate was 0.9 per 100,000 live births in 2018 (Centers for Disease Control and Prevention, 2020a). The decline predominantly stems from prenatal HIV testing and antiretroviral therapy (ART) for the woman and then her neonate.

The CDC (2006b) and the American College of Obstetricians and Gynecologists (2020f) recommend prenatal HIV screening using an *opt-out approach*. With this, HIV testing is routinely included in antenatal testing, but this testing may be declined. Women are given information regarding HIV but are not required to sign a specific consent. This opt-out strategy has raised HIV testing rates and is permitted in every United States jurisdiction (Centers for Disease Control and Prevention, 2020b).

Repeat screening during the third trimester, preferably before 36 weeks' gestation, is *considered* for all pregnant women. Retesting is *recommended* in areas where HIV rates exceed 1 case per 1000 pregnant women screened or for those with risk factors. These include incarceration, injection drug use, prostitution, a suspected or known HIV-infected sexual partner, a new or multiple sexual partners, or diagnosis of another STI (American College of Obstetricians and Gynecologists, 2020f).

The initial laboratory screening test for HIV is an antigen/antibody combination immunoassay that detects antibodies against HIV-1 and HIV-2 and detects HIV-1 p24 antigen (Centers for Disease Control and Prevention, 2018a). No further testing is required for specimens that yield negative results on the initial immunoassay unless a known recent exposure to HIV has occurred. Antibody can be detected in most patients within 1 month of infection, and thus a test for antibodies alone may not exclude early infection. Instead, for acute primary HIV infection, identification of viral p24 core antigen or viral RNA is necessary.

Specimens with a "reactive" (that is, a positive) antigen/antibody combination immunoassay result should be tested with an antibody immunoassay that differentiates HIV-1 antibodies from HIV-2 antibodies (Fig. 68-6). The HIV-1/HIV-2 antibody differentiation immunoassay provides results that are reported as positive or negative for HIV-1 antibodies, for HIV-2 antibodies, or for HIV antibodies, undifferentiated. If these two serial immunoassays (the initial screen and the differentiation assay) are discordant, an HIV-1 NAAT—qualitative or quantitative HIV RNA test—is performed (Centers for Disease Control and Prevention, 2018a).

At delivery, women with undocumented HIV status should have a fourth-generation HIV antigen/antibody combination screening test performed on a blood sample. A negative screening test result does not need confirmation. However, in cases of recent HIV exposure, consideration is given to peripartum interventions to reduce perinatal transmission despite negative HIV testing. Repeat interval testing is recommended to exclude very early infection not identified with the initial screen. With a positive fourth-generation HIV testing result, peripartum and neonatal interventions to reduce perinatal transmission are initiated. These include intravenous zidovudine infusion during labor and avoidance of breastfeeding, although breast

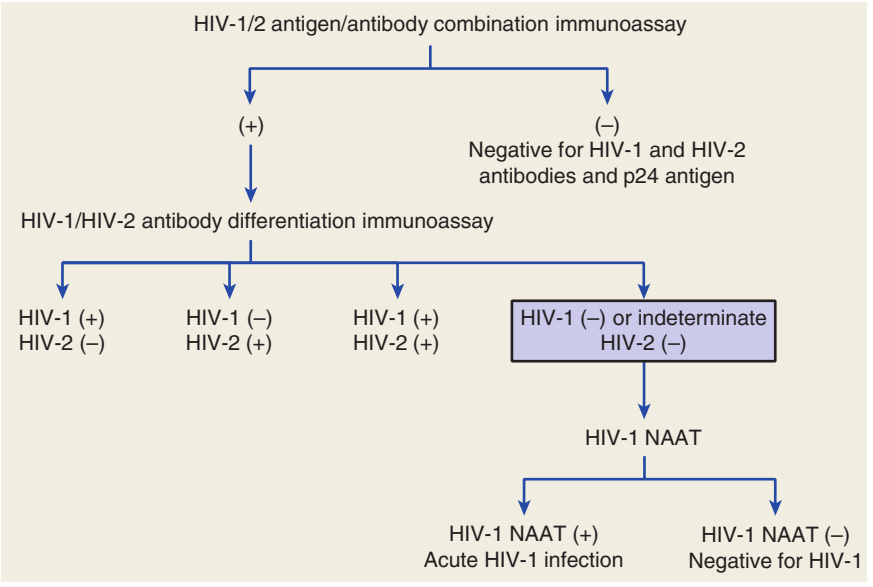

FIGURE 68-6 Algorithm for HIV testing. For specimens that are reactive on the initial antigen/antibody combination immunoassay and nonreactive or indeterminate on the HIV-1/HIV-2 antibody differentiation immunoassay, a nucleic acid amplification test (NAAT) is performed. Following a nonreactive HIV-1/HIV-2 antibody differentiation immunoassay, a positive HIV-1 NAAT indicates laboratory evidence for acute HIV-1 infection. A positive HIV-1 NAAT result following indeterminate HIV-1/HIV-2 antibody differentiation immunoassay indicates the presence of HIV-1 infection confirmed by HIV-1 NAAT. A negative HIV-1 NAAT result following nonreactive or indeterminate HIV-1/HIV-2 antibody differentiation immunoassay indicates a false-positive result on the initial antigen/antibody combination immunoassay. (Reproduced with permission from Centers for Disease Control and Prevention, 2018a.)

milk may be stored until confirmatory test results are available (Panel on Treatment of Pregnant Women with HIV Infection and Prevention of Perinatal Transmission, 2021). Interventions are continued until the results of an antibody differentiation assay—and qualitative or quantitative RNA test if indicated—is known. Interventions can be discontinued if confirmatory testing is negative. To confirm a positive result from any initial HIV test, the laboratory testing algorithm in Figure 68-6 is used and begins with the antigen/antibody combination immunoassay.

Vertical Transmission

Viral burden and neonatal infection rates are directly related. In one cohort, neonatal infection was 1 percent with <400 copies/mL, and it was 23 percent when maternal viral RNA levels were >30,000 copies/mL (Cooper, 2002). Among 2615 neonates born to mothers taking ART before conception and during pregnancy, no cases of vertical transmission occurred when maternal viral loads were <50 copies/mL at delivery (Mandelbrot, 2015). Transmission of HIV infection, however, has been observed at all HIV RNA levels, including those that were nondetectable by current assays. Transplacental HIV transmission can occur early, and the virus has even been identified in specimens from elective abortion (Lewis, 1990). Kourtis and colleagues (2001) estimated that 20 percent of vertical transmission occurs before 36 weeks' gestation, 50 percent in the days before delivery, and 30 percent intrapartum. Transmission rates for breastfeeding may be as high as 30 to 40 percent and are associated with increasing HIV viral burden (Kourtis, 2006, 2007; Slyker, 2012). In nonpregnant individuals, concomitant STIs and horizontal HIV transmission are linked. Evidence also supports that vertical transmission rates may be increased by comorbid STIs (Schulte, 2001; Watts, 2012).

Antepartum Care

Pregnant women with HIV infection need special attention and are seen in consultation by physicians with special interest in this field. An additional resource is the National Perinatal HIV Hotline (1–888–448–8765), which provides free antepartum, intrapartum, or postpartum consultation to providers. At Parkland Hospital, a pregnant woman with HIV infection is initially assessed with the following:

- Standard prenatal laboratory surveys that include serum creatinine, complete blood count, and bacteriuria screening
- Plasma HIV RNA quantification, which establishes the "viral load" value, and antiretroviral resistance testing if the viral load is at least 500 to 1000 copies/mL
- CD4 T-cell count
- Screening for chlamydial infection, gonorrhea, syphilis, and trichomoniasis, if not previously performed with new HIV diagnosis
- Serum hepatic aminotransferase levels
- HSV-1 and -2, cytomegalovirus, toxoplasmosis, and hepatitis B and C serological screening
- Baseline chest radiograph
- Tuberculosis testing with purified protein derivative (PPD) skin testing or with interferon-gamma release assay
- Evaluation of need for pneumococcal, hepatitis A, hepatitis B, Tdap, COVID-19, and influenza vaccines
- Sonographic evaluation to establish gestational age.

During pregnancy, the risk of HIV transmission does not appear to be increased with amniocentesis or other invasive diagnostic procedures in women receiving effective ART that results in viral suppression (Floridia, 2017). For women not receiving ART, the risk rises approximately twofold (Mandelbrot, 1996). If amniocentesis is performed, efforts are taken to avoid passing through the placenta (Panel on Treatment of Pregnant Women with HIV Infection and Prevention of Perinatal Transmission, 2021).

Antiretroviral Therapy

In overview, the ideal strategy to suppress viral load and minimize vertical HIV transmission includes (1) preconceptional ART, (2) antepartum ART, (3) intrapartum continuation of the antepartum oral ART regimen plus IV zidovudine, and (4)

newborn ART prophylaxis. ART is recommended for all pregnant women with HIV infection, and it should be initiated as early in pregnancy as possible. Treatment reduces the risk of perinatal transmission regardless of CD4 T-cell count or HIV RNA level. Regimen adherence is emphasized to help prevent viral drug resistance. Gravidas are treated with at least three antiretroviral (ARV) agents.

The Panel on Treatment of Pregnant Women with HIV Infection and Prevention of Perinatal Transmission (2021) has issued guidelines for four different scenarios during pregnancy (Table 68-10). The following paragraphs summarize these recommendations.

First, women already taking ART at pregnancy onset are encouraged to continue their regimen if viral suppression is adequate and if the ARV is safe and tolerated. Didanosine, stavudine, and full-dose ritonavir, which differs from ritonavir-boosted agents, are exceptions due to pregnancy toxicity but not teratogenicity. The lopinavir/ritonavir combination is no longer recommended based on risks for preterm and small-for-gestational-age neonates.

Second, women who have never received antiretroviral therapy—*antiretroviral naïve*—are given ART regardless of trimester. In general, the starting regimen comprises two nucleoside reverse transcriptase inhibitors that are coupled into a single agent *plus* either a ritonavir-boosted protease inhibitor or an integrase inhibitor.

Third, women who have previously received antiretroviral therapy but are currently not taking medications should undergo HIV-resistance testing because prior ART use raises the risk of drug resistance. However, ART is initiated prior to receiving results of these drug-resistance tests. In this case, initial ART selection should factor results of any prior resistance testing, if available; prior ART regimen; and current ART pregnancy guidelines, that is, those for ART-naïve women. Drug-resistance testing may then modify the initial regimen.

TABLE 68-10. Recommendations for HIV Antiviral Drug Use During Pregnancy

Clinical Scenario	Recommendations
Taking ART and becomes pregnant	Continue current medication if viral suppression adequate and patient tolerating
ART naïve	Initiate ART: combine two NRTIs with either a ritonavir-boosted PI or an integrase inhibitor – Preferred NRTI dual combinations: abacavir/lamivudine, tenofovir disoproxil fumarate (TDF)/emtricitabine, or TDF/lamivudine. If abacavir is used, HLA-B*5701 testing is completed to identify potential hypersensitivity reaction – Preferred PI: atazanavir/ritonavir or darunavir/ritonavir – Preferred integrase inhibitor: dolutegravir or raltegravir. Dolutegravir should not be administered within 2 hr of prenatal vitamins, iron, or calcium
Prior ART use but not currently	Initiate ART, with regimen based on prior therapy history and resistance testing
No ART use and presents in labor	IV ZDV (see Intrapartum care below)
Antepartum care	See antepartum screening test list (p. 1220) Initiate ART as early as possible For those with HIV RNA levels >500–1000 copies/mL, order HIV antiretroviral drug-resistance testing but do not delay ART initiation while awaiting results Repeat HIV RNA levels 2–4 wks after initiating (or changing) ART drugs; monthly until RNA levels are undetectable; then at least every 3 mo; and finally at 34–36 weeks' gestation for delivery planning CD4+ count should be monitored at the initial visit and every 3–6 mo
Intrapartum care	If HIV RNA level >1000 copies/mL or is unknown, plan cesarean delivery at 38 weeks' gestation before labor or ROM If HIV RNA levels >1000 copies/mL or is unknown but labor or ROM has ensued, benefits of cesarean delivery are unclear and labor plans are individualized If HIV RNA level ≤1000 copies/mL, vaginal delivery is permitted; cesarean delivery is not routinely recommended Start IV ZDV unless the following criteria are met: taking a prescribed oral ART regimen, HIV RNA level <50 copies/mL at 34 to 36 weeks' gestation or 3–4 weeks before delivery. Dosing is a 2-mg/kg IV load over 1 hr, then 1 mg/kg/hr until delivery. IV ZDV should begin 3 hr before scheduled cesarean delivery Those taking oral antepartum ART should continue during labor with sips of water

ART = antiretroviral therapy; NRTI = nucleoside reverse transcriptase inhibitor; ROM = rupture of membranes; ZDV = zidovudine.
Adapted from the Panel on Treatment of Pregnant Women with HIV Infection and Prevention of Perinatal Transmission, 2021.

For these three categories of women taking antepartum ART, therapy surveillance is outlined in Table 68-10. Most patients with adequate viral response have at least a 1-log viral load decline within 1 to 4 weeks after starting therapy. Newer integrase inhibitors rapidly decrease viral loads and are useful for women presenting late to prenatal care (Lockman, 2021). For those who fail to achieve this degree of decline, regimen compliance is assessed, resistance studies are reviewed, and ART modification is considered.

During labor and delivery, an oral ART regimen is continued with sips of water. Additionally, IV zidovudine is administered to women during labor and before cesarean delivery. An exception to this addition is the patient who is strictly adherent to her prescribed oral ART regimen and who has an HIV RNA level that was previously documented to be <50 copies/mL at 34 to 36 weeks' gestation or at 3 to 4 weeks before delivery. At Parkland Hospital, we administer intrapartum IV zidovudine to all HIV-positive women, regardless of viral load. A 2-mg/kg loading dose is infused over 1 hour and is followed with zidovudine, 1 mg/kg/hr until delivery. Women with HIV undergoing a scheduled cesarean delivery are given IV zidovudine as a loading dose followed by 2 more hours of continuous maintenance therapy—a total of 3 hours of infused zidovudine prior to surgery.

The fourth group includes women who present in labor and who are taking no ART regimen. These women are given IV zidovudine intrapartum as just described.

Delivery Planning

In some cases, cesarean delivery lowers HIV prenatal transmission rates (International Perinatal HIV Group, 1999). The American College of Obstetricians and Gynecologists (2020c) suggests that scheduled cesarean delivery be discussed and recommended for HIV-infected women with HIV-1 RNA load >1000 copies/mL. Scheduled delivery is recommended at 38 weeks' gestation in these women to avoid spontaneous labor. Management of women with either HIV-1 RNA load >1000 copies/mL or unknown viral load who present in labor or with ruptured membranes is individualized. For these women, IV zidovudine is recommended as previously described. In the case of early labor, cesarean delivery is preferred to vaginal birth.

For women with HIV RNA load ≤1000 copies/mL, cesarean delivery to reduce the risk of vertical HIV transmission is not recommended and is unlikely to confer additional benefit to women already taking ART and achieving viral suppression (Briand, 2013; Jamieson, 2007). Vaginal delivery in this group is the goal, and awaiting spontaneous onset of labor is suitable. Labor is not induced to prevent perinatal HIV transmission.

During labor, artificial membrane rupture, fetal scalp electrode placement, episiotomy, and operative vaginal delivery are performed for standard obstetrical indications but are avoided if possible in women with detectable RNA viral load (Peters, 2016). Labor augmentation is used when needed to shorten the interval to delivery to help further lower the transmission risk. For the benefits described in Chapter 27 (p. 500), delayed cord clamping in preterm neonates is acceptable and may be considered for term newborns**.** Neuraxial analgesia is suitable. Postpartum hemorrhage is best managed with oxytocin and prostaglandin analogues. *Methylergonovine (Methergine) and other ergot alkaloids adversely interact with reverse transcriptase and protease inhibitors to cause severe vasoconstriction.*

Postpartum Care

Vertical transmission rates rise with breastfeeding, and it generally is not recommended for women with HIV infection in the United States, where formula is readily available (Committee on Pediatric AIDS, 2013). In nutritionally deprived countries, where infectious disease and malnutrition are primary causes of infant death, the World Health Organization (2016) recommends exclusive breastfeeding during the first 6 to 12 months.

The Panel on Treatment of Pregnant Women with HIV Infection and Prevention of Perinatal Transmission (2021) strongly recommends that ART regimens not be discontinued postpartum but continued lifelong for the advantages of viral suppression. Ideally, all those planning pregnancy should be receiving ART and have a viral load below detectable levels before conception. As one benefit, interpregnancy viral load suppression is associated with less vertical transmission in a subsequent pregnancy (French, 2014; Stewart, 2014). Reassuringly, for those seeking subsequent pregnancy, when ART is available, repeated pregnancy in a healthy woman with HIV has no significant effect on disease progression (Calvert, 2015). Transition postpartum to general HIV care is critical to maintain viral suppression (Swain, 2016).

Prevention

For adults without HIV infection but with risks for HIV acquisition, the USPSTF (2019b) recommends offering preexposure prophylaxis (PrEP) to decrease the risk of acquiring HIV. Risk factors for heterosexually active women without HIV infection are a partner with HIV, syphilis or gonorrhea within the past 6 months, and inconsistent condom use with a high-risk partner. The last is a partner with injection drug use or with multiple other sexual partners. Current guidance from the CDC (2018b) emphasizes the use of ART to achieve viral suppression in the infected partner and barrier use as primary methods of preventing horizontal transmission. However, PrEP for the HIV-negative partner is considered, including during pregnancy to reduce the risk of HIV acquisition and also vertical transmission. PrEP with tenofovir disoproxil fumarate (TDF)/emtricitabine taken orally daily is acceptable during pregnancy and is encouraged particularly if the HIV viral load of the infected partner is unknown or unsuppressed. Barrier methods are reinforced.

For conception in HIV-serodiscordant couples, assisted reproductive technologies are available. In lower-resource settings, acceptable approaches combine *safer conception methods*. These include combinations of treatment to achieve viral suppression for the HIV-seropositive partner, PrEP for the HIV-seronegative partner, STI screening and treatment, timed condomless sex during peak fertility days, and self-insemination, (American Society for Reproductive Medicine, 2021; Schwartz, 2019).

If pregnancy is undesired, contraception options are discussed (Chap. 38, p. 664). Counseling also includes education

for decreasing high-risk sexual behaviors to prevent HIV transmission or acquisition and to decrease other STI acquisition.

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APPENDIX

APPENDIX I. Serum and Blood Constituents

HEMATOLOGY

	Nonpregnant Adult[a]	1st Trimester	2nd Trimester	3rd Trimester	References
Erythropoietin[b] (U/L)	4–27	12–25	8–67	14–222	8, 11, 58
Ferritin[b] (ng/mL)	10–150[d]	6–130	2–230	0–116	8, 11, 46, 52, 56, 58, 73, 82
Folate, red blood cell (ng/mL)	150–450	137–589	94–828	109–663	56, 57, 84
Folate, serum (ng/mL)	5.4–18.0	2.6–15.0	0.8–24.0	1.4–20.7	8, 53, 56, 57, 64, 69, 84
Haptoglobin (mg/mL)	25–250	130 ± 43	115 ± 50	135 ± 65	31
Hemoglobin[b] (g/dL)	12–15.8[d]	11.6–13.9	9.7–14.8	9.5–15.0	11, 56, 58, 69, 73
Hematocrit[b] (%)	35.4–44.4	31.0–41.0	30.0–39.0	28.0–40.0	7, 8, 11, 52, 56 69, 77
Iron, total binding capacity (TIBC)[b] (μg/dL)	251–406	278–403	Not reported	359–609	73
Iron, serum[b] (μg/dL)	41–141	72–143	44–178	30–193	11, 73
Mean corpuscular hemoglobin (MCH) (pg/cell)	27–32	30–32	30–33	29–32	52
Mean corpuscular volume (MCV) ($\times m^3$)	79–93	81–96	82–97	81–99	7, 52, 56, 69
Platelet ($\times 10^9$/L)	165–415	174–391	155–409	146–429	5, 7, 18, 52, 56
Mean platelet volume (MPV) (μm^3)	6.4–11.0	7.7–10.3	7.8–10.2	8.2–10.4	52
Red blood cell count (RBC) ($\times 10^6/mm^3$)	4.00–5.20[d]	3.42–4.55	2.81–4.49	2.71–4.43	7, 52, 56, 69
Red cell distribution width (RDW) (%)	<14.5	12.5–14.1	13.4–13.6	12.7–15.3	52
White blood cell count (WBC) ($\times 10^3/mm^3$)	3.5–9.1	5.7–13.6	5.6–14.8	5.9–16.9	7, 10, 52, 56, 69
Neutrophils ($\times 10^3/mm^3$)	1.4–4.6	3.6–10.1	3.8–12.3	3.9–13.1	5, 7, 10, 52
Lymphocytes ($\times 10^3/mm^3$)	0.7–4.6	1.1–3.6	0.9–3.9	1.0–3.6	5, 7, 10, 52
Monocytes ($\times 10^3/mm^3$)	0.1–0.7	0.1–1.1	0.1–1.1	0.1–1.4	7, 10, 52
Eosinophils ($\times 10^3/mm^3$)	0–0.6	0–0.6	0–0.6	0–0.6	7, 10
Basophils ($\times 10^3/mm^3$)	0–0.2	0–0.1	0–0.1	0–0.1	7, 10
Transferrin (mg/dL)	200–400[c]	254–344	220–441	288–530	46, 52
Transferrin, saturation without iron (%)	22–46[b]	Not reported	10–44	5–37	58
Transferrin, saturation with iron (%)	22–46[b]	Not reported	18–92	9–98	58

COAGULATION

	Nonpregnant Adult[a]	1st Trimester	2nd Trimester	3rd Trimester	References
Antithrombin III, functional (%)	70–130	89–114	78–126	82–116	17, 18, 47
D-Dimer (μg/mL)	0.22–0.74	0.05–0.95	0.32–1.29	0.13–1.7	18, 28, 29, 43, 47, 51, 62
Factor V (%)	50–150	75–95	72–96	60–88	49
Factor VII (%)	50–150	100–146	95–153	149–2110	18
Factor VIII (%)	50–150	90–210	97–312	143–353	18, 49
Factor IX (%)	50–150	103–172	154–217	164–235	18
Factor XI (%)	50–150	80–127	82–144	65–123	18
Factor XII (%)	50–150	78–124	90–151	129–194	18
Fibrinogen (mg/dL)	233–496	244–510	291–538	301–696	18, 28, 29, 47, 51, 52, 62
Fibronectin (mg/L)	290 ± 85	377 ± 309	315 ± 295	334 ± 257	33
Homocysteine (μmol/L)	4.4–10.8	3.34–11	2.0–26.9	3.2–21.4	53, 56, 57, 64, 84
International normalized ratio (INR)	0.9–1.04[g]	0.86–1.08	0.83–1.02	0.80–1.09	17, 51
Partial thromboplastin time, activated (aPTT) (sec)	26.3–39.4	23.0–38.9	22.9–38.1	22.6–35.0	17, 18, 51, 52
Prothrombin time (PT) (sec)	12.7–15.4	9.7–13.5	9.5–13.4	9.6–12.9	18, 51, 52
Protein C, functional (%)	70–130	78–121	83–133	67–135	17, 27, 49
Protein S, total (%)	70–140	39–105	27–101	33–101	18, 27, 49
Protein S, free (%)	70–140	34–133	19–113	20–65	27, 49
Protein S, functional activity (%)	65–140	57–95	42–68	16–42	49
Thrombin time (TT) (sec)	17.7 ± 2.8	16.1 ± 1.5	15.4 ± 2.7	16.5 ± 2.4	33
Thrombomodulin (ng/mL)	2.7 ± 3.1	4.3 ± 1.3	4.2 ± 1.2	3.6 ± 1.3	33
Tissue plasminogen activator (ng/mL)	1.6–13[h]	1.8–6.0	2.36–6.6	3.34–9.20	17, 18, 29
Tissue plasminogen activator inhibitor-1 (ng/mL)	4–43	16–33	36–55	67–92	18, 29
von Willebrand disease					
von Willebrand factor antigen (%)	75–125	62–318	90–247	84–422	47, 55, 85
ADAMTS-13, von Willebrand cleaving protease (%)	40–170[i]	40–160	22–135	38–105	47, 55

BLOOD CHEMICAL CONSTITUTENTS

	Nonpregnant Adult[a]	1st Trimester	2nd Trimester	3rd Trimester	References
Alanine aminotransferase (ALT) (U/L)	7–41	3–30	2–33	2–25	6, 46, 52, 82
Albumin (g/dL)	4.1–5.3[d]	3.1–5.1	2.6–4.5	2.3–4.2	3, 6, 30, 35, 46, 52, 84
Alkaline phosphatase (U/L)	33–96	17–88	25–126	38–229	3, 6, 46, 52, 82
Alpha-1 antitrypsin (mg/dL)	100–200	225–323	273–391	327–487	52
Alpha-fetoprotein (ng/mL)	—	—	~130–400	~130–590	48
Ammonia (μM)	31 ± 3.2	—	—	27.3 ± 1.6	39
Amylase (U/L)	20–96	24–83	16–73	15–81	40, 46, 52, 80
Anion gap (mmol/L)	7–16	13–17	12–16	12–16	52
Aspartate aminotransferase (AST) (U/L)	12–38	3–23	3–33	4–32	6, 46, 52, 82
Bicarbonate (mmol/L)	22–30	20–24	20–24	20–24	52
Bilirubin, total (mg/dL)	0.3–1.3	0.1–0.4	0.1–0.8	0.1–1.1	6, 46
Bilirubin, unconjugated (mg/dL)	0.2–0.9	0.1–0.5	0.1–0.4	0.1–0.5	6, 52
Bilirubin, conjugated (mg/dL)	0.1–0.4	0–0.1	0–0.1	0–0.1	6
Bile acids (μmol/L)	0.3–4.8[j]	0–4.9	0–9.1	0–11.3	6, 16
CA-125 (μg/mL)	7.2–27	2.2–268	12–25.1	16.8–43.8	4, 37, 79
Calcium, ionized (mg/dL)	4.5–5.3	4.5–5.1	4.4–5.0	4.4–5.3	30, 52, 59, 67
Calcium, total (mg/dL)	8.7–10.2	8.8–10.6	8.2–9.0	8.2–9.7	3, 35, 46, 52, 59, 67, 74
Ceruloplasmin (mg/dL)	25–63	30–49	40–53	43–78	52, 54
Chloride (mEq/L)	102–109	101–105	97–109	97–109	22, 46, 52
Creatinine (mg/dL)	0.5–0.9[d]	0.4–0.7	0.4–0.8	0.4–0.9	46, 52, 56
Gamma-glutamyl transpeptidase (GGT) (U/L)	9–58	2–23	4–22	3–26	6, 46, 52, 82
Lactate dehydrogenase (U/L)	115–221	78–433	80–447	82–524	35, 46, 52, 82
Lipase (U/L)	3–43	21–76	26–100	41–112	40
Magnesium (mg/dL)	1.5–2.3	1.6–2.2	1.5–2.2	1.1–2.2	3, 30, 35, 46, 52, 59, 74
Osmolality (mOsm/kg H_2O)	275–295	275–280	276–289	278–280	19, 74
Phosphate (mg/dL)	2.5–4.3	3.1–4.6	2.5–4.6	2.8–4.6	3, 30, 41, 46, 52
Potassium (mEq/L)	3.5–5.0	3.6–5.0	3.3–5.0	3.3–5.1	22, 30, 35, 46, 52, 74, 77
Prealbumin (mg/dL)	17–34	15–27	20–27	14–23	52
Protein, total (g/dL)	6.7–8.6	6.2–7.6	5.7–6.9	5.6–6.7	30, 35, 52
Sodium (mEq/L)	136–146	133–148	129–148	130–148	19, 30, 35, 46, 52, 74, 77
Urea nitrogen (mg/dL)	7–20	7–12	3–13	3–11	22, 46, 52
Uric acid (mg/dL)	2.5–5.6[d]	2.0–4.2	2.4–4.9	3.1–6.3	19, 46, 52

METABOLIC AND ENDOCRINE TESTS

	Nonpregnant Adult[a]	1st Trimester	2nd Trimester	3rd Trimester	References
Aldosterone (ng/dL)	2–9	6–104	9–104	15–101	23, 42, 81
Angiotensin-converting enzyme (ACE) (U/L)	9–67	1–38	1–36	1–39	22, 65
Cortisol (μg/dL)	0–25	7–19	10–42	12–50	52, 81
Hemoglobin A_{1C} (%)	4–6	4–6	4–6	4–7	59, 60, 70
Parathyroid hormone (pg/mL)	8–51	10–15	18–25	9–26	3
Parathyroid hormone-related protein (pmol/L)	<1.3[e]	0.7–0.9	1.8–2.2	2.5–2.8	3
Renin, plasma activity (ng/mL/hr)	0.3–9.0[e]	Not reported	7.5–54.0	5.9–58.8	22, 42
Thyroid stimulating hormone (TSH) (μIU/mL)	0.34–4.25	0.60–3.40	0.37–3.60	0.38–4.04	46, 52, 68
Thyroxine-binding globulin (mg/dL)	1.3–3.0	1.8–3.2	2.8–4.0	2.6–4.2	52
Thyroxine, free (fT_4) (ng/dL)	0.8–1.7	0.8–1.2	0.6–1.0	0.5–0.8	52, 68
Thyroxine, total (T_4) (μg/dL)	5.4–11.7	6.5–10.1	7.5–10.3	6.3–9.7	35, 52
Triiodothyronine, free (fT_3) (pg/mL)	2.4–4.2	4.1–4.4	4.0–4.2	Not reported	68
Triiodothyronine, total (T_3) (ng/dL)	77–135	97–149	117–169	123–162	52

VITAMINS AND MINERALS

	Nonpregnant Adult[a]	1st Trimester	2nd Trimester	3rd Trimester	References
Copper (μg/dL)	70–140	112–199	165–221	130–240	2, 36, 52
Selenium (μg/L)	63–160	116–146	75–145	71–133	2, 52
Vitamin A (retinol) (μg/dL)	20–100	32–47	35–44	29–42	52
Vitamin B_{12} (pg/mL)	279–966	118–438	130–656	99–526	56, 84
Vitamin C (ascorbic acid) (mg/dL)	0.4–1.0	Not reported	Not reported	0.9–1.3	75
Vitamin D, 1,25-dihydroxy (pg/mL)	25–45	20–65	72–160	60–119	3, 59
Vitamin D, 24,25-dihydroxy (ng/mL)	0.5–5.0[e]	1.2–1.8	1.1–1.5	0.7–0.9	71
Vitamin D, 25-hydroxy (ng/mL)	14–80	18–27	10–22	10–18	3, 71
Vitamin E (α-tocopherol) (μg/mL)	5–18	7–13	10–16	13–23	52
Zinc (μg/dL)	75–120	57–88	51–80	50–77	2, 52, 69

AUTOIMMUNE AND INFLAMMATORY MEDIATORS

	Nonpregnant Adult[a]	1st Trimester	2nd Trimester	3rd Trimester	References
C3 complement (mg/dL)	83–177	62–98	73–103	77–111	52
C4 complement (mg/dL)	16–47	18–36	18–34	22–32	52
C-reactive protein (CRP) (mg/L)	0.2–3.0	Not reported	0.4–20.3	0.4–8.1	34
Erythrocyte sedimentation rate (ESR) (mm/hr)	0–20[d]	4–57	7–47	13–70	83
IgA (mg/dL)	70–350	95–243	99–237	112–250	52
IgG (mg/dL)	700–1700	981–1267	813–1131	678–990	52
IgM (mg/dL)	50–300	78–232	74–218	85–269	52

SEX HORMONES

	Nonpregnant Adult[a]	1st Trimester	2nd Trimester	3rd Trimester	References
Dehydroepiandrosterone sulfate (DHEAS) (μmol/L)	1.3–6.8[e]	2.0–16.5	0.9–7.8	0.8–6.5	63
Estradiol (pg/mL)	<20–443[d,f]	188–2497	1278–7192	6137–3460	15, 63
Progesterone (ng/mL)	<1–20[d]	8–48		99–342	15, 63
Prolactin (ng/mL)	0–20[d]	36–213	110–330	137–372	3, 15, 45, 60
Sex hormone binding globulin (nmol/L)	18–114[d]	39–131	214–717	216–724	1, 63
Testosterone (ng/dL)	6–86[d]	25.7–211.4	34.3–242.9	62.9–308.6	63
17-Hydroxyprogesterone (nmol/L)	0.6–10.6[d,e]	5.2–28.5	5.2–28.5	15.5–84	63

LIPIDS

	Nonpregnant Adult[a]	1st Trimester	2nd Trimester	3rd Trimester	References
Cholesterol, total (mg/dL)	<200	141–210	176–299	219–349	9, 20, 38, 52
HDL-cholesterol (mg/dL)	40–60	40–78	52–87	48–87	9, 20, 38, 52, 66
LDL-cholesterol (mg/dL)	<100	60–153	77–184	101–224	9, 20, 38, 52, 66
VLDL-cholesterol (mg/dL)	6–40[e]	10–18	13–23	21–36	38
Triglycerides (mg/dL)	<150	40–159	75–382	131–453	9, 20, 38, 46, 52, 66
Apolipoprotein A-I (mg/dL)	119–240	111–150	142–253	145–262	20, 46, 60
Apolipoprotein B (mg/dL)	52–163	58–81	66–188	85–238	20, 46, 60

CARDIAC

	Nonpregnant Adult[a]	1st Trimester	2nd Trimester	3rd Trimester	References
Atrial natriuretic peptide (ANP) (pg/mL)	Not reported	Not reported	28.1–70.1	Not reported	12
B-type natriuretic peptide (BNP) (pg/mL)	22 ± 10	22 ± 10	32 ± 15	31 ± 21	14
Creatine kinase (U/L)	39–238[d]	27–83	25–75	13–101	50, 52
Creatine kinase-MB (U/L)	<6[k]	Not reported	Not reported	1.8–2.4	50
NT-pro-BNP (pg/mL)	50 ± 26	60 ± 45	60 ± 40	43 ± 34	14
Troponin I (ng/mL)	0–0.08	Not reported	Not reported	0–0.064 (intrapartum)	44, 76

BLOOD GAS

	Nonpregnant Adult[a]	1st Trimester	2nd Trimester	3rd Trimester	References
Bicarbonate (HCO_3^-) (mEq/L)	22–26	Not reported	Not reported	16–22	25
Pco_2 (mm Hg)	38–42	Not reported	Not reported	25–33	25
Po_2 (mm Hg)	90–100	93–100	90–98	92–107	25, 78
pH	7.38–7.42 (arterial)	7.36–7.52 (venous)	7.40–7.52 (venous)	7.41–7.53 (venous) 7.39–7.45 (arterial)	25, 30

RENAL FUNCTION TESTS

	Nonpregnant Adult[a]	1st Trimester	2nd Trimester	3rd Trimester	References
Effective renal plasma flow (mL/min)	492–696[d,e]	696–985	612–1170	595–945	21, 24
Glomerular filtration rate (GFR) (mL/min)	106–132[d]	131–166	135–170	117–182	21, 24, 61
Filtration fraction (%)	16.9–24.7[l]	14.7–21.6	14.3–21.9	17.1–25.1	21, 24, 61
Osmolarity, urine (mOsm/kg)	500–800	326–975	278–1066	238–1034	72
24-hr albumin excretion (mg/24 hr)	<30	5–15	4–18	3–22	32, 72
24-hr calcium excretion (mmol/24 hr)	<7.5[e]	1.6–5.2	0.3–6.9	0.8–4.2	77
24-hr creatinine clearance (mL/min)	91–130	69–140	55–136	50–166	24, 77
24-hr creatinine excretion (mmol/24 hr)	8.8–14[e]	10.6–11.6	10.3–11.5	10.2–11.4	72
24-hr potassium excretion (mmol/24 hr)	25–100[e]	17–33	10–38	11–35	77
24-hr protein excretion (mg/24 hr)	<150	19–141	47–186	46–185	32
24-hr sodium excretion (mmol/24 hr)	100–260[e]	53–215	34–213	37–149	19, 77

[a]Unless otherwise specified, all normal reference values are from the seventeenth edition of *Harrison's Principles of Internal Medicine* (26).
[b]Range includes references with and without iron supplementation.
[c]Reference values are from *Laboratory Reference Handbook*, Pathology Department, Parkland Hospital, 2005.
[d]Normal reference range is specific range for females.
[e]Reference values are from the 15th edition of *Harrison's Principles of Internal Medicine* (13).
[f]Range is for premenopausal females and varies by menstrual cycle phase.
[g]Reference values are from Cerneca et al: Coagulation and fibrinolysis changes in normal pregnancy increased levels of procoagulants and reduced levels of inhibitors during pregnancy induce a hypercoagulable state, combined with a reactive fibrinolysis (17).
[h]Reference values are from Cerneca et al and Choi et al: Tissue plasminogen activator levels change with plasma fibrinogen concentrations during pregnancy (17, 18).
[i]Reference values are from Mannucci et al: Changes in health and disease of the metalloprotease that cleaves von Willebrand factor (55).
[j]Reference values are from Bacq et al: Liver function tests in normal pregnancy: a prospective study of 102 pregnant women and 102 matched controls (6).
[k]Reference values are from Leiserowitz et al: Creatine kinase and its MB isoenzyme in the third trimester and the peripartum period (50).
[l]Reference values are from Dunlop: Serial changes in renal haemodynamics during normal human pregnancy (21).
Appendix courtesy of Dr. Mina Abbassi-Ghanavati and Dr. Laura G. Greer.

APPENDIX II. Maternal Echocardiographic Measurements

Left Ventricle	Pregnancy			Postpartum
	1st Trimester	2nd Trimester	3rd Trimester	
Geometry				
IVS_d (mm)	7.3 ± 1.0	7.4 ± 1.1	7.8 ± 1.2	7.1 ± 0.9
LVEDD (mm)	45–47.8	47–48.9	47–49.6	46–48.8
LVESD (mm)	28–30	29–30.1	30–30.8	28–30.6
PW_d	6.3 ± 0.7	6.6 ± 0.7	6.9 ± 1.0	6.1 ± 0.6
RWT	0.26–0.36	0.27–0.37	0.28–0.38	0.25–0.35
LV mass (g)	111–121	121–135	136–151	114–119
LV mass (g/m^2)	66 ± 13	70 ± 12	76 ± 16	67 ± 11
Systolic function				
FS (%)	37–38	76–78	80–85	67–69
SW thickening (%)	47 ± 17	53 ± 16	51 ± 15	54 ± 19
PW thickening (%)	66 ± 16	72 ± 16	74 ± 16	71 ± 14
VCFC (circ/sec)	1.15–0.3	1.18–0.16	1.18–0.12	1.18–0.12
ESS (g/cm^2)	59 ± 9	53 ± 11	52 ± 11	66 ± 12
Diastolic function				
Heart rate	75–76	76–78	80–85	67–69
Mitral E wave (m/sec)	0.85 ± 0.13	0.84 ± 0.16	0.77 ± 0.15	0.77 ± 0.11
Mitral A wave (m/sec)	0.5 ± 0.09	0.5 ± 0.1	0.55 ± 0.1	0.46 ± 0.1
Deceleration time (ms)	176 ± 44	188 ± 40	193 ± 33	201 ± 48
IVRT (ms)	90 ±19	79 ± 18	72 ± 16	69 ± 10
E wave duration (ms)	263 ± 50	276 ± 43	282 ± 37	288 ± 48
E and A wave duration (ms)	454 ± 121	412 ± 79	375 ± 63	523 ± 88

Values are ranges or means ± SD.
Circ = circumference; d = diastolic; ESS = end-systolic wall stress; FS = fractional shortening; IVRT = isovolumic relaxation time; IVS_d = interventricular septum–diastole; LV = left ventricle; LVEDD = left ventricular end-diastolic dimension; LVESD = left ventricular end-systolic dimension; PW = posterior wall; RWT = relative wall thickness; SW = septal wall; VCFC = rate-adjusted mean velocity of circumferential fiber thickening.
Data from Savu, 2012; Vitarelli, 2011.

APPENDIX III. Sonographic Measurements of the Embryo and Fetus

TABLE III-1. Mean Gestational Sac Diameter and Crown-Rump Length and Corresponding Menstrual Age

Menstrual Age (day)	Menstrual Age (wk)	Gestational Sac Size (mm)	Crown-Rump Length (cm)
30	4.3		
32	4.6	3	
34	4.9	5	
36	5.1	6	
38	5.4	8	
40	5.7	10	0.2
42	6.0	12	0.4
44	6.3	14	0.5
46	6.6	16	0.7
48	6.9	18	0.9
50	7.1	20	1.0
52	7.4	22	1.2
54	7.7	24	1.4
56	8.0	26	1.6
58	8.3	27	1.8
60	8.6	29	2.0
62	8.9	31	2.2
64	9.1	33	2.4
66	9.4	35	2.6
68	9.7	37	2.9
70	10.0	39	3.1
72	10.3	41	3.4
74	10.6	43	3.7
76	10.9	45	4.0
78	11.1	47	4.2
80	11.4	49	4.6
82	11.7	51	5.0
84	12.0	53	5.4

From Daya, 1991; Hadlock, 1992; Nyberg, 1987; Robinson; 1975.

TABLE III-2. Fetal Weight Percentiles According to Gestational Age

Gestational Age (wk)	Fetal Weight Percentiles (g)				
	3rd	10th	50th	90th	97th
10	26	29	35	41	44
11	34	37	45	53	56
12	43	48	58	68	73
13	54	61	73	85	92
14	69	77	93	109	117
15	87	97	117	137	147
16	109	121	146	171	183
17	135	150	181	212	227
18	166	185	223	261	280
19	204	227	273	319	342
20	247	275	331	387	415
21	298	331	399	467	500
22	357	397	478	559	599
23	424	472	568	664	712
24	500	556	670	784	840
25	586	652	785	918	984
26	681	758	913	1068	1145
27	787	876	1055	1234	1323
28	903	1005	1210	1415	1517
29	1029	1145	1379	1613	1729
30	1163	1294	1559	1824	1955
31	1306	1454	1751	2048	2196
32	1457	1621	1953	2285	2449
33	1613	1795	2162	2529	2711
34	1773	1973	2377	2781	2981
35	1936	2154	2595	3026	3254
36	2098	2335	2813	3291	3528
37	2259	2514	3028	3542	3797
38	2414	2687	3236	3785	4058
39	2563	2852	3435	4018	4307
40	2700	3004	3619	4234	4538
41	2825	3144	3787	4430	4749
42	2935	3266	3934	4602	4933

Reproduced with permission from Hadlock, 1991.

TABLE III-3. Smoothed Birth Weight Percentiles for Twins with Dichorionic Placentation

GA (wk)	Smoothed Birth Weight Percentiles				
	5th	10th	50th	90th	95th
23	477	513	632	757	801
24	538	578	712	853	903
25	606	652	803	962	1018
26	684	735	906	1085	1148
27	771	829	1021	1223	1294
28	870	935	1152	1379	1459
29	980	1054	1298	1554	1645
30	1102	1186	1460	1748	1850
31	1235	1328	1635	1958	2072
32	1374	1477	1819	2179	2306
33	1515	1630	2007	2403	2543
34	1653	1778	2190	2622	2775
35	1781	1916	2359	2825	2989
36	1892	2035	2506	3001	3176
37	1989	2139	2634	3155	3339
38	2079	2236	2753	3297	3489
39	2167	2331	2870	3437	3637
40	2258	2428	2990	3581	3790
41	2352	2530	3115	3731	3948

GA = gestational age.
Reproduced with permission from Ananth, 1998.

TABLE III-4. Smoothed Birth Weight Percentiles for Twins with Monochorionic Placentation

GA (wk)	Smoothed Birth Weight Percentiles				
	5th	10th	50th	90th	95th
23	392	431	533	648	683
24	456	501	620	753	794
25	530	582	720	875	922
26	615	676	836	1017	1072
27	713	784	970	1178	1242
28	823	904	1119	1360	1433
29	944	1037	1282	1559	1643
30	1072	1178	1457	1771	1867
31	1204	1323	1637	1990	2097
32	1335	1467	1814	2205	2325
33	1457	1601	1980	2407	2537
34	1562	1716	2123	2580	2720
35	1646	1808	2237	2719	2866
36	1728	1899	2349	2855	3009
37	1831	2012	2489	3025	3189
38	1957	2150	2660	3233	3408
39	2100	2307	2854	3469	3657
40	2255	2478	3065	3726	3927
41	2422	2661	3292	4001	4217

Reproduced with permission from Ananth, 1998.

TABLE III-5. Head Circumference Standard Deviations Below the Mean (cm) According to Gestational Age

GA (wk)	50th Percentile (cm)	Standard Deviations Below the Mean				
		−1	−2	−3	−4	−5
20	17.5	16.0	14.5	13.1	11.6	10.1
21	18.7	17.2	15.7	14.3	12.8	11.3
22	19.8	18.4	16.9	15.4	14.0	12.5
23	21.0	19.5	18.0	16.6	15.1	13.6
24	22.1	20.6	19.1	17.7	16.2	14.7
25	23.2	21.7	20.2	18.8	17.3	15.8
26	24.2	22.7	21.3	19.8	18.3	16.9
27	25.2	23.8	22.3	20.8	19.4	17.9
28	26.2	24.7	23.3	21.8	20.3	18.9
29	27.1	25.7	24.2	22.7	21.3	19.8
30	28.1	26.6	25.1	23.6	22.2	20.7
31	28.9	27.4	26.0	24.5	23.0	21.6
32	29.7	28.3	26.8	25.3	23.9	22.4
33	30.5	29.0	27.6	26.1	24.6	23.2
34	31.2	29.7	28.3	26.8	25.3	23.9
35	31.9	30.4	28.9	27.5	26.0	24.5
36	32.5	31.0	29.5	28.1	26.6	25.1
37	33.0	31.6	30.1	28.6	27.2	25.7
38	33.5	32.0	30.6	29.1	27.6	26.2
39	33.9	32.5	31.0	29.5	28.1	26.6
40	34.3	32.8	31.4	29.9	28.4	27.0

Abbreviated with permission from Chervenak, 1984.

TABLE III-6. Fetal Thoracic Circumference Measurements (cm) According to Gestational Age

Gestational Age (wk)	Percentiles				
	2.5th	5th	50th	95th	97.5th
16	5.9	6.4	9.1	11.9	12.4
17	6.8	7.3	10.0	12.8	13.3
18	7.7	8.2	11.0	13.7	14.2
19	8.6	9.1	11.9	14.6	15.1
20	9.6	10.0	12.8	15.5	16.0
21	10.4	11.0	13.7	16.4	16.9
22	11.3	11.9	14.6	17.3	17.8
23	12.2	12.8	15.5	18.2	18.8
24	13.2	13.7	16.4	19.1	19.7
25	14.1	14.6	17.3	20.0	20.6
26	15.0	15.5	18.2	21.0	21.5
27	15.9	16.4	19.1	21.9	22.4
28	16.8	17.3	20.0	22.8	23.3
29	17.7	18.2	21.0	23.7	24.2
30	18.6	19.1	21.9	24.6	25.1
31	19.5	20.0	22.8	25.5	26.0
32	20.4	20.9	23.7	26.4	26.9
33	21.3	21.8	24.6	27.3	27.8
34	22.2	22.8	25.5	28.2	28.7
35	23.1	23.7	26.4	29.1	29.6
36	24.0	24.6	27.3	30.0	30.6
37	24.8	25.5	28.2	30.9	31.5
38	25.9	26.4	29.1	31.9	32.4
39	26.8	27.3	30.0	32.8	33.3
40	27.7	28.2	30.9	33.7	34.2

Adapted with permission from Chitkara, 1987.

TABLE III-7. Length of Fetal Long Bones (mm) According to Gestational Age

	Humerus Percentile			Ulna Percentile			Radius Percentile			Femur Percentile			Tibia Percentile			Fibula Percentile		
Week	3	50	97	3	50	97	3	50	97	3	50	97	3	50	97	3	50	97
14	11	14	18	9	12	16	8	11	15	11	14	18	8	11	15	7	11	14
15	14	17	21	12	15	19	10	14	17	14	17	21	11	14	18	10	14	17
16	17	20	24	15	18	22	13	17	20	17	20	24	13	17	21	13	16	20
17	20	23	27	17	21	25	16	19	23	19	23	27	16	20	24	16	19	23
18	22	26	30	20	24	28	18	22	26	22	26	30	19	23	27	18	22	26
19	25	29	33	23	27	31	20	24	28	25	29	33	22	26	30	21	25	29
20	27	32	36	25	29	34	23	27	31	28	32	36	25	29	33	24	28	32
21	30	34	38	28	32	36	25	29	33	31	35	39	27	31	35	26	31	35
22	32	36	41	30	34	39	27	31	35	33	38	42	30	34	38	29	33	37
23	34	39	43	32	37	41	29	33	37	36	40	45	32	36	41	31	36	40
24	36	41	45	34	39	43	30	35	39	38	43	48	34	39	43	34	38	42
25	38	43	47	36	41	46	32	37	41	41	46	50	37	41	46	36	40	45
26	40	45	49	38	43	48	34	38	43	43	48	53	39	43	49	38	42	47
27	42	47	51	40	45	50	35	40	44	45	50	55	41	45	50	40	44	49
28	44	49	53	42	47	51	37	41	46	48	53	58	43	47	52	41	46	51
29	46	50	55	43	48	53	38	43	47	50	55	60	44	49	54	43	48	53
30	47	52	57	45	50	55	39	44	49	52	57	62	46	51	56	45	50	55
31	49	54	58	46	51	56	34	44	50	54	59	65	48	53	58	46	52	57
32	50	55	60	48	43	58	40	45	51	56	61	67	49	54	60	48	53	58
33	51	56	62	49	54	59	41	46	53	58	63	69	51	56	61	49	55	60
34	53	58	63	50	55	61	43	49	54	59	65	71	52	58	63	51	56	61
35	54	59	64	51	57	62	44	50	55	61	67	72	54	59	64	52	58	63
36	55	60	66	52	58	64	45	51	56	62	68	74	55	60	66	53	59	64
37	56	62	67	53	59	65	46	52	57	64	70	76	56	62	67	54	60	66
38	57	63	68	54	60	66	47	53	58	65	71	77	57	63	69	56	61	67
39	58	64	69	55	61	67	48	53	59	66	72	79	58	64	70	57	63	68
40	59	65	70	56	62	68	48	54	60	67	74	81	59	65	71	58	64	70

Data from Chitty, 2002.

TABLE III-8. Ocular Parameter Percentiles According to Gestational Age

	Binocular Distance (mm)			Interocular Distance (mm)			Ocular Diameter (mm)		
Age (wk)	5th	50th	95th	5th	50th	95th	5th	50th	95th
15	15	22	30	6	10	14	4	6	9
16	17	25	32	6	10	15	5	7	9
17	19	27	34	6	11	15	5	8	10
18	22	29	37	7	11	16	6	9	11
19	24	31	39	7	12	16	7	9	12
20	26	33	41	8	12	17	8	10	13
21	28	35	43	8	13	17	8	11	13
22	30	37	44	9	13	18	9	12	14
23	31	39	46	9	14	18	10	12	15
24	33	41	48	10	14	19	10	13	15
25	35	42	50	10	15	19	11	13	16
26	36	44	51	11	15	20	12	14	16
27	38	45	53	11	16	20	12	14	17
28	39	47	54	12	16	21	13	15	17
29	41	48	56	12	17	21	13	15	18
30	42	50	57	13	17	22	14	16	18
31	43	51	58	13	18	22	14	16	19
32	45	52	60	14	18	23	14	17	19
33	46	53	61	14	19	23	15	17	19
34	47	54	62	15	19	24	15	17	20
35	48	55	63	15	20	24	15	18	20
36	49	56	64	16	20	25	16	18	20
37	50	57	65	16	21	25	1	18	21
38	50	58	65	17	21	26	16	18	21
39	51	59	66	17	22	26	16	19	21
40	52	59	67	18	22	26	16	19	21

Adapted with permission from Romero, 1988.

TABLE III-9. Transverse Cerebellar Diameter Percentiles According to Gestational Age

Gestational Age (wk)	Cerebellum Diameter (mm)		
	5th	50th	95th
14	13	14	15
15	14	15	16
16	15	16	17
17	16	17	18
18	17	18	18
19	18	19	20
20	19	20	22
21	20	22	23
22	22	23	25
23	23	25	27
24	25	27	28
25	26	28	30
26	28	30	32
27	29	32	34
28	31	34	36
29	33	35	38
30	35	37	40
31	36	39	42
32	38	41	44
33	40	43	46
34	42	45	48
35	44	47	50
36	45	49	52
37	47	51	54
38	49	52	56
39	50	54	58
40	52	56	60

Adapted with permission from Sherer, 2007.

TABLE III-10. Reference Values for Umbilical Artery Doppler Indices

	Percentiles					
	5th		50th		95th	
GA (wk)	Resistive Index	Systolic-Diastolic Ratio	Resistive Index	Systolic-Diastolic Ratio	Resistive Index	Systolic-Diastolic Ratio
16	0.70	3.39	0.80	5.12	0.90	10.50
17	0.69	3.27	0.79	4.86	0.89	9.46
18	0.68	3.16	0.78	4.63	0.88	8.61
19	0.67	3.06	0.77	4.41	0.87	7.90
20	0.66	2.97	0.76	4.22	0.86	7.30
21	0.65	2.88	0.75	4.04	0.85	6.78
22	0.64	2.79	0.74	3.88	0.84	6.33
23	0.63	2.71	0.73	3.73	0.83	5.94
24	0.62	2.64	0.72	3.59	0.82	5.59
25	0.61	2.57	0.71	3.46	0.81	5.28
26	0.60	2.50	0.70	3.34	0.80	5.01
27	0.59	2.44	0.69	3.22	0.79	4.76
28	0.58	2.38	0.68	3.12	0.78	4.53
29	0.57	2.32	0.67	3.02	0.77	4.33
30	0.56	2.26	0.66	2.93	0.76	4.14
31	0.55	2.21	0.65	2.84	0.75	3.97
32	0.54	2.16	0.64	2.76	0.74	3.81
33	0.53	2.11	0.63	2.68	0.73	3.66
34	0.52	2.07	0.62	2.61	0.72	3.53
35	0.51	2.03	0.61	2.54	0.71	3.40
36	0.50	1.98	0.60	2.47	0.70	3.29
37	0.49	1.94	0.59	2.41	0.69	3.18
38	0.47	1.90	0.57	2.35	0.67	3.08
39	0.46	1.87	0.56	2.30	0.66	2.98
40	0.45	1.83	0.55	2.24	0.65	2.89

GA = gestational age.
Adapted with permission from Kofinas, 1992.

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