NOTICE

Medicine is an ever-changing science. As new research and clinical experience broaden our knowledge, changes in treatment and drug therapy are required. The authors and the publisher of this work have checked with sources believed to be reliable in their efforts to provide information that is complete and generally in accord with the standards accepted at the time of publication. However, in view of the possibility of human error or changes in medical sciences, neither the authors nor the publisher nor any other party who has been involved in the preparation or publication of this work warrants that the information contained herein is in every respect accurate or complete, and they disclaim all responsibility for any errors or omissions or for the results obtained from use of the information contained in this work. Readers are encouraged to confirm the information contained herein with other sources. For example and in particular, readers are advised to check the product information sheet included in the package of each drug they plan to administer to be certain that the information contained in this work is accurate and that changes have not been made in the recommended dose or in the contraindications for administration. This recommendation is of particular importance in connection with new or infrequently used drugs.
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These are the times that try men’s souls.

—Thomas Paine, *The American Crisis*, 1776–1783

This 23rd edition of *Williams Obstetrics* arrives at a time of economic uncertainty for our country—indeed, for the world. There is especial anxiety provoked by the anticipated tumultuous reorganization of our healthcare system. We dedicate this book to those who are fair minded and who strive to bring about these changes with equanimity. We include all those who work to construct a system that is the best for all, includes those who are disadvantaged, but does not diminish the quality of healthcare for those who will ultimately finance the system—a tall order indeed. We echo the philosophy of the American College of Obstetricians and Gynecologists that all women and their unborn children should have access to obstetrical care and family planning services.
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In this 23rd edition of *Williams Obstetrics*, we continue to emphasize the science-based underpinnings and evidence-based practices of our specialty. Most professional and academic organizations embrace these principles, and while some promulgate guidelines and recommendations, others provide funding for such investigations. Our policy is to cite these whenever possible. A major impetus for these studies comes from the *Eunice Shriver Kennedy* National Institute of Child Health and Human Development—also called the NICHD. For many decades, this Institute has supported basic and clinical research to improve healthcare for women and children. We especially rely on investigations performed through NICHD-sponsored Maternal-Fetal Medicine Units and Neonatal Units Networks. There is also fiscal support for young investigators in obstetrics and allied specialties that comes from a number of societies and organizations. Among others, these include the American College of Obstetricians and Gynecologists, the American Gynecological and Obstetrical Society, the Society for Maternal-Fetal Medicine, the Society for Gynecological Investigation, and the American Board of Obstetrics and Gynecology.

A major objective of this book is to provide a convenient source that will aid the busy practitioner—those “in the trenches.” To this end, we summarize new data that has influenced evidence-based management to improve pregnancy outcomes. And while we cite numerous sources to accomplish this, we again mention some important caveats. For example, while we try to avoid—or at least soften—dogmatism that creeps into obstetrical practice, we often cite our combined clinical experiences drawn from large teaching services. We remain convinced that these are disciplined examples of evidence-based obstetrics. Importantly, we do not represent that these constitute the sole method of management.

To succeed in these self-imposed mandates, we have again added new editors with especial expertise in important areas to ensure accurate interpretation of recent scientific and clinical advances. To allow for this, two editors who have served with distinction for several editions of this book have passed their pens on to others. Dr. Larry Gilstrap has traded the Chair of Obstetrics, Gynecology, and Reproductive Sciences at the University of Texas-Houston Medical School to become Executive Director of the American Board of Obstetrics and Gynecology. Dr. Kathy Wenstrom has left the University of Alabama at Birmingham to become Chief of Maternal-Fetal Medicine at Brown University. We will miss them both and value their contributions. To fill their shoes, two associate editors have assumed their duties. Dr. Dwight Rouse from the University of Alabama at Birmingham continues to lend his expertise in many areas of obstetrics, maternal-fetal medicine, and epidemiology. He has many years of experience as a leading investigator in the Maternal-Fetal Medicine Units Network.

Dr. Catherine Spong continues her ever-increasing duties as Chief of the Pregnancy and Perinatology Branch of the *Eunice Shriver Kennedy* National Institute of Child Health and Human Development. Cathy also serves as program scientist for the vitally important Maternal-Fetal Medicine Units Network cited above. A third vacancy in the associate editorship is Dr. William Rainey, who left UT Southwestern and is a Regents’ Professor of Physiology at the Medical College of Georgia. Bill performed a fantastic job for the 22nd edition in dissecting basic science principles of human reproduction in a textbook written primarily for clinicians.

Dr. George Wendel remains on the team as associate editor. He is internationally recognized for his expertise in obstetrical, perinatal, and sexually transmitted infections. He is widely published in these fields and has mentored numerous fellows who have followed in his footsteps. Also joining us from UT Southwestern as associate editor is Dr. Diane Twickler, Professor of Radiology as well as Obstetrics and Gynecology. Her incredible wealth of knowledge and clinical and research experience with a variety of imaging techniques used during pregnancy have been unsung contributions for many previous editions of this book.

Reflecting the rapidly accruing knowledge in clinical obstetrics is the further addition of six extremely talented contributing editors, all from UT Southwestern Medical Center. Dr. Jodi Dashe uses her extensive experience and incredible skills with obstetrical sonography, fetal diagnosis, and prenatal genetics to provide input for this 23rd edition as she has namelessly done now for many previous ones. Dr. Barbara Hoffman has widespread clinical expertise with contraception and sterilization issues, embryology and anatomy, and especial interest in congenital and acquired genital tract anomalies. Equally importantly, she has served as the in-house production editor for the 22nd and 23rd editions and has spent countless evenings and weekends applying her considerable editorial talents and creative illustration production. Dr. Mala Mahendroo is a basic scientist who performs a magnificent job of providing a coherent clinical translational version of basic science aspects of human reproduction. To do so, she draws from her own research experience with cervical remodeling during pregnancy and initiation of human labor. Dr. Jim Alexander brings his expertise with the conduct of normal as well as abnormal labor and delivery, cesarean delivery, conduction analgesia, preeclampsia, and obstetrical hemorrhage. Dr. Brian Casey lends his in-depth clinical and research experience with diabetes, fetal growth disorders, and thyroid physiology. Dr. Jeanne Sheffield joins us as a vital member of the obstetrical infectious diseases group. In addition to her wealth of clinical and research experience with maternal, perinatal, and sexually transmitted infections, she also has extensive experience in managing drug dependency as well as a
host of other medical and surgical disorders that complicate pregnancy.

We continue to rely heavily on other colleagues for their intellectual and clinical input and the use of photographs and other illustrations that improve immensely the readability of this 23rd edition. Although these colleagues are too numerous to mention individually, we attempt to thank those with special contributions. From UT Southwestern and Parkland Hospital, we cite the entire faculty of the Maternal-Fetal Medicine Division, who, in addition to providing expert content, graciously helped us cover clinical duties when writing and editing were especially time consuming. These include Drs. Oscar Andujo, Morris Bryant, Susan Cox, Jennifer Hernandez, Robyn Horsager, Julie Lo, Mark Peters, Scott Roberts, Vanessa Rogers, Patricia Santiago-Munoz, Steve Shivers, Ed Wells, Kevin Worley, and Mike Zaretsky. Also in the division, our special thanks go to Dr. Don McIntire, who retrieved and tabulated electronically stored data for Parkland Hospital obstetrical outcomes that are shown in numerous tables and figures throughout this book. Dr. Barry Schwarz shared his extensive knowledge of contraceptive management for preparation of that chapter. Dr. Kelly Carrick of the Department of Pathology contributed numerous photographs illustrating both normal and abnormal features of the female reproductive tract. Dr. Gerda Zeeman from the University of Groningen in The Netherlands—but who remains in Dallas in spirit—graciously provided magnetic resonance images from women with eclampsia. We also thank the fellows of our Maternal-Fetal Medicine Division and our many residents in obstetrics and gynecology. Their vigilant search for perfect examples of normal and abnormal findings has led to many of the photographs in this edition. We specifically thank Drs. Mina Abbassi-Ghanavati and Laura Greer for their time-consuming efforts to provide the first-ever appendix of normal values during pregnancy for common and uncommon laboratory tests. We predict that this will be a priceless resource for practitioners.

From the University of Alabama at Birmingham, Ms. Suzanne Cliver provided material for tables and figures from the perinatal database. Drs. Ona Marie Faye-Petersen and Michael Conner of the Department of Pathology generously contributed pictures and photomicrographs of placental pathology. From Bethesda, Dr. Rosemary Higgins of the Neonatal Units Network provided expert input for disorders of the fetus and newborn.

Thanks to generous funding from The McGraw-Hill Companies, this 23rd edition has full-color photographs and illustrations. Many were either replaced or redrawn for consistency of style. More than 200 of the new color illustrations were created by two talented medical illustrationists. Ms. Marie Sena was one of the major artist contributors to the inaugural edition of Williams Gynecology. To even further her experiences for the current book, she logged countless hours in labor and delivery, in the anatomy laboratory, and in model simulations. Ms. Erin Frederikson, also a veteran of our art team, added insightful images depicting cesarean delivery, peripartum hysterectomy, and fetal development. Additional artwork was generously provided by Mr. Jordan Pietz and Ms. Jennifer Hulsey. All of these talented artists trained on campus under the stimulative leadership of Mr. Lewis Calver, who is Chair of the Biomedical Communications Graduate Program. More artistic support came from Mr. Joseph Varghese and his team at Thomson Digital, who provided the full-color graphs and line art that completes this edition’s art program. They were aided by medical content expert Dr. Anuradha Majumdar, who precisely translated our academic vision to each image. Both tirelessly coordinated efforts between our authors and their art team and graciously accommodated our numerous changes and tweaks. In addition to these artists, we were grateful for photographic contributions from academic giants in their field. We boast seminal placental images generously donated by a dear friend, Dr. Kurt Benirschke, laparoscopic images of ectopic pregnancies from Dr. Togas Tolandi, and fetal surgery images from Dr. Timothy Crombleholme.

Production of the 5,000-page typewritten manuscript would be impossible without a dedicated team to bring these efforts together. Once again, we are deeply indebted to Ms. Connie Utterback for her untiring efforts as production coordinator for Dallas, Birmingham, and Washington, D.C. She received able assistance with manuscript production from the Dallas group that included Ms. Minnie Tregaskis, Ms. Melinda Epstein, Ms. Mary Kay McDonald, Ms. Dina Trujillano, and Ms. Ellen Watkins. From Birmingham, production coordination and manuscript preparation were ably provided by Ms. Belinda Rials and Ms. Sue Capps. Ms. Cherry Neely coordinated database analysis and presentation with help from research nurses Ms. Allison Northen and Ms. Rachel Copper. Graphic illustration for the Birmingham group was provided by Ms. Jo Taylor.

It again has been a privilege and a pleasure to work with the dedicated personnel from McGraw-Hill. A number of individuals were crucial to the success of this 23rd edition. Dr. Anne Sydor helped us to conceive the project, and she provided the inspiration and obtained financial support to present this full-color edition. Ms. Marsha Loeb served as senior editor during the bulk of its production, and she was an efficient and steadfast advocate who frequently went above and beyond to accommodate our needs. Her responsibilities were assumed in the “home stretch” by Ms. Alyssa Fried, who has ably led us to completion. We appreciate her efforts and thank her for her help and her patience. Integral to a project of this scope and complexity is attention to detail. This 23rd edition would have never seen the light of day without the considerable talents of Mr. Phil Galea, Mr. John Williams, and Mr. Armen Ovsepian. They have been long-standing members of the Williams team and have lent their considerable talents to several editions. An especially warm thank you is extended to a long-time colleague, Ms. Karen Davis, who coordinated production of this edition. Karen has been a tireless and committed member of our Williams family. Over the many years that we have worked with her, she has always handled problems quickly and expertly as soon as they arose. Her dedication to creating the best textbook possible equaled our efforts, and we are in awe of her unflappable, gracious, and effective style. Finally, McGraw-Hill enlisted Aptara Inc. for composition. We thank Ms. Satvinder Kaur for her talents in coordinating and overseeing composition. Her attention to detail and organization skills were vital to completion of our project.
Our goal at the outset of this 23rd edition was to create a visual landmark to equal the written content. To this end, almost 90 percent of images in this edition have been upgraded or revised. Of these, 220 images were rendered by our medical illustrators cited above. It will also be apparent that almost all previous black-and-white photographs have been replaced by those in vivid color. This is supplanted by a thorough canvass of the literature with stated efforts to emphasize evidence-based management. To do this, almost 2000 new journal and textbook references were added, and more than 400 of these were published in 2009. All of this talent and hard work has come to fruition in what we hope is the best edition so far of *Williams Obstetrics*. We further hope that the reader will enjoy studying its content as much as we have enjoyed conveying it.
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According to the Oxford English Dictionary, the word obstetrics is defined as “that branch of medicine that deals with childbirth and the care and treatment of the mother before and after birth.” Its derivation is from the Latin obstetrix, meaning midwife—from “mid”—with, and “wif”—meaning woman. Petraglia (2008) describes evidence of midwifery from records found in ancient Egypt and the Roman Empire. The Egyptian Ebers Papyrus (1900 to 1550 BC) recognized midwifery as a female occupation concerned with obstetrics and gynecology, and specifically with the acceleration of parturition and the birth process. Petraglia further reports that midwifery services were described through the Middle Ages and into the 18th century, at which time the role of the surgeon superseded that of the midwife. It was at this time that medicine began to assert that its modern scientific processes were better for mothers and infants than those of folk-medical midwives.

In the contemporaneous sense, obstetrics is concerned with reproduction of humans. The specialty promotes health and well-being of the pregnant woman and her fetus through quality prenatal care. Such care entails appropriate recognition and treatment of complications, supervision of their labor and delivery, ensuring care of the newborn, and management of the puerperium to include follow-up care that promotes health and provides family planning options.

The importance of obstetrics is attested to by the use of maternal and neonatal outcomes as an index of the quality of health and life in human society. Intuitively, indices that reflect poor obstetrical and perinatal outcomes would lead to the assumption that medical care for the entire population is lacking. With those thoughts, we now provide a synopsis of the current state of maternal and newborn health in the United States as it relates to obstetrics.

The National Vital Statistics System of the United States is the oldest and most successful example of intergovernmental data sharing in public health. The National Center for Health Statistics (NCHS) collects and disseminates official statistics through contractual agreements with vital registration systems operated in various jurisdictions legally responsible for registration of births, fetal deaths, deaths, marriages, and divorces. Legal authority 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. Schoendorf and Branum (2006) provide a thoughtful review of the use of these statistics to conduct obstetrical and perinatal research.

Standard certificates for the registration of live births and deaths were first developed in 1900. An act of Congress in 1902 established the Bureau of the Census to develop a system for the annual collection of vital statistics. The Bureau retained authority until 1946, when the function was transferred to the United States Public Health Service. It is presently assigned to the Division of Vital Statistics of the NCHS, which is a division of the Centers for Disease Control and Prevention (CDC). The standard birth certificate was extensively revised in 1989 to include more information on medical and lifestyle risk factors and also obstetrical care practices.

Further revisions were initiated in some states in 2003, but full implementation in all states will not be completed for several more years. The 2003 revision focuses on fundamental changes in data collection aimed at improving accuracy.
Changes also include a format conducive to electronic processing, to collect more explicit parental demographic data, and to improve selection of information regarding antepartum and intrapartum complications. Some examples of new data to be collected include those related to uterine rupture, blood transfusion, and pregnancy resulting from infertility treatment.

**Definitions**

The uniform use of standard definitions is encouraged by the World Health Organization as well as the American Academy of Pediatrics and the American College of Obstetricians and Gynecologists (2007). Such uniformity allows comparison of data not only between states or regions of the country, but also between countries. Still, not all of these definitions are uniformly applied, as illustrated by the example of definitions of inclusive fetal birthweights. To wit, these two organizations recommend reporting to include all fetuses and neonates born weighing at minimum 500 g, whether alive or dead. But not all of the 50 states follow this recommendation. For example, 28 states stipulate that fetal deaths beginning at 20 weeks’ gestation should be recorded as such; 8 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 deaths. To further the confusion, the National Vital Statistics Reports tabulates fetal deaths as those 20 weeks’ gestation or older (Centers for Disease Control and Prevention, 2009). But the 50th percentile for fetal weight at 20 weeks approximates 325 to 350 g—considerably less than the 500-g definition. Indeed, a birthweight of 500 g corresponds closely with the 50th percentile for 22 weeks.

Definitions recommended by the NCHS and the CDC are as follows:

**Perinatal period.** The period after birth of an infant born after 20 weeks and ending at 28 completed days after birth. When perinatal rates are based on birthweight, rather than gestational age, it is recommended that the perinatal period be defined as commencing at 500 g.

**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 as births, but rather are termed abortuses for purposes of vital statistics.

**Birthweight.** The weight of a neonate 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 or after 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 anytime after 37 completed weeks of gestation and up until 42 completed weeks of gestation (260 to 294 days).

**Preterm neonate.** A neonate born before 37 completed weeks (the 259th day).

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

**Abortus.** A fetus or embryo removed or expelled from the uterus during 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 with the intention other than to produce a liveborn neonate, and which 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.

**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.

**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-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.

Pregnancy in the United States

Data from diverse sources have been used to provide the following snapshot of pregnancy in the United States during the first decade of the 21st century.

- **Pregnancy Rates**

  According to the Centers for Disease Control and Prevention (2009), and as shown in Table 1-1, the fertility rate in 2006 of women aged 15 to 44 years was 68.5 live births per 1000 women. This rate began trending downward in 1990 and decreased even lower than that for replacement births, indicating a population decline (Hamilton, 2004). However, this was offset by considerable net migration into the United States that is discussed further on page 10. For example, there were more than 1 million migrants each year from 2000 to 2002.

  There were nearly 4.3 million births in 2006, and this constituted a birth rate for the United States of 14.2 per 1000 population. This rate was up from that in 2002, which was the lowest rate ever recorded—13.9 per 1000 population. Hispanic women accounted for more than 1 in 5 births. The average American woman has 3.2 pregnancies in her lifetime, and 1.8 of these are considered wanted pregnancies (Ventura and colleagues, 1999). After exclusion of fetal losses and induced terminations, American women on average deliver 2.0 live births per pregnancy. Assuming another 15 percent for spontaneous abortion, there are approximately 6 million pregnancies in this country each year.

  ![TABLE 1-1. Some Statistics Concerning Reproductive Outcome for the United States in 2005 or 2006](Data from Centers for Disease Control and Prevention (2008, 2009).)

- **MEASURES OF OBSTETRICAL CARE**

  There are a number of indices—several among the vital statistic definitions described above—that are used as a yardstick of obstetrical and perinatal outcomes to assess quality of care.

- **Healthy People 2010 and 2020**

  Objectives for maternal and infant health for the decade now ending were promulgated by the Centers for Disease Control and Prevention and the Health Resources and Service Administration (2000) and included in the nationwide goals termed Healthy People 2010. Progress toward some of these goals has been disappointing. Notably, one major objective was to lower the number of preterm births, but these have actually increased since 2000. Also, the disparity in pregnancy outcomes between whites and racial/ethnic minorities has persisted, and the infant mortality rate in African-American women is now almost twice that of white mothers. Other objectives were concerned with decreasing the rates of maternal, perinatal, and infant morbidity and mortality.

  Planning for Healthy People 2020 began in 2008 guided by the Office of Disease Prevention and Health Promotion (2009). Goals are being determined using science-based findings that have accrued over the current decade with launch expected in 2010.

- **Perinatal Mortality**

  As previously defined, the perinatal mortality rate includes the numbers of stillbirths and neonatal deaths per 1000 total births. According to the National Vital Statistics Reports by MacDorman and Kirmeyer (2009), in 2005 there were 25,894 fetal deaths of 20 weeks’ gestation or more. As shown in Figure 1-1, the fetal death rate declined gradually from 1999 but plateaued in 2003. Most of the improvement was a decrease in fetal deaths between 20 and 27 weeks.

  Fetal deaths after 20 weeks are an important public health issue. Although there is appropriate concern concentrated on infant mortality—death in the first year of life—a focus on fetal mortality may provide further opportunities for prevention. For
example, racial and ethnic disparity associated with fetal death is obvious as shown in Figure 1-2. In 2004, approximately a fourth of the 18,593 neonatal deaths were due to preterm delivery and approximately a fifth was caused by a congenital malformation (Heron, 2007). Worldwide, approximately 4 million babies are stillborn each year, and another 4 million die in the first 4 weeks of life (Lawn and colleagues, 2005).

### Infant Deaths

There were 28,384 infant deaths in 2005, a rate of 6.9 per 1000 live births compared with 6.8 in 2001 (Mathews and MacDorman, 2008). The three leading causes of infant death—congenital malformations, low birthweight, and sudden infant death syndrome—accounted for 44 percent of all deaths. Infants born at the lowest gestational ages and birthweights have a large impact on these mortality rates. For example, 55 percent of all infant deaths in 2005 occurred in 2 percent of infants born before 32 weeks’ gestation. Indeed, the percentage of infant deaths related to preterm birth increased from 34.6 percent in 2000 to 36.5 percent in 2005. When analyzed by birthweight, two thirds of infant deaths were in low-birthweight neonates. Of particular interest are those birthweights less than 500 g, for which neonatal intensive care can now be offered. In 2001, there were 6450 liveborn infants weighing less than 500 g, but 86 percent of these infants died during the first 28 days of life. Of the 1044 who survived the first 28 days of life, there were 934 who lived for at least 1 year. Thus, only 11 percent of all neonates weighing < 500 g survived infancy. Importantly, developmental and neurological sequelae are common in the survivors (see Chap. 36, p. 807).

St. John and associates (2000) have estimated the total cost of initial care in the United States for all newborns as $10.2 billion annually. Almost 60 percent of this expenditure is attributed to preterm births before 37 weeks, and 12 percent is spent on neonates born between 24 and 26 weeks.

### Maternal Mortality

Pregnancy and childbirth have never been safer for women in the United States. In fact, pregnancy-related deaths are so uncommon as to be measured per 100,000 births. Still, some women die from early pregnancy complications related to ectopic pregnancy, miscarriage, and induced abortion and later complications such as hypertensive disorders, hemorrhage, and infection. Kung and colleagues (2008) reported for the National Vital Statistics System that there were 623 pregnancy-related deaths in the United States in 2005. Some of the more common causes of pregnancy-related maternal deaths are shown in Table 1-2. Hemorrhage and infection cause half of deaths associated with ectopic pregnancy and abortion. Taken together, embolism, hemorrhage, hypertension, and infection accounted for 65 percent of maternal deaths after midpregnancy. It is also important to consider the role that the increasing cesarean delivery rate has on maternal mortality risks (Clark and associates, 2008; Deneux-Tharaux and co-workers, 2006; Lang and King, 2008).

There are a number of other factors important to the discussion of maternal mortality. First, maternal deaths are notoriously underreported, possibly by as much as half (Koonin and colleagues, 1997). Even so, there is no doubt that a major accomplishment of obstetrical care is the markedly decreased risk of death from pregnancy complications. As shown in Figure 1-3, maternal mortality rates decreased by two orders of magnitude—almost 99 percent—in the United States during the 20th century. Still, it is unfortunate that mortality rates have plateaued since 1982 (Lang and King, 2008). This may be due in part to an artificial increase caused by a classification system change. For example, new International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10) codes were implemented in 1999.

A second important consideration is the obvious disparity of increased mortality rates in indigent and minority women as shown in Figure 1-4. The disparity with indigent women is exemplified by the study of maternal deaths in women cared for in a third-party payer system, the Hospital Corporation of America. In this study of nearly 1.5 million pregnant women, Clark and associates (2008) reported an impressively low maternal mortality rate of 6.5 per 100,000.
The third important consideration is that many of the reported maternal deaths are considered preventable. According to Berg and colleagues (2005), this may be up to a third of pregnancy-related deaths in white women and up to half of those in black women. And even in the insured women described above and reported by Clark and co-workers (2008), 28 percent of 98 maternal deaths were judged preventable. Thus, although significant progress has been made, measures to prevent more deaths are imperative for obstetrics in the 21st century.

## Severe Maternal Morbidity

The concept of “near miss” maternal mortality has led to development of statistical data systems that measure indicators of severe maternal morbidities. This evolution followed inadequacies in hospitalization coding to reflect the severity of maternal complications. Thus, coding indicators or modifiers are used to allow analysis of clinical “near misses.” Such a system has been implemented in Britain and is termed the UK Obstetric Surveillance System—UKOSS (Knight and colleagues, 2005, 2008).

Ad hoc studies of severe maternal morbidity for the United States have been reported. From the Centers for Disease Control and Prevention, Callaghan and colleagues (2008) analyzed nearly 425,000 records from the National Hospital Discharge Summary (NHDS) from 1991 through 2003. Selected International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes were used to tabulate a number of severe morbidities, and some of those most commonly encountered are listed in Table 1-3. These investigators reported that 5 per 1000 of these 50.6 million pregnant women had at least one indicator for severe

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### Table 1-2. Causes of Pregnancy-Related Maternal Deaths in the United States Compared with Those of Pooled Data from Developed Countries

<table>
<thead>
<tr>
<th>Cause of Death</th>
<th>United States 1991–1999 (n = 4200)</th>
<th>Pooled Data for Developed Countries after 1990 (n = 2047)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Embolism</td>
<td>19.6</td>
<td>20.5</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>17.2</td>
<td>18.5</td>
</tr>
<tr>
<td>Gestational hypertension</td>
<td>15.7</td>
<td>22.2</td>
</tr>
<tr>
<td>Infection</td>
<td>12.6</td>
<td>2.8</td>
</tr>
<tr>
<td>Other pregnancy-related</td>
<td>34.1</td>
<td>29.4</td>
</tr>
<tr>
<td>Cardiomyopathy</td>
<td>8.3</td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>5.0</td>
<td></td>
</tr>
<tr>
<td>Anesthesia</td>
<td>1.6</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>19.2</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>0.7</td>
<td>6.6</td>
</tr>
</tbody>
</table>

*Data from Centers for Disease Control and Prevention reported by Chang and colleagues (2003).  
*Data from the World Health Organization reported by Khan and associates (2006).  
Includes abortion and ectopic pregnancy.  
Excludes abortion and ectopic pregnancy.  
Includes cardiovascular, pulmonary, neurological, and other medical conditions.

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![Figure 1-3](image1.png)  
**Figure 1-3** Maternal mortality rates for the United States from 1915 to 2003. (From the National Center for Health Statistics reported by Hoyert, 2007.)

![Figure 1-4](image2.png)  
**Figure 1-4** Maternal mortality ratio (deaths per 100,000 live births) by age and according to race for the United States, 1991 through 1999. (Data from the Centers for Disease Control and Prevention as reported by Chang and co-workers, 2003.)
Rising Cesarean Delivery Rate

In the preceding edition we noted that in 2002, the cesarean delivery rate climbed to the highest level ever reported in the United States—26.1 percent. Since that time, this record has subsequently been broken each year with the new record of 31.1 percent in 2006 (Martin and colleagues, 2009). This rise in the total rate is a result of upward trends in both the primary and the repeat cesarean rate. Indeed, more than 90 percent of women with prior cesarean deliveries now undergo repeat procedures. The forces involved in these changes in cesarean delivery rates are multifactorial and complex. We cite a few examples:

1. As discussed in Chapter 20 (p. 465), the major indication for primary cesarean delivery is dystocia, and there is evidence that this diagnosis has increased.
2. As discussed throughout Chapter 26, the sharp decline in vaginal births after cesarean—VBAC—deliveries is likely related to the uterine rupture risk associated with VBAC.
3. As discussed in Chapter 25 (p. 548), a new and controversial factor is cesarean delivery on maternal request—CDMR. This is defined as a cesarean delivery at term for a singleton pregnancy on maternal request in the absence of any medical or obstetrical indications (Reddy and Spong, 2006). The magnitude of the CDMR phenomenon in American obstetrics has been difficult to quantify. Meikle and co-workers (2005) estimated that the rate of such elective procedures increased from 20 percent of all primary cesareans in 1994 to 28 percent in 2001. Thus, such elective cesarean deliveries constitute between 3 and 7 percent of all deliveries to women without a previous cesarean delivery (Menacker and colleagues, 2006). To address this issue, the National Institute of Child Health and Human Development (NICHD) convened a State-of-the-Science Conference in 2006 to provide an in-depth evaluation of the evidence, raise public awareness, identify research goals, and guide practitioners in assessing risks and benefits. According to Dr. James Scott, editor of Obstetrics & Gynecology, more than 500 people attended, and it was apparent that there were numerous advocacy groups concerned about and opposed to the direction that CDMR has taken. In a summary of the meeting—NIH State-of-the-Science Conference Statement on Cesarean Delivery on Maternal Request (2006)—it was concluded that there was insufficient evidence to evaluate fully the benefits and risks of CDMR versus planned vaginal delivery. Importantly, CDMR was not recommended for women desiring several children because the risks of placenta previa and accreta increase with each cesarean delivery. Moreover, it was concluded that CDMR should not be performed before 39 completed weeks’ gestation or before verification of fetal lung maturity. It is hoped that some evidence-based guidelines will soon be available.

### Table 1-3. Severe Obstetrical Morbidities Identified during Delivery Hospitalizations—United States, 1991–2003

<table>
<thead>
<tr>
<th>Category</th>
<th>Percent of Morbidities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transfusions</td>
<td>48</td>
</tr>
<tr>
<td>Eclampsia</td>
<td>14</td>
</tr>
<tr>
<td>Hysterectomy</td>
<td>12</td>
</tr>
<tr>
<td>Cardiac events</td>
<td>7.6</td>
</tr>
<tr>
<td>Respiratory failure</td>
<td>6.7</td>
</tr>
<tr>
<td>Anesthesia complications</td>
<td>4.6</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>4.2</td>
</tr>
<tr>
<td>Septicemia</td>
<td>4.2</td>
</tr>
<tr>
<td>Renal failure</td>
<td>2.5</td>
</tr>
<tr>
<td>Stroke</td>
<td>2.5</td>
</tr>
<tr>
<td>Invasive monitoring</td>
<td>1.8</td>
</tr>
<tr>
<td>Hemorrhagic shock</td>
<td>1.5</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>0.8</td>
</tr>
</tbody>
</table>

*Identified by International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes.
†Percent exceeds 100 because some patients had multiple diagnoses.

Data from the Centers for Disease Control and Prevention reported by Callaghan and colleagues (2008).

### TIMELY TOPICS IN OBSTETRICS

A variety of topics have been in the forefront for obstetrical providers in the 4 years since the last edition of this textbook. Our purpose here is to review some of these topics selected because of their likely impact on our specialty in the coming years.

#### Measuring Healthcare Outcomes

Much publicity followed the report by the Institute of Medicine entitled To Err Is Human (Kohn and colleagues, 2000). The report greatly increased interest in measuring healthcare outcomes and adverse events (Grobman, 2006). Even the U.S. Congress has determined that reimbursements by Medicare and Medicaid should be indexed to selected healthcare outcomes. Specifically, wide and often dizzying spectra of benchmarks have...
been proposed for measurement of the quality and safety of obstetrical care. Pearlman (2006) reviewed the present state of quality outcome measures in obstetrics and provided an agenda for the future. In our view, the greatest impediment to deriving meaningful measures of obstetrical care is the continued use of administrative and financial data—instead of clinical data—to set benchmarks for outcomes such as rates of perinatal deaths, cesarean delivery, or third- or fourth-degree perineal lacerations.

Residency Training Work Hours

In 2003, the Accreditation Council for Graduate Medical Education (ACGME) set a national standard restructuring the resident physician workweek to a maximum 80 hours per week averaged over 4 weeks and limiting the longest consecutive period of work to 30 hours. These and other 2003 ACGME guidelines are shown in Table 1-4. Following this, the Institute of Medicine (IOM) (2008) commissioned a study to determine factors of patient safety vis-a-vis resident work hours. The Institute recommended changes that are also listed in Table 1-4. These investigators concluded that costs incurred would range annually from $1.1 to $2.5 billion in 2006 dollars, but with unknown effectiveness.

As expected, some disagree with the IOM recommendation for swift implementation of these changes. Citing lack of evidence-based efficacy, inflexibility of the guidelines, and possible adverse effects on resident training, Blanchard and associates (2009) called for studies to determine factual effects before implementation. Indeed, there is evidence that the guidelines will likely adversely affect residency training in neurosurgery (Grady and colleagues, 2009; Jagannathan and co-workers, 2009).

At least in 2009, the plan is for the ACGME Duty Hours Congress to review available data as well as responses from various professional societies and boards. In 2010, the ACGME plans to revise Common Program Requirements. After this, individual Residency Review Committees will revise these for

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**Table 1-4. Recommended Adjustments to Current ACGME Resident Guidelines for Work Hours**

<table>
<thead>
<tr>
<th>2003 ACGME Guidelines</th>
<th>2008 IOM Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximum hours of work per week</td>
<td>80 hours, averaged over 4 weeks</td>
</tr>
<tr>
<td>Maximum shift length</td>
<td>30 hours (admitting patients up to 24 hours then 6 additional hours for transitional and educational activities)</td>
</tr>
<tr>
<td>Maximum in-hospital on-call frequency</td>
<td>Every third night, on average</td>
</tr>
<tr>
<td>Minimum time off between scheduled shifts</td>
<td>10 hours after shift length</td>
</tr>
<tr>
<td>Maximum frequency of in-hospital night shifts</td>
<td>Not addressed</td>
</tr>
<tr>
<td>Mandatory time off duty</td>
<td>Internal moonlighting is counted against 80-hour weekly limit</td>
</tr>
<tr>
<td>Moonlighting</td>
<td>Internal moonlighting is counted against 80-hour weekly limit</td>
</tr>
<tr>
<td>Limit on hours for exceptions</td>
<td>88 hours for select programs with a sound educational rationale</td>
</tr>
<tr>
<td>Emergency room limits</td>
<td>12-hour shift limit, at least an equivalent period of time off between shifts; 60-hour workweek with additional 12 hours for education</td>
</tr>
</tbody>
</table>

ACGME = Accreditation Council for Graduate Medical Education; IOM = Institute of Medicine.

From the Institute of Medicine (2008).
their own specialty specific requirements, which likely will be implemented in July 2011.

**Electronic Medical Records**

Rising costs and inconsistent quality are both significant challenges in the delivery of healthcare in the United States. Electronic health records have been identified as a means of improving the efficiency and effectiveness of healthcare providers (Jha and co-workers, 2009). Methods to speed the adoption of health information technology have received bipartisan support in Congress, and the American Recovery and Reinvestment Act of 2009 has made such a system a national priority. Jha and colleagues (2009) surveyed hospitals nationwide and found that only 1.5 percent had a comprehensive electronic records system. And only 17 percent of physicians reported using some type of electronic records system (DesRoches and colleagues, 2008). Obviously, implementation of an interconnected national system is a daunting task that will require many years.

**Conflicts of Interest**

According to Brennan and colleagues (2006), physician commitment to altruism, putting the interests of patients first, scientific integrity, and an absence of bias in medical decision making are regularly in conflict with financial interests. Although physician groups have instituted self-regulation, it is now widely perceived that more stringent regulation is necessary. To this end, the American College of Obstetricians and Gynecologists (2008b) has published a Committee Opinion that details recommendations for relationships between physicians and industry.

**Research**

It has become increasingly recognized that although per capita healthcare expenditures in the United States are the highest in the world, healthcare outcomes not infrequently lag behind those in nations spending far less. A major factor in this disparity is thought to be expenditure overuse, underuse, and misuse driven by rationale—instead of evidence-based health care. To this end, the National Institutes of Health began a nationwide research program of Clinical and Translational Science Awards (CTSA) to enhance evidence-based health care. (National Center for Research Resources, 2009). The neutral premise of this approach is that successful healthcare interventions require systematic translation of developments from the basic sciences. We applaud this decision.

**Medical Liability**

The American College of Obstetricians and Gynecologists periodically surveys its fellows concerning the impact of professional liability on their practice. The 2006 Survey on Professional Liability is the ninth such survey since 1981 (Wilson and Strunk, 2007). The survey reflects experiences of more than 10,500 members, and some of these findings are listed in Table 1-5.

<table>
<thead>
<tr>
<th>TABLE 1-5. 2006 Survey of Fellows on Professional Liability by the American College of Obstetricians and Gynecologists</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Since 2003 Survey</strong></td>
</tr>
<tr>
<td>Practice change(s)</td>
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<td>Open or closed claims</td>
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<td>Average paid claims</td>
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<td>Co-defendants</td>
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<sup>a</sup>Percentages rounded off.

VBAC = vaginal birth after cesarean.

Data from Wilson and Strunk (2007).
Importantly, 70 percent of fellows responded that some aspect(s) of liability had changed their practice since last surveyed in 2003. Some of these changes undoubtedly were not positive.

Thus, by all accounts, there is still a “liability crisis” that is complex. Because it is largely driven by money and politics, a consensus seems unlikely. Although some interests are diametrically opposite, other factors contribute to its complexity. For example, each state has its own laws and opinions of “tort reforms.” Meanwhile, liability claims remain a “hot button” in obstetrics because of their inherent adversarial nature and the sometimes outlandish plaintiff verdicts that contribute to increasing liability insurance premiums. In some states, annual premiums for obstetricians approach $300,000—expenses that at least partially are borne by the patient, and certainly by the entire healthcare system. Liability issues are daunting, and in 2002, all tort costs in the United States totaled $233 billion—an astounding 2.2 percent of the gross domestic product and averaging $890 per citizen (Tillinghast-Towers Perrin, 2009).

Related to plaintiff awards, Hankins and co-workers (2006) reported that only 6 percent of premium payments will be used to underwrite medical expenses for a patient. This is in contrast to 22 percent for plaintiff lawyers’ expenses and contingency fees. According to the New York Times, “The very phrase ‘trial lawyer’ has become associated with unadulterated greed; the Association of Trial Lawyers of America now calls itself the ‘American Association of Trial Lawyers for Justice’” (Glater, 2008). In their review, Berkowitz and colleagues (2009) compared them with Willie Sutton, the infamous bank robber who stole more than $600 million in his prolific career from the 1920s until the early 1950s.

The American College of Obstetricians and Gynecologists has taken a lead in adopting a fair system for malpractice litigation—or maloccurrence litigation. The Committee on Professional Liability has produced a number of related documents that help fellows cope with the stresses of litigation (2008a), provide advice for the obstetrician giving expert testimony (2007c), and that outline recommendations for disclosure of adverse events (2007b).

National liability reform likely will come in some form with the push for universal medical insurance coverage. President Obama, in his 2009 address to the American Medical Association, indicated that national malpractice liability reform was negotiable. U.S. Congressman Michael Burgess asked the president to reaffirm this commitment. We applaud their efforts and wish for their success.

These interferences have disparately affected indigent women and teenagers. An example from the recent past is the consideration by Congress in 1998 of the Title X Parental Notification Act to mandate parental notification for minors seeking contraception at federally funded clinics. Reddy and colleagues (2002) reported that this would have dissuaded almost half of girls younger than 17 years from seeking contraceptive services and testing or treatment for sexually transmitted disease. The increased number of unintended teenage pregnancies and abortions that would inevitably ensue are discussed subsequently.

A recent example is the tug-of-war over emergency contraception, and more specifically over the morning-after pill (see Chap. 32, p. 692). The 2004 decision by the Bush Administration to override the 23 to 4 vote to approve Plan B for over-the-counter sales to 17-year-old women was decried appropriately by editorials in the New England Journal of Medicine (Drazen and colleagues, 2004; Steinbrook, 2004). This was overturned in April 2009 by a federal district court in New York that ordered the Food and Drug Administration (FDA) to make emergency contraception available over the counter to women 17 years or older. The American College of Obstetricians and Gynecologists (2009b) lauded the decision, citing the more than 800,000 yearly teenage pregnancies in this country and the fact that many are terminated. Also cited were data showing that most adolescents have sex for the first time at age 17.

Perhaps the most egregious example of both federal and state governmental intrusion into women’s reproductive rights is the often poor availability of federally funded family planning services for indigent women. This is despite all reports of the overwhelming success of such programs. According to the Guttmacher Institute (2009), publicly funded family planning services in 2006 prevented nearly 2 million unintended pregnancies and 800,000 abortions in the United States (Fig. 1-5). They conclude that without such funding the abortion rate would be nearly two thirds higher for all women, and nearly twice as high for poor women.

### Teenage Pregnancy

In 2006, there were almost a half million births to women aged 15 to 19 years (Centers for Disease Control and Prevention, 2009). The national rate was 42 births per 1000 females aged 15 to 19 years. Although this rate is substantively reduced compared with 77 per 1000 in 1990, measures to lower it further should remain a priority.

### Births to Immigrants

Persons born outside the United States comprised an estimated 11 percent of the population—more than 30 million people (Gold, 2003). Approximately a third are undocumented—here illegally or with an expired visa—and this proportion has increased tenfold over the past 30 years (Goldman and colleagues, 2006). According to the Pew Hispanic Center (2009), 57 percent of immigrants are from Mexico, 24 percent from Latin America, and the remainder from Asia, Europe, and Africa. The American College of Obstetricians and Gynecologists (2009a) has taken the position that all immigrants within our borders should receive basic healthcare.

### Family Planning Services

Politics and religion over the years have led to a variety of governmental interferences with the reproductive rights of women.
top priority. Like abortion, teen pregnancy is a complex situation and is influenced by strong opinions and religious ideology that have in some cases resulted in blocked access to family planning services for teenagers. Another confounding factor is that it is related to the prevalence of sex education in schools.

Despite the successes of family planning programs described above, and usually driven by sociopolitical concerns, a number of states have linked funding to “abstinence-only” counseling and to exclusion of family planning counseling that include abortion topics. Writing in *Newsweek*, Anna Quindlen (2009) concluded that “Congress has poured $1.5 billion into what is essentially anti-sex ed, abstinence-only programs, despite the following facts: They don’t work. They’re actually counterproductive.”

Even worse, some states have diverted funds from family planning services and put them into programs for abstinence-only counseling. In this regard, Texas may serve as the worst-case example. According to the *Dallas Morning News* (2009), 96 percent of Texas school districts, yielding to pressure from the Board of Education, either teach abstinence-only counseling or avoid talking about sex entirely. It is thus not surprising to many that Texas has been ranked in the top five states for teenage-pregnancy rates over the past several years. In 2006, according to the Centers for Disease Control and Prevention as reported by Ventura (2009), Texas ranked number one with 63 births per 1000 females aged 15 to 19 years. This compared with the national average of 42 per 1000. And Alaska—another state that has recently showcased its abstinence programs—led the nation with a 19-percent increase in the teenage birth rate from 2005 to 2006.

### Abortion

It continues to be a sad fact that up to a fourth of pregnancies in this country are terminated by elective abortion. According to the American College of Obstetricians and Gynecologists (2007a): “The most effective way to reduce the number of abortions is to prevent unwanted and unintended pregnancies.” Importantly, the negative attitudes, beliefs, and policies toward family planning services and sex education discussed above have helped to contribute to the 1 million or so abortions performed yearly in the United States.

The history of legislative regulation and federal court decisions regarding abortions is considered in Chapter 9 (p. 227). At the time of the 22nd edition of this book, the *Partial Birth Abortion Ban Act of 2003* had been signed into law. In 2007, the United States Supreme Court ruled that the ban—officially known as *Gonzales v. Carhart*—is constitutional. This again caused editorialists in the *New England Journal of Medicine* to decry the intrusion of government in medicine (Charo, 2007; Drazen, 2007; Greene, 2007). Since that time, negative effects on abortion services and training have been reported (Haddad and colleagues, 2009; Weitz and Yanow, 2008).

### Healthcare Reform

Many readers of this textbook can remember when the Clinton administration was unsuccessful in passing healthcare reform legislation. Now, more than 15 years later, healthcare reform once again has been made a priority by the Obama administration. By mid-2009, momentum was building for policies that would move the United States toward universal health insurance (Mello and associates, 2009, Oberlander, 2009).

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American College of Obstetricians and Gynecologists: *Coping with the stress of medical professional liability litigation. Committee Opinion No. 406. May 2008* a

American College of Obstetricians and Gynecologists: *Relationships with industry. Committee opinion No. 401. March 2008* b


American College of Obstetricians and Gynecologists: ACOG lends court decision regarding emergency contraception. ACOG News Release, 2009b


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**TABLE 1-6. Four Key Factors Implicated in the High Costs of Health Care in the United States**

<table>
<thead>
<tr>
<th>Number</th>
<th>Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Higher administrative costs</td>
</tr>
<tr>
<td>2</td>
<td>Higher wages for healthcare workers and professionals</td>
</tr>
<tr>
<td>3</td>
<td>Greater use of expensive technological interventions</td>
</tr>
<tr>
<td>4</td>
<td>Unnecessary or inappropriate care</td>
</tr>
</tbody>
</table>

From Sessions and Detsky (2009).
SECTION 2
MATERNAL AND FETAL
ANATOMY AND PHYSIOLOGY
An understanding of the anatomy of the female pelvis and lower abdominal wall is essential for obstetrical practice. There may be marked variation in anatomical structures in individual women, and this is especially true for major blood vessels and nerves.

**ANTERIOR ABDOMINAL WALL**

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.

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

- **Subcutaneous Layer**
  
  This layer can be separated into a superficial, predominantly fatty layer—*Camper fascia*, and a deeper, more membranous layer—*Scarpa fascia*. These are not discrete layers but instead represent a continuum of the subcutaneous tissue layer.

- **Rectus Sheath**
  
  The fibrous aponeuroses of the external oblique, internal oblique, and transversus abdominis muscles join in the midline to create the *rectus sheath* (Fig. 2-1). The construction of this sheath varies above and below a demarcation line, termed the *arcuate line*. Cephalad to this line, the aponeuroses invest the rectus abdominis bellies above and below. Caudal to this line, all aponeuroses lie anterior to the rectus abdominis muscle, and only the thin transversalis fascia and peritoneum lie beneath.

  In the lower abdomen, transition from the muscular to the fibrous aponeurotic component of the external oblique muscles takes place along a vertical line through the anterosuperior iliac spine. Transition from muscle to aponeurosis for the internal oblique and transversus abdominis muscles takes place more medially. For this reason, muscle fibers of the internal oblique are often noted below the aponeurotic layer of the external oblique during creation of low transverse incisions.

- **Blood Supply**
  
  **Femoral Artery Branches**
  
  The superficial epigastric, superficial circumflex iliac, and external pudendal arteries arise from the femoral artery just below the inguinal ligament in the region of 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 course diagonally toward the umbilicus. During low transverse skin incision creation, the superficial epigastric vessels can usually be identified at a depth halfway between the skin and the rectus fascia, several centimeters from the midline.
External Iliac Artery Branches

The inferior “deep” epigastric vessels and deep circumflex iliac vessels are branches of the external iliac vessels. They supply the muscles and fascia of the anterior abdominal wall. The inferior epigastric vessels initially course lateral to, then posterior to the rectus muscles, which they supply. They then pass anterior to the posterior rectus sheath and course between the sheath and the rectus muscles. Near the umbilicus, the inferior epigastric vessels anastomose with the superior epigastric artery and veins, branches of the internal thoracic vessels.

**Hesselbach triangle** is the region in the anterior abdominal wall bounded inferiorly by the inguinal ligament, medially by the lateral border of the rectus muscles, and laterally by the inferior epigastric vessels. Direct hernias protrude through the abdominal wall in Hesselbach triangle, whereas indirect hernias do so through the deep inguinal ring lying lateral to this triangle.

**Innervation**

The anterior abdominal wall is innervated by the abdominal extensions of the intercostal nerves (T7–11), the subcostal nerve (T12), and the iliohypogastric and the ilioinguinal nerves (L1). The T10 dermatome approximates the level of the umbilicus.

The iliohypogastric nerve provides sensation to the skin over the suprapubic area. The ilioinguinal nerve supplies the skin of the lower abdominal wall and upper portion of the labia majora and medial portion of the thigh through its inguinal branch. These two nerves pass 2 to 3 cm medial to the anterior superior iliac spine and course between the layers of the rectus sheath (Whiteside and colleagues, 2003). The ilioinguinal and iliohypogastric nerves can be entrapped during closure of low transverse incisions, especially if incisions extend beyond the lateral borders of the rectus muscle. These nerves carry sensory information only, and injury leads to loss of sensation within the areas supplied.

**EXTERNAL GENERATIVE ORGANS**

**Vulva**

The pudenda—commonly designated the vulva—includes all structures visible externally from the pubis to the perineal body. This includes the mons pubis, labia majora and minora, clitoris, hymen, vestibule, urethral opening, and greater vestibular or Bartholin glands, minor vestibular glands, and paraurethral glands (Fig. 2-2). The embryology of the external genitalia is discussed in Chapter 4 (p. 98).

**Mons Pubis**

Also called the mons veneris, this fat-filled cushion overlies the symphysis pubis. After puberty, the skin of the mons pubis is covered by curly hair that forms the escutcheon. In women, it is distributed in a triangular area, the base of which is formed by the upper margin of the symphysis. In men and in some hirsute women, the escutcheon is not so well circumscribed and extends onto the anterior abdominal wall toward the umbilicus.

**Labia Majora**

Embryologically, the labia majora are homologous with the male scrotum. These structures vary somewhat in appearance,
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principally according to the amount of fat they contain. They are 7 to 8 cm in length, 2 to 3 cm in depth, and 1 to 1.5 cm in thickness. They are continuous directly with the mons pubis superiorly, and the round ligaments terminate at their upper borders. Posteriorly, the labia majora taper and merge into the area overlying the perineal body to form the posterior commissure.

The outer surface of the labia majora is covered with hair, whereas on their inner surface, it is absent. In addition, apocrine and sebaceous glands are abundant. Beneath the skin, there is a dense connective tissue layer, which is nearly void of muscular elements but is rich in elastic fibers and adipose tissue. This mass of fat provides bulk to the labia majora and is supplied with a rich venous plexus. During pregnancy, this vasculature commonly develops varicosities, especially in parous women, from increased venous pressure created by advancing uterine weight. They present as engorged tortuous veins or as small grapelike clusters but are typically asymptomatic.

**Labia Minora**

Each is a thin fold of tissue, which lies medial to each labia majora. In males, its homologue forms the ventral shaft of the penis. The labia minora extend superiorly, where each divides into two lamellae. The lower pair fuses to form the frenulum of the clitoris, and the upper pair merges to form the prepuce. Inferiorly, the labia minora extend to approach the midline as low ridges of tissue that fuse to form the fourchette.

Structurally, the labia minora are composed of connective tissue with many vessels, elastin fibers, and some smooth muscle fibers. They are supplied with a variety of nerve endings and are extremely sensitive. The epithelia of the labia minora vary with location. Stratified squamous epithelium covers the outer surface of each labium. The lateral portion of the inner surface is covered by stratified squamous epithelium to a demarcating line—the Hart line. Medial to this line, each labium is covered by squamous epithelium that is nonkeratinized. Although the labia minora lack hair follicles, eccrine glands, and apocrine glands, there are many sebaceous glands.

**Clitoris**

This principal female erogenous organ is the erectile homologue of the penis and is located beneath the prepuce and above the urethra. It projects downward between the branched extremities of the labia minora, and the free end points downward and inward 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, is composed of spindle-shaped cells, and is covered by stratified squamous epithelium that is richly innervated. The clitoral body contains two corpora cavernosa. Beneath the ventral surface of this body, homologues of the corpora spongiosa unite to form a commissure. These homologues are anterior extensions of the vestibular bulbs (O’Connell and DeLancey, 2006). Extending from the clitoral body, each corpora cavernosa diverges laterally to form the long, narrow crura. These lie along the inferior surface of the ischiopubic rami and deep to the ischiocavernosus muscles.

**Vestibule**

The vestibule is the functionally mature female structure derived from the embryonic urogenital membrane. In adult women, it is an almond-shaped area that is enclosed by Hart line laterally, the external surface of the hymen medially, the
clitoral frenulum anteriorly, and the fourchette posteriorly. The vestibule usually is perforated by six openings: the urethra, the vagina, two Bartholin gland ducts, and at times, two ducts of the largest paraurethral glands—the Skene glands (see Fig. 2-2). The posterior portion of the vestibule between the fourchette and the vaginal opening is called the fossa navicularis. It is usually observed only in nulliparous women.

**Vestibular Glands**

The pair of Bartholin glands, also termed greater vestibular glands, are the major glands. They measure 0.5 to 1 cm in diameter. They lie inferior to the vestibular bulbs and deep to the inferior ends of the bulbocavernous muscle on either side of the vaginal opening. Their ducts are 1.5 to 2 cm long and open distal to the hymenal ring at 5 and 7 o’clock. Following trauma or infection, either duct may swell and obstruct to form a cyst or if infected, an abscess.

The paraurethral glands are collectively an arborization of glands whose ducts open predominantly along the entire inferior aspect of the urethra. The two largest are called Skene glands, and their ducts typically lie distally near the urethral meatus. Inflammation and duct obstruction of any of the paraurethral glands can lead to urethral diverticulum formation. The minor vestibular glands are shallow glands lined by simple mucin-secreting epithelium and open along Hart line.

**Urethral Opening**

The lower two thirds of the urethra lie immediately above the anterior vaginal wall. 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.

**Vestibular Bulbs**

Embryologically, the vestibular bulbs correspond to the corpus spongiosum of the penis. These are almond-shaped aggregations of veins, 3 to 4 cm long, 1 to 2 cm wide, and 0.5 to 1 cm thick, which lie beneath the bulbocavernous muscle on either side of the vestibule. 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 childhood, the vestibular bulbs may be injured and may even rupture to create a vulvar hematoma.

**Vaginal Opening and Hymen**

The vaginal opening is rimmed distally by the hymen or its remnants. In adult women, the hymen is a membrane of varying thickness that surrounds the vaginal opening more or less completely. It is composed mainly of elastic and collagenous connective tissue, and both outer and inner surfaces are covered by stratified squamous epithelium. The aperture of the hymen is thick, and the tissue is rich in glycogen. Changes produced in the hymen by childbirth are usually readily recognizable. Over time, the hymen consists of several nodules of various sizes, also termed hymenal caruncles.

**Vagina**

This musculomembranous structure extends from the vulva to the uterus and is interposed anteriorly and posteriorly between the bladder and the rectum. The upper portion arises from the müllerian ducts, and the lower portion is formed from the urogenital sinus (see Fig. 40-1, p. 891). 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, there are similar tissues that together form the rectovaginal septum. The upper fourth of the vagina is separated from the rectum by the recto-uterine pouch, also called the cul-de-sac of Douglas.

Normally, the anterior and posterior vaginal walls lie in contact, with only a slight space intervening between the lateral margins. Vaginal length varies considerably, but commonly, the anterior and posterior vaginal walls are, respectively, 6 to 8 cm and 7 to 10 cm in length. During her lifetime, the average woman may have a shortening of her vagina by 0.8 cm (Tan and associates, 2006). The upper end of the vaginal vault is subdivided into anterior, posterior, and two lateral fornices by the cervix. These are of considerable clinical importance because the internal pelvic organs usually can be palpated through their thin walls. Moreover, the posterior fornix provides surgical access to the peritoneal cavity.

At the midportion of the vagina, its lateral walls are attached to the pelvic walls by visceral connective tissue. These lateral attachments blend into investing fascia of the levator ani muscles. In doing so, they create the anterior and posterior lateral vaginal sulci. These run the length of the vaginal sidewalls and give the vagina an H shape when viewed in cross section. There are numerous thin transverse ridges, known as rugae, found along the length of the anterior and posterior vaginal walls.

**Histology**

The vaginal lining is composed of nonkeratinized stratified squamous epithelium and underlying lamina propria. Below this there is a muscular layer, which consists of smooth muscle, collagen, and elastin. Beneath this muscularis lies an adventitial layer consisting of collagen and elastin (Weber and Walters, 1997). There are no vaginal glands. Instead, the vagina is lubricated by a transudate that originates from the vaginal subepithelial capillary plexus and crosses the permeable epithelial layer (Gorodeski, 2005). Due to increased vascularity during pregnancy, vaginal secretions are notably increased. At times, this may be confused with amnionic fluid leakage, and clinical differentiation of these two is described in Chapter 17 (p. 392).

After birth, fragments of stratified epithelium occasionally are embedded beneath the vaginal surface. Similar to its native tissue, this buried epithelium continues to shed degenerated cells and keratin. As a result, firm epidermal inclusion cysts, which are filled with keratin debris, may form.
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Vascular and Lymphatic Supply

The vagina has an abundant vascular supply (Fig. 2-3). 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, inferior vesical, or directly from the internal iliac artery. The middle rectal artery contributes to supply the posterior vaginal wall, whereas the distal walls receive contributions from the internal pudendal artery. At each level, blood supply from each side anastomoses on the anterior and posterior vaginal walls with contralateral corresponding vessels.

An extensive venous plexus immediately 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 middle third drain into the internal iliac nodes, and those from the upper third drain into the external, internal, and common iliac nodes.

Perineum

The perineum is the diamond-shaped area between the thighs. The anterior, posterior, and lateral boundaries of the perineum are the same as those of the bony pelvic outlet: the pubic symphysis anteriorly, ischiopubic rami and ischial tuberosities anterolaterally, sacrotuberous ligaments posterolaterally, and coccyx posteriorly.

Anterior Triangle

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. 2-4). The anterior triangle is bounded by the pubic rami superiorly, the ischial tuberosities laterally, and the superficial transverse perineal muscle posteriorly.

The anterior triangle is further divided into superficial and deep spaces by the perineal membrane. This is a sheet of dense fibrous tissue and 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, and posteriorly to the perineal body. Anteriorly, it attaches to the arcuate ligament of the pubis.

Superficial Space of the Anterior Triangle. This space is bounded deeply by the perineal membrane and superficially by Colles fascia. It is a closed compartment, and infection or bleeding within it remains contained. The anterior triangle contains several important structures that include the ischiocavernosus, bulbocavernosus, and superficial transverse perineal muscles; Bartholin glands; vestibular bulbs; clitoral body and crura; and branches of the pudendal vessels and nerve (see Fig. 2-4).

The ischiocavernosus muscle attaches to the medial aspect of the ischial tuberosities inferiorly and the ischiopubic rami laterally. Anteriorly, it attaches to the crus of the clitoris. This muscle helps maintain clitoral erection by compressing the crus to obstruct venous drainage. The bulbocavernosus muscles overlie the vestibular bulbs and Bartholin glands. They attach to the body of the clitoris anteriorly and the perineal body posteriorly. The muscles constrict the vaginal lumen and aid release of secretions from the Bartholin glands. They also may contribute to clitoral erection by compressing the deep dorsal vein of the clitoris. The bulbocavernosus and ischiocavernosus muscles also pull the clitoris downward. The superficial transverse perineal muscles are narrow strips that attach to the ischial tuberosities laterally and the perineal body medially. They may be attenuated or even absent, but when present, they contribute to the perineal body (Corton and Cunningham, 2008).
Deep Space of the Anterior Triangle. This space lies deep to the perineal membrane and extends up into the pelvis (Mirlas and Skandalakis, 2004). In contrast to the superficial perineal space, which is a closed compartment, the deep space is continuous superiorly with the pelvic cavity (Corton, 2005). It contains the compressor urethrae and urethrovaginal sphincter muscles, external urethral sphincter, parts of urethra and vagina, branches of the internal pudendal artery, and the dorsal nerve and vein of the clitoris (Fig. 2-5).

Posterior Triangle

This triangle contains the ischiorectal fossa, anal canal, anal sphincter complex, and branches of the internal pudendal vessels and pudendal nerve (see Figs. 2-4 and 2-5).

Ischiorectal Fossae. These are two fat-filled wedge-shaped spaces found on either side of the anal canal and comprise the bulk of the posterior triangle (Fig. 2-6). Their structure reflects their function. They provide support to surrounding organs, yet allow distension of the rectum during defecation and stretching of the vagina during delivery.

The anal canal and sphincter complex lie in the center of these fossae. Deeply, there is no fascial boundary between the fossa and the tissues above the perineal membrane. Thus, the two fossae communicate posteriorly, behind the anal canal. This continuity of the ischioanal fossa across perineal compartments allows fluid, infection, and malignancy to spread from one side of the anal canal to the other as well as into the areas deep to the perineal membrane. This can be clinically important if episiotomy infection extends to involve either fossa.

Pudendal Nerve and Vessels

The pudendal nerve is formed from the anterior rami of the second through fourth sacral nerves. It courses between the piriformis and coccygeus muscles and exits through the greater sciatic foramen in a location posteromedial to the ischial spine (Barber and colleagues, 2002). This anatomy is important when injecting local anesthetic for a pudendal nerve block. The ischial spine serves an easily identifiable landmark for anesthetic infiltration around this nerve (see Chap. 19, p. 450).

The pudendal nerve then courses along the obturator internus muscle. Along this muscle, the nerve lies within the pudendal canal, also known as Alcock canal, which is formed by splitting of the obturator fascia (Shafik, 1999). The pudendal nerve leaves this canal to enter the perineum and divides into three terminal branches (see Fig. 2-6). The dorsal nerve of the clitoris supplies the skin of the clitoris. The perineal nerve serves the muscles of the anterior triangle and labial skin. The inferior rectal branch supplies the external anal sphincter, the mucous membrane of the anal canal, and the perianal skin (Mahanakanukrua and associates, 2005).

The major blood supply to the perineum is via the internal pudendal artery and its branches. These include the inferior rectal artery and posterior labial artery.
Anus

Anal Sphincters

Two sphincters surround the anal canal to provide continence—the external and internal anal sphincter (Fig. 2-6). Both lie proximate to the vagina, and one or both may be torn during vaginal delivery. Of these disruptions, many are not clinically identified at delivery. For example, Sultan (1993) performed endoanal sonography 6 weeks following delivery and found that 28 of 79 primiparas—35 percent—had sphincter defects, more commonly involving the internal sphincter. Clinically, these defects can have functional consequences. Oberwalder and colleagues (2003) performed a meta-analysis of 717 women after a vaginal delivery and found that almost 80 percent of those with anal sphincter defects had impaired control of stool or flatus.

**External Anal Sphincter (EAS).** This ring of striated muscle attaches to the perineal body anteriorly and the coccyx posteriorly. It maintains a constant state of resting contraction that provides increased tone and strength when continence is
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threatened, and it relaxes for defecation. Hsu and colleagues (2005) studied structure of the EAS using magnetic resonance (MR) imaging. They identified three structures: the main body—EAS-M, the subcutaneous sphincter—EAS-SQ, and the wing-shaped end—EAS-W, which has fibers with lateral origins near the ischiopubic ramus. The external sphincter receives blood supply from the inferior rectal artery. Somatic motor fibers from the inferior rectal branch of the pudendal nerve supply innervation.

Internal Anal Sphincter (IAS). This sphincter contributes the bulk of anal canal resting pressure for fecal continence, and it relaxes prior to defecation. The sphincter is formed by distal continuation of the inner circular smooth muscle layer of the rectum and colon. 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 and co-workers, 1997; Rociu and associates, 2000). Thus, the IAS may be involved in fourth-degree lacerations, and reunion of this ring is incorporated in their repair (see Chap. 17, p. 400).

Anal Cushions

Within the anal canal, there are highly vascularized cushions, which when apposed aid complete closure of the anal canal and fecal continence. Increasing uterine size, excessive straining, and hard stools can increase venous engorgement within these cushions to form hemorrhoids (Fig. 2-7). External hemorrhoids are those that arise distal to the dentate 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 dentate line and are covered by insensate anorectal mucosa. These may prolapse or bleed but rarely become painful unless they develop thrombosis and necrosis.

Hemorrhoids form commonly in pregnancy (see Chap. 8, p. 211). Abramowitz and colleagues (2002) evaluated 165 consecutive pregnant women proctoscopically and found thrombosed hemorrhoids in 9 percent during their last 3 months of pregnancy and an even greater percentage postpartum.

Perineal Body

The median raphe of the levator ani, between the anus and the vagina, is reinforced by the central tendon of the perineum. The bulbocavernosus, superficial transverse perineal, and external anal sphincter muscles also converge on the central tendon. Thus, these structures contribute to the perineal body, which provides significant perineal support as shown in Table 2-1. The perineal body is incised by an episiotomy incision and is torn with second-, third-, and fourth-degree lacerations.

INTERNAL GENERATIVE ORGANS

Uterus

The nonpregnant uterus is situated in the pelvic cavity between the bladder anteriorly and the rectum posteriorly. Almost the entire posterior wall of the uterus is covered by serosa, that is, visceral peritoneum. The lower portion of this peritoneum forms the anterior boundary of the recto-uterine cul-de-sac, or pouch of Douglas. Only the upper portion of the anterior wall of the uterus is so covered (Fig. 2-8). The peritoneum in this area reflects forward onto the bladder dome to create the vesicouterine pouch. The lower portion of the anterior uterine wall is united to the posterior wall of the bladder by a well-defined loose layer of connective tissue. This is the vesicouterine space. During cesarean delivery, the peritoneum of the vesicouterine pouch is sharply incised and the vesicouterine space is entered. Dissection caudally within this space lifts the bladder off the lower uterine segment for hysterotomy and delivery (see Chap. 25, p. 550).

Size and Shape

The uterus is described as being pyriform or pear-shaped, and as shown in Figure 2-9, it resembles a flattened pear. It consists of two major but unequal parts: an upper triangular portion—the

FIGURE 2-7 Veins within the anal cushions engorge to form hemorrhoids. Those above the dentate line are termed internal, whereas those below it are called external hemorrhoids.

<table>
<thead>
<tr>
<th>TABLE 2-1. Perineal Body</th>
</tr>
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<tbody>
<tr>
<td><strong>Function</strong></td>
</tr>
<tr>
<td>Anchors the anorectum</td>
</tr>
<tr>
<td>Anchors the vagina</td>
</tr>
<tr>
<td>Helps maintain urinary and fecal continence</td>
</tr>
<tr>
<td>Maintains the orgasmic platform</td>
</tr>
<tr>
<td>Prevents expansion of the urogenital hiatus</td>
</tr>
<tr>
<td>Provides a physical barrier between the vagina and rectum</td>
</tr>
<tr>
<td><strong>Potential Morbidity</strong></td>
</tr>
<tr>
<td>Episiotomy may injure the perineal body</td>
</tr>
<tr>
<td>Pudendal nerve injury may be associated with concurrent perineal body injury</td>
</tr>
</tbody>
</table>

Adapted from Woodman and Graney (2002).
body or corpus, and a lower, cylindrical portion—the cervix, which projects into the vagina. The isthmus is that portion of the uterus between the internal cervical os and the endometrial cavity (Fig. 2-10). It is of special obstetrical significance because it forms the lower uterine segment during pregnancy (see Chap. 6, p. 142). The fallopian tubes, also called oviducts, emerge from the cornua of the uterus at the junction of the superior and lateral margins. The fundus is the convex upper segment between the points of insertion of the fallopian tubes.

The bulk of the body of the uterus, but not the cervix, is composed of muscle. The inner surfaces of the anterior and posterior walls lie almost in contact, and the cavity between these...
Walls forms a mere slit. The uterus of adult nulliparous women measures 6 to 8 cm in length as compared with 9 to 10 cm in multiparous women. In nonparous women, the uterus averages 50 to 70 g, whereas in parous women it averages 80 g or more (Langlois, 1970). In nulliparous women, the fundus and cervix are approximately equal length, but in multiparous women, the cervix is only a little more than a third of the total length.

**Pregnancy-Induced Uterine Changes**

Pregnancy stimulates remarkable uterine growth due to hypertrophy of muscle fibers. Uterine weight increases from 70 g to approximately 1100 g at term. Its total volume averages about 5 L. The uterine fundus, a previously flattened convexity between tubal insertions, now becomes dome shaped (Fig. 2-11). The round ligaments now 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.

**Congenital Anomalies**

Abnormal müllerian fusion may give rise to a number of uterine anomalies that are discussed in Chapter 40 (p. 891).

**Cervix**

The cervical portion of the uterus is fusiform and open at each end by small apertures—the internal and external os (see Fig. 2-10). Anteriorly, the upper boundary of the cervix is the internal os, which corresponds to the level at which the peritoneum is reflected up onto the bladder. The upper segment of the cervix—the portio supravaginalis, lies above the vaginal attachment to the cervix. It is covered by peritoneum on its posterior surface, the cardinal ligaments attach laterally, and it is separated from the overlying bladder by loose connective tissue. The lower vaginal portion of the cervix is called the portio vaginalis.

Before childbirth, the external cervical os is a small, regular, oval opening (Fig. 2-12). After labor, and especially vaginal childbirth, the orifice is converted into a transverse slit that is divided such that there are the so-called anterior and posterior lips of the cervix. If torn deeply during delivery, the cervix may heal in such a manner that it appears to be irregular, nodular, or stellate. These changes are sufficiently characteristic to permit an examiner to ascertain with some certainty whether a woman

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**FIGURE 2-11** Uterus of near-term pregnancy. The fundus is now dome shaped, and the tubes and round ligaments appear to insert in the upper middle portion of the uterine body. Note the markedly hypertrophied vascular supply.
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has borne children by vaginal delivery. If a woman undergoes cesarean delivery, however, then the postoperative cervical appearance reflects the degree of dilatation prior to surgery. Cervices without labor may appear nulliparous, whereas as those with intrapartum dilatation may appear parous.

The portion of the cervix exterior to 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.” Mucus produced by the endocervical epithelia changes during pregnancy. It becomes thick and forms a mucus plug within the endocervical canal.

Commonly during pregnancy, the endocervical epithelia moves out and onto the ectocervix during enlargement of the cervix in a process termed eversion (see Chap. 5, p. 109). As a result, a band of columnar epithelium may ring the external os. With time, this evverted columnar epithelium, under the influence of vaginal acidity or during reparative healing, may be replaced by squamous epithelium in a process termed squamous metaplasia. This replacement with squamous epithelium may block endocervical clefts.

If so, accumulated mucus from the underlying clefts forms nabothian cysts, which are benign, firm, smooth, rounded, opaque-yellow or ground-glass gray elevations on the ectocervix.

The cervical stroma is composed mainly of collagen, elastin, and proteoglycans, but very little smooth muscle. Changes in the amount, composition, and orientation of these components lead to cervical ripening prior to labor onset (see Chap. 6, p. 138). In early pregnancy, increased vascularity and edema within the cervix stroma leads to the blue tint and softening characteristics of Chadwick and Hegar signs, respectively.

Endometrium
This mucosal layer lines the uterine cavity in nonpregnant women. It is a thin, pink, velvet-like membrane, which on close examination, is perforated by many minute ostia of the uterine glands. The endometrium normally varies greatly in thickness. It is composed of surface epithelium, glands, and interglandular mesenchymal tissue in which there are numerous blood vessels (Fig. 2-13).

The epithelium is comprised of a single layer of closely packed, high columnar cells that rests on a thin basement membrane (see Fig. 3-2 p. 38). The tubular uterine glands are invaginations of the epithelium. The glands extend through the entire thickness of the endometrium to the myometrium, which is occasionally penetrated for a short distance. The connective tissue between the surface epithelium and the myometrium is a mesenchymal stroma. Histologically, the stroma varies remarkably throughout the ovarian cycle. Specifically, following ovulation, decidualization of the stromal compartment develops in the mid-luteal phase. As discussed further in Chapter 3 (p. 42), this process of endometrial remodeling prepares for pregnancy and includes secretory transformation of the uterine glands and vascular remodeling (Gellersen and colleagues, 2003, 2007).

The vascular architecture of the uterus and endometrium is of signal importance in pregnancy. The uterine and ovarian arteries branch and penetrate the uterine wall obliquely inward

and reach its middle third. They then ramify in a plane that is parallel to the surface and are therefore named the arcuate arteries (DuBose and colleagues, 1985). Radial branches extend from the arcuate arteries at right angles and enter the endometrium to become coiled or spiral arteries. Also from the radial arteries, basal or straight arteries branch at a sharp angle. The spiral arteries supply most of the midportion and all of the superficial third of the endometrium. These vessels respond—especially by vasoconstriction, to a number of hormones and thus probably serve an important role in the mechanism(s) of menstruation. The basal arteries extend only into the basal layer of the endometrium and are not responsive to hormonal influences.

**Myometrium**

This layer comprises most of the uterus. It is composed of bundles of smooth muscle united by connective tissue in which there are many elastic fibers. The interlacing myometrial fibers that surround the myometrial vessels are integral to control of bleeding from the placental site during the third stage of labor. As shown in Fig. 2-14, vessels are compressed by smooth muscle contraction. According to Schwalm and Dubrauszky (1966), the number of muscle fibers of the uterus progressively diminishes caudally such that, in the cervix, muscle comprises only 10 percent of the tissue mass. In the inner wall of the body of the uterus, there is relatively more muscle than in the outer layers; and in the anterior and posterior walls, there is more muscle than in the lateral walls. During pregnancy, the upper myometrium undergoes marked hypertrophy, but there is no significant change in cervical muscle content.

**Ligaments**

Several ligaments extend from the lateral surface of the uterus toward the pelvic sidewalls and include the round, broad, and cardinal ligaments. The round ligaments originate somewhat below and anterior to the origin of the fallopian tubes (see Fig. 2-8). Each round ligament extends laterally and downward to the inguinal canal, through which it passes to terminate in the upper portion of the labium majus. Sampson artery, a branch of the uterine artery, runs within this ligament. The location of the round ligament anterior to the fallopian tube can help distinguish surgical anatomy such as with puerperal tubal sterilization (see Chap. 33, p. 698). This may be especially true if pelvic adhesions limit tubal mobility and thus, limit identification of fimbria prior to tubal ligation.

The round ligament corresponds embryologically to the gubernaculum testis of men. In nonpregnant women, it varies from 3 to 5 mm in diameter and is composed of smooth muscle (Ozdeğirmenci and colleagues, 2005). During pregnancy, the round ligaments undergo considerable hypertrophy and increase appreciably in both length and diameter.

The broad ligaments are composed of two winglike structures that extend from the lateral uterine margins of the uterus to the pelvic sidewalls. They divide the pelvic cavity into anterior and posterior compartments. Each broad ligament consists of a fold of peritoneum termed the anterior and posterior leaves. This peritoneum drapes over structures extending from the cornua. Peritoneum that overlies the fallopian tube is termed the mesosalpinx; that around the round ligament is the mesoteras, and that over the uterovarian ligament is the mesovarium (see Fig. 2-8). Peritoneum that extends beneath the fimbriated end of the fallopian tube to the pelvic wall forms the infundibulopelvic ligament or suspensory ligament of the ovary, through which the ovarian vessels traverse. During pregnancy, these vessels, especially the venous plexuses, are dramatically hypertrophied.

The thick base of the broad ligament is continuous with the connective tissue of the pelvic floor. The densest portion is usually referred to as the cardinal ligament—also called the transverse cervical ligament or Mackenrodt ligament. It is composed of connective tissue that medially is united firmly to the supravaginal portion of the cervix. A vertical section through the uterine end of the broad ligament is triangular, and the uterine vessels and ureter are found within its broad base (see Fig. 2-8). In its lower part, it is widely attached to the connective tissues that are adjacent to the cervix, that is, the parametrium.

Each uterosacral ligament extends from an attachment posterolaterally to the supravaginal portion of the cervix and inserts into the fascia over the sacrum. Umek and colleagues (2004) used magnetic resonance imaging to describe anatomical variations of these ligaments. The ligaments are composed of connective tissue, small bundles of vessels and nerves, and some smooth muscle. They are covered by peritoneum and form the lateral boundaries of the pouch of Douglas.

**FIGURE 2-14** The smooth muscle fibers compress traversing blood vessels when contracted.
Blood Vessels

The vascular supply of the uterus is derived principally from the uterine and ovarian arteries. The uterine artery, a main branch of the internal iliac artery—previously called the hypogastric artery—enters the base of the broad ligament and makes its way medially to the side of the uterus. Immediately adjacent to the supravaginal portion of the cervix, the uterine artery divides. The smaller cervicovaginal artery supplies blood to the lower cervix and upper vagina. The main branch turns abruptly upward and extends as a highly convoluted vessel that traverses along the margin of the uterus. Just before the main branch of the uterine artery reaches the fallopian tube, it divides into three terminal branches (Fig. 2-15). The ovarian branch of the uterine artery anastomoses with the terminal branch of the ovarian artery; the tubal branch makes its way through the mesosalpinx and supplies part of the fallopian tube; and the fundal branch is distributed to the uppermost uterus.

Approximately 2 cm lateral to the cervix, the uterine artery crosses over the ureter. The proximity of the uterine artery and vein to the ureter at this point is of great surgical significance. Because of their close proximity, the ureter may be injured or ligated during a hysterectomy when the vessels are clamped and ligated.

The ovarian artery is a direct branch of the aorta. It enters the broad ligament through the infundibulopelvic ligament. At the ovarian hilum, it divides into a number of smaller branches that enter the ovary. Its main stem, however, traverses the entire length of the broad ligament and makes its way to the upper lateral portion of the uterus. Here it anastomoses with the ovarian branch of the uterine artery. There are numerous additional communications among the arteries on both sides of the uterus.

When the uterus is in a contracted state, its numerous venous lumens are collapsed. But in injected specimens, the greater part of the uterine wall appears to be occupied by dilated venous sinuses. On either side, the arcuate veins unite to form the uterine vein, which empties into the internal iliac 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. Within the broad ligament, these veins form the large pampiniform plexus that terminates in the ovarian vein. The right ovarian vein empties into the vena cava, whereas the left ovarian vein empties into the left renal vein. During pregnancy, there is marked hypertrophy of the uterine vasculature (see Fig. 2-11).

Blood supply to the pelvis is predominantly supplied from branches of the internal iliac artery (Fig. 2-16). These branches are organized into anterior and posterior divisions and subsequent branches are highly variable between individuals. The anterior division provides substantial blood supply to the pelvic organs and perineum, whereas the posterior division branches extend to the buttock and thigh. In some cases, branches of these vessels traverse close to the presacral space (Wieslander and associates, 2006). The surgical anatomy of the internal iliac artery is discussed further in Chapter 35, p. 796.
The pelvis has extensive collateral circulation, and the internal iliac artery shares anastomoses with branches of the aorta and external iliac and femoral artery. As a result, ligation of the anterior division of the internal iliac artery can be performed without compromise to pelvic organ viability. For this reason, during internal iliac ligation to control obstetrical hemorrhage, many advocate internal iliac ligation distal to the posterior division to avoid compromised blood flow to the areas supplied by this division (Bleich and colleagues, 2007; Burchell, 1968).

**Lymphatics**

The endometrium is abundantly supplied with true lymphatic vessels that are confined largely to the basal layer. The lymphatics of the underlying myometrium are increased in number toward the serosal surface and form an abundant lymphatic plexus just beneath it. Lymphatics from the cervix terminate mainly in the internal iliac nodes, which are situated near the bifurcation of the common iliac vessels. The lymphatics from the uterine corpus are distributed to two groups of nodes. One set of vessels drains into the internal iliac nodes. The other set, after joining certain lymphatics from the ovarian region, terminates in the para-aortic lymph nodes.

**Innervation**

The pelvic nerve supply is derived principally from the sympathetic nervous system, but also partly from the cerebrospinal and parasympathetic systems. The parasympathetic system is represented on either side by the pelvic nerve, which is made up of a few fibers that are derived from the second, third, and fourth sacral nerves. It loses its identity in the cervical ganglion of Frankenhäuser. The sympathetic system enters the pelvis by way of the internal
iliac plexus that arises from the aortic plexus just below the promontory of the sacrum (Wieslander and colleagues, 2006). After descending on either side, it also enters the uterovaginal plexus of Frankenhäuser, which is made up of ganglia of various sizes, but particularly of a large ganglionic plate that is situated on either side of the cervix, proximate to the uterosacral ligaments and just above the posterior fornix in front of the rectum.

Branches from these plexuses supply the uterus, bladder, and upper vagina. In the 11th and 12th thoracic nerve roots, there are sensory fibers from the uterus that transmit the painful stimuli of contractions to the central nervous system. The sensory nerves from the cervix and upper part of the birth canal pass through the pelvic nerves to the second, third, and fourth sacral nerves. Those from the lower portion of the birth canal pass primarily through the pudendal nerve. Knowledge of the innervation of dermatomes and its clinical application to providing epidural or spinal analgesia for labor and vaginal or cesarean delivery is illustrated in Figures 19-1 and 19-3 (p. 447).

### Fallopian Tubes

These tubular extensions from the uterus vary in length from 8 to 14 cm, and each tube is divided into an interstitial portion, isthmus, ampulla, and infundibulum. The interstitial portion is embodied within the muscular wall of the uterus. The isthmus, or the narrow portion of the tube that adjoins the uterus, passes gradually into the wider, lateral portion, or ampulla. The infundibulum, or fimbriated extremity, is the funnel-shaped opening of the distal end of the fallopian tube (Fig. 2-17). The fallopian tube varies considerably in thickness. The narrowest portion of the isthmus measures from 2 to 3 mm in diameter, and the widest portion of the ampulla measures from 5 to 8 mm. The fimbriated end of the infundibulum opens into the abdominal cavity. One projection, the fimbria ovarica, which is considerably longer than the other fimbriae, forms a shallow gutter that approaches or reaches the ovary.

Tubal smooth muscle is arranged in an inner circular and an outer longitudinal layer. In the distal portion, the two layers are
less distinct and near the fimbriated extremity, are replaced by an interlacing network of muscular fibers. The tubal musculature undergoes rhythmic contractions constantly, the rate of which varies with ovarian cyclical hormonal changes. The greatest frequency and intensity of contractions is reached during transport of ova.

The fallopian tubes are lined by a single layer of columnar cells, some of them ciliated and others secretory. The ciliated cells are most abundant at the fimbriated extremity, elsewhere, they are found in discrete patches. There are differences in the proportions of these two types of cells in different phases of the ovarian cycle. Because there is no submucosa, the epithelium is in close contact with the underlying muscular layer. In the tubal mucosa, there are cyclical histological changes similar to those of the endometrium, but much less striking. The mucosa is arranged in longitudinal folds that are more complex toward the fimbriated end. On cross-sections through the uterine portion, four simple folds are found that form a figure that resembles a Maltese cross. The isthmus has a more complex pattern. In the ampulla, the lumen is occupied almost completely by the arborescent mucosa, which consists of very complicated folds. The current produced by the tubal cilia is such that the direction of flow is toward the uterine cavity. Tubal peristalsis is believed to be an extraordinarily important factor in ovum transport.

The tubes are supplied richly with elastic tissue, blood vessels, and lymphatics. Sympathetic innervation of the tubes is extensive, in contrast to their parasympathetic innervation. Diverticula may extend occasionally from the lumen of the tube for a variable distance into the muscular wall and reach almost to the serosa. These diverticula may play a role in the development of ectopic pregnancy (see Chap. 10, p. 240).

### Ovaries

Compared with each other, as well as between women, the ovaries vary considerably in size. During childbearing years, they are from 2.5 to 5 cm in length, 1.5 to 3 cm in breadth, and 0.6 to 1.5 cm in thickness. Their position also varies, but they usually lie in the upper part of the pelvic cavity and rest in a slight depression on the lateral wall of the pelvis. This ovarian fossa of Waldeyer is between the divergent external and internal iliac vessels.

The ovary is attached to the broad ligament by the mesovarium. The utero-ovarian ligament extends from the lateral and posterior portion of the uterus, just beneath the tubal insertion, to the uterine pole of the ovary. Usually, it is a few centimeters long and 3 to 4 mm in diameter. It is covered by peritoneum and is made up of muscle and connective tissue fibers. The infundibulopelvic or suspensory ligament of the ovary extends from the upper or tubal pole to the pelvic wall; through it course the ovarian vessels and nerves.

The ovary consists of the cortex and medulla. In young women, the outermost portion of the cortex is smooth, has a dull white surface, and is designated the tunic albuginea. On its surface, there is a single layer of cuboidal epithelium, the germinal epithelium of Waldeyer. The cortex contains oocytes and developing follicles. The medulla is the central portion, which is composed of loose connective tissue. There are a large number of arteries and veins in the medulla and a small number of smooth muscle fibers.

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. Others are derived from the plexus that surrounds the ovarian branch of the uterine artery. The ovary is richly supplied with nonmyelinated nerve fibers, which for the most part accompany the blood vessels.

### MUSCULOSKELETAL PELVIC ANATOMY

#### Pelvic Bones

The pelvis is composed of four bones: the sacrum, coccyx, and two innominate bones (Fig. 2-18). Each innominate bone is formed by the fusion of the ilium, ischium, and pubis. The innominate bones are joined to the sacrum at the sacroiliac synchondroses and to one another at the symphysis pubis.

The false pelvis lies above the linea terminalis and the true pelvis below this anatomical boundary (Fig. 2-19). 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 the portion important in childbearing. It is bounded above by the promontory and alae of the sacrum, the linea terminalis, and the upper margins of the pubic bones, and below by the pelvic outlet. The cavity of the true pelvis can be described as an obliquely truncated, bent cylinder with its greatest height posteriorly.

The walls of the true pelvis are partly bony and partly ligamentous. The posterior boundary is the anterior surface of the sacrum, and the lateral limits are formed by the inner surface of the ischial bones and the sacrosciatic notches and ligaments. In front, the true pelvis is bounded by the pubic bones, the ascending superior rami of the ischial bones, and the obturator foramen.

The sidewalls of the true pelvis of an adult woman converge somewhat. Extending from the middle of the posterior margin of each ischium are the ischial spines. These are of great obstetrical importance because the distance between them usually represents the shortest diameter of the pelvic cavity. They also serve as valuable landmarks in assessing the level to which the presenting part of the fetus has descended into the true pelvis (see Chap. 17, p. 392).

The sacrum forms the posterior wall of the pelvic cavity. Its upper anterior margin corresponds to the promontory that may be felt during bimanual pelvic examination in women with small pelves. It can provide a landmark for clinical pelvimetry. Normally, the sacrum has a marked vertical and a less pronounced horizontal concavity, which in abnormal pelves may undergo important variations. A straight line drawn from the promontory to the tip of the sacrum usually measures 10 cm, whereas the distance along the concavity averages 12 cm.

The descending inferior rami of the pubic bones unite at an angle of 90 to 100 degrees to form a rounded arch under which the fetal head must pass.

#### Pelvic Joints

##### Symphysis Pubis

Anteriorly, the pelvic bones are joined together by the symphysis pubis. This structure consists of fibrocartilage and the superior and inferior pubic ligaments. The latter are frequently designated the arcuate ligament of the pubis.
Maternal and Fetal Anatomy and Physiology

Posteriorly, the pelvic bones are joined by articulations between the sacrum and the iliac portion of the innominate bones to form the sacroiliac joints. These joints also have a certain degree of mobility.

Relaxation of the Pelvic Joints
During pregnancy, there is remarkable relaxation of these joints, although the cause(s) is unclear. It likely results from hormonal stimulation (see Chap. 5, p. 130). Abramson and co-workers (1934) observed that relaxation of the symphysis pubis commenced in women in the first half of pregnancy and increased during the last 3 months. They also observed that this laxity began to regress immediately after parturition and that regression was completed within 3 to 5 months. The symphysis pubis also increases in width during pregnancy—more so in multiparas than in primigravidas—and returns to normal soon after delivery.

There are important changes in sacroiliac joint mobility. Borell and Fernstrom (1957) demonstrated that the rather marked mobility of the pelvis at term was caused by an upward gliding
movement of the sacroiliac joint. The displacement, which is greatest in the dorsal lithotomy position, may increase the diameter of the outlet by 1.5 to 2.0 cm. **This is the main justification for placing a woman in this position for a vaginal delivery.** But increase in diameter of the pelvic outlet occurs only if the sacrum is allowed to rotate posteriorly. Thus, it will not occur if the sacrum is forced anteriorly by the weight of the maternal pelvis against the delivery table or bed (Russell, 1969, 1982). Sacroiliac joint mobility is also the likely reason that the McRoberts maneuver often is successful in releasing an obstructed shoulder in a case of shoulder dystocia (see Chap. 20, p. 483). These changes have also been attributed to the success of the modified squatting position to hasten second-stage labor (Gardosi and co-workers, 1989). The squatting position may increase the interspinous diameter and the diameter of the pelvic outlet (Russell, 1969, 1982). These latter observations are unconfirmed, but this position is assumed for birth in many primitive societies.

**Planes and Diameters of the Pelvis**

The pelvis is described as having 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 superior strait or pelvic inlet is bounded posteriorly by the promontory and alae of the sacrum, laterally by the linea terminalis, and anteriorly by the horizontal pubic rami and the symphysis pubis. The inlet of the female pelvis—compared with the male pelvis—typically is more nearly round than ovoid. Caldwell (1934) identified radiographically a nearly round or gynecoid pelvic inlet in approximately half of white women.

Four diameters of the pelvic inlet are usually described: anteroposterior, transverse, and two oblique diameters. The obstetrically important anteroposterior diameter is the shortest distance between the promontory of the sacrum and the symphysis pubis and is designated the obstetrical conjugate (Fig. 2-20). Normally, this measures 10 cm or more. This diameter is distinct from the anteroposterior diameter of the pelvic inlet that has been identified as the true conjugate. The obstetrical conju-

**FIGURE 2-20** Three anteroposterior diameters of the pelvic inlet are illustrated: the true conjugate, the more important obstetrical conjugate, and the clinically measurable diagonal conjugate. The anteroposterior diameter of the midpelvis is also shown. (p = sacral promontory; sym = symphysis pubis.)

**FIGURE 2-21** Vaginal examination to determine the diagonal conjugate. (p = sacral promontory; s = symphysis pubis.)
Pelvic Shapes

Caldwell and Moloy (1933, 1934) developed a classification of the pelvis that is still used. The classification is based on the shape of the pelvis, and its familiarity helps the clinician understand better the mechanisms of labor.

The Caldwell-Moloy classification is based on measurement of the greatest transverse diameter of the inlet and its division into anterior and posterior segments. The shapes of these are used to classify the pelvis as gynecoid, anthropoid, android, or platypeloid (Fig. 2-24). The character of the posterior segment determines the type of pelvis, and the character of 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 in shape.

From viewing the four basic types in Figure 2-24, the configuration of the gynecoid pelvis would intuitively seem suited for delivery of most fetuses. Indeed, Caldwell and co-workers (1939) reported that the gynecoid pelvis was found in almost half of women.

Muscular Support

The pelvic diaphragm forms a broad muscular sling and provides substantial support to the pelvic viscera (Fig. 2-25). This
**FIGURE 2-24** The four parent pelvic types of the Caldwell-Moloy classification. A line passing through the widest transverse diameter divides the inlets into posterior (P) and anterior (A) segments.

**FIGURE 2-25** Pelvic floor muscles.
Efforts are aimed at minimizing these injuries. Rortveit and co-workers, 2003. For this reason, current research seeks strategies to prevent damage to the pelvic floor muscles. DeLancey and associates, 2007a, b; Weidner and colleagues, 2007. Evidence supports that these injuries may predispose women to greater risk of pelvic organ prolapse or urinary incontinence (DeLancey and associates, 2003; Weidner and colleagues, 2006). Of these muscles, the pubovisceral muscle is more commonly damaged (DeLancey and associates, 2003; Weidner and colleagues, 2006). Of these muscles, the pubovisceral muscle is more commonly damaged (Lien, 2006; Margulies RU, Huebner M, DeLancey JO: Origin and insertion points in-...

As shown in Figure 2-26, vaginal birth conveys significant risk for damage to the levator ani muscle or to its innervation (DeLancey and associates, 2003; Weidner and colleagues, 2006). Of these muscles, the pubovisceral muscle is more commonly damaged (Lien, 2006; Margulies RU, Huebner M, DeLancey JO: Origin and insertion points in-...

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**FIGURE 2-26** Illustration of levator ani muscle stretch during delivery.

Muscle group is comprised of the levator ani and the coccygeus muscle. The levator ani is composed of the pubococcygeus, pubo-
rectalis, and ischioococcygeus muscles. The pubococcygeus muscle now is preferably termed the pubovisceral muscle and is subdivi-
ded based on points of insertion and function. These include the pubovaginalis, puboperinealis, and puboanalis muscles, which insert into the vaginal, perineal body, and anus, respectively (Kearney and co-workers, 2004).

As shown in Figure 2-26, vaginal birth conveys significant risk for damage to the levator ani muscle or to its innervation (DeLancey and associates, 2003; Weidner and colleagues, 2006). Of these muscles, the pubovisceral muscle is more commonly damaged (Lien and associates, 2004; Margulies and colleagues, 2007). Evidence supports that these injuries may pre-
dispose women to greater risk of pelvic organ prolapse or urinary incontinence (DeLancey and associates, 2007a, b; Rortveit and co-workers, 2003). For this reason, current research efforts are aimed at minimizing these injuries.
All obstetricians should be aware of the basic reproductive biological processes required for women to successfully achieve pregnancy. A number of abnormalities can affect each of these processes and lead to infertility or pregnancy loss. In most women, spontaneous, cyclical ovulation at 25- to 35-day intervals continues during almost 40 years between menarche and menopause. Without contraception, there are approximately 400 opportunities for pregnancy, which may occur with intercourse on any of 1200 days—the day of ovulation and its two preceding days. This narrow window for fertilization is controlled by tightly regulated production of ovarian steroids. These hormones promote optimal regeneration of endometrium after menstruation ends in preparation for the next implantation window.

Should fertilization occur, the events that unfold after initial implantation of the blastocyst onto the endometrium and through to parturition result from a unique interaction between fetal trophoblasts and maternal endometrium-decidua. The ability of mother and fetus to coexist as two distinct immunological systems results from endocrine, paracrine, and immunological modification of fetal and maternal tissues in a manner not seen elsewhere. The placenta mediates a unique fetal–maternal communication system, which creates a hormonal environment that helps initially to maintain pregnancy and eventually initiates the events leading to parturition. The following sections address the physiology of the ovarian-endometrial cycle, implantation, placenta, and fetal membranes, and specialized endocrine arrangements between fetus and mother.

### The Ovarian–Endometrial Cycle

The endometrium-decidua is the anatomical site of blastocyst apposition, implantation, and placental development. From an evolutionary perspective, the human endometrium is highly developed to accommodate endometrial implantation and a hemochorial type of placentation. Endometrial development of a magnitude similar to that observed in women—that is, with special spiral (or coiling) arteries—is restricted to only a few primates, such as humans, great apes, and Old World monkeys. Trophoblasts of the blastocyst invade these endometrial arteries during implantation and placentation to establish uteroplacental vessels.

These primates are the only mammals that menstruate, which is a process of endometrial tissue shedding with hemorrhage and is dependent on sex steroid hormone-directed changes in blood flow in the spiral arteries. With nonfertile, but ovulatory, ovarian cycles, menstruation effects endometrial desquamation. New growth and development must be initiated with each cycle so that endometrial maturation corresponds rather precisely with the next opportunity for implantation and pregnancy. There seems to be a narrow window of endometrial receptivity to blastocyst implantation that corresponds approximately to menstrual cycle days 20 to 24.

#### The Ovarian Cycle

The development of predictable, regular, cyclical, and spontaneous ovulatory menstrual cycles is regulated by complex interactions of the hypothalamic-pituitary axis, the ovaries, and the genital tract (Fig. 3-1). The average cycle duration is approximately...
approximately 1000 follicles per month until age 35, when this rate accelerates (Faddy and colleagues, 1992). Only 400 follicles are normally released during female reproductive life. Therefore, more than 99.9 percent of follicles undergo atresia through a process of cell death termed *apoptosis* (Gougeon, 1996; Kaipia and Hsueh, 1997).

Follicular development consists of several stages, which include gonadotropin-independent recruitment of primordial follicles from the resting pool and their growth to the antral stage. This appears to be under the control of locally produced growth factors. Two members of the transforming growth factor-β family—growth differentiation factor 9 (GDF9) and bone morphogenetic protein 15 (BMP-15)—regulate proliferation and differentiation of granulosa cells as primary follicles grow (Trombly and co-workers, 2009; Yan and colleagues, 2001). They

28 days, with a range of 25 to 32 days. The sequence of hormonal events leading to ovulation directs the menstrual cycle. The cyclical changes in endometrial histology are faithfully reproduced during each ovulatory cycle.

In 1937, Rock and Bartlett suggested that endometrial histological features were sufficiently characteristic to permit “dating” of the cycle. These changes are illustrated in Figure 3-2. The follicular—proliferative—phase and the postovulatory—luteal or secretory—phase of the cycle are customarily divided into early and late stages.

**Follicular or Preovulatory Ovarian Phase**

There are 2 million oocytes in the human ovary at birth, and about 400,000 follicles are present at the onset of puberty (Baker, 1963). The remaining follicles are depleted at a rate of approximately 1000 follicles per month until age 35, when this rate accelerates (Faddy and colleagues, 1992). Only 400 follicles are normally released during female reproductive life. Therefore, more than 99.9 percent of follicles undergo atresia through a process of cell death termed *apoptosis* (Gougeon, 1996; Kaipia and Hsueh, 1997).

Follicular development consists of several stages, which include gonadotropin-independent recruitment of primordial follicles from the resting pool and their growth to the antral stage. This appears to be under the control of locally produced growth factors. Two members of the transforming growth factor-β family—growth differentiation factor 9 (GDF9) and bone morphogenetic protein 15 (BMP-15)—regulate proliferation and differentiation of granulosa cells as primary follicles grow (Trombly and co-workers, 2009; Yan and colleagues, 2001). They
also stabilize and expand the cumulus oocyte complex (COC) in the oviduct (Aaltonen and associates, 1999; Hreinsson and colleagues, 2002). These factors are produced by oocytes, suggesting that the early steps in follicular development are, in part, oocyte controlled. As antral follicles develop, surrounding stromal cells are recruited, by a yet-to-be-defined mechanism, to become thecal cells.

Although not required for early stages of follicular development, follicle-stimulating hormone (FSH) is required for further development of large antral follicles (Hillier, 2001). During each ovarian cycle, a group of antral follicles, known as a cohort, begins a phase of semisynchronous growth as a result of their maturation state during the FSH rise of the late luteal phase of the previous cycle. This FSH rise leading to

FIGURE 3-2 Photomicrographs illustrating endometrial changes during the menstrual cycle. A. Proliferative phase: straight to slightly coiled, tubular glands are lined by pseudostratified columnar epithelium with scattered mitoses. B. Early secretory phase: coiled glands with a slightly widened diameter are lined by simple columnar epithelium that contains clear subnuclear vacuoles. Luminal secretions are seen. C. Late secretory phase: serrated, dilated glands with intraluminal secretion are lined by short columnar cells. D. Menstrual phase: fragmented endometrium with condensed stroma and glands with secretory vacuoles are seen in a background of blood. (Courtesy of Dr. Kelley Carrick.) E. Early pregnancy: a hypersecretory effect demonstrated by cell clearing and cytoplasmic blebs is seen. (Courtesy of Dr. Raheela Ashfaq.)
follicle development is called the selection window of the ovarian cycle (Macklon and Fauser, 2001). Only the follicles progressing to this stage develop the capacity to produce estrogen.

During the follicular phase, estrogen levels rise in parallel to growth of a dominant follicle and the increase in its number of granulosa cells (see Fig. 3-1). These cells are the exclusive site of FSH receptor expression. The increase in circulating FSH during the late luteal phase of the previous cycle stimulates an increase in FSH receptors and subsequently, the ability of cytochrome P<sub>450</sub> aromatase to convert androstenedione into estradiol. The requirement for thecal cells, which respond to luteinizing hormone (LH), and granulosa cells, which respond to FSH, represents the two-gonadotropin, two-cell hypothesis for estrogen biosynthesis (Short, 1962). As shown in Figure 3-3, FSH induces aromatase and expansion of the antrum of growing follicles. The follicle within the cohort that is most responsive to FSH is likely to be the first to produce estradiol and initiate expression of LH receptors.

After the appearance of LH receptors, the preovulatory granulosa cells begin to secrete small quantities of progesterone. The preovulatory progesterone secretion, although somewhat limited, is believed to exert positive feedback on the estrogen-primed pituitary to either cause or augment LH release. In addition, during the late follicular phase, LH stimulates thecal cell production of androgens, particularly androstenedione, which are then transferred to the adjacent granulosa cells where they are aromatized to estradiol (see Fig. 3-3). During the early follicular phase, granulosa cells also produce inhibin B, which can feed back on the pituitary to inhibit FSH release (Groome and colleagues, 1996). As the dominant follicle begins to grow, the production of estradiol and the inhibins increases, resulting in a decline of follicular-phase FSH. This drop in FSH is responsible for the failure of other follicles to reach preovulatory status—the Graafian follicle stage—during any one cycle. Thus, 95 percent of plasma estradiol produced at this time is secreted by the dominant follicle—the follicle destined to ovulate. During this time, the contralateral ovary is relatively inactive.
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ERS produced in response to LH by theca-lutein and granulosa-
the once avascular granulosa may be due to angiogenic factors
invade the granulosa cell layer. The rapid neovascularization of
down, and by day 2 postovulation, blood vessels and capillaries
of the corpus luteum (Browning, 1973). The basement membrane
physiological and chemical changes leading to transformation into
luteinization. (Curry and Smith, 2006; Ny and colleagues, 2002).

The onset of the gonadotropin surge resulting from increasing
estrogen secretion by preovulatory follicles is a relatively precise
predictor of ovulation. It occurs 34 to 36 hours before release of
the ovum from the follicle (see Fig. 3-1). LH secretion peaks 10
to 12 hours before ovulation and stimulates the resumption of
meiosis in the ovum with the release of the first polar body. Cur-
current studies suggest that in response to LH, increased proges-
terone and prostaglandin production by the cumulus cells, as
well as GDF9 and BMP-15 by the oocyte, activates expression of
genes critical to formation of a hyaluronan-rich extracellular
matrix by the COC (Richards, 2007). As seen in Figure 3-4,
during synthesis of this matrix, cumulus cells lose contact with
one another and move outward from the oocyte along the
hyaluronan polymer—this process is called expansion. This re-
sults in a 20-fold increase in the volume of the complex. Stud-
ies in mice indicate that COC expansion is critical for mainte-
nance of fertility. In addition, LH induces remodeling of the
ovarian extracellular matrix to allow release of the mature
oocyte with surrounding cumulus cells through the surface ep-
thelium. Activation of proteases likely plays a pivotal role in
weakening of the follicular basement membrane and ovulation
(Curry and Smith, 2006; Ny and colleagues, 2002).

Ovulation

The human corpus luteum is a transient endocrine organ
that, in the absence of pregnancy, will rapidly regress 9 to
11 days after ovulation. The mechanisms that control luteoly-
sis remain unclear. However, in part, it results from decreased
levels of circulating LH in the late luteal phase and decreased
LH sensitivity of luteal cells (Duncan and colleagues, 1996;
Ficiori and colleagues, 1986). The role of other luteotropic
factors is less clear, however, prostaglandin F2α (PGF2α) appears
to be luteolytic in nonhuman primates (Auletta, 1987; Wenz
and Jones, 1973). Within the corpus luteum, luteolysis is char-
acterized by a loss of luteal cells by apoptotic cell death (Vask-
ivuo and colleagues, 2002). The endocrine effects, consisting of
a dramatic drop in circulating estradiol and progesterone
levels, are critical to allow the follicular development and
ovulation during the next ovarian cycle. In addition, corpus
luteum regression and decrease in circulating steroids signal
the endometrium to initiate molecular events that lead to
menstruation.

FIGURE 3-4 An ovulated cumulus-oocyte complex (COC). An
oocyte is at the center of the complex. Cumulus cells are widely
separated from each other in the cumulus layer by the hyaluro-
nan-rich extracellular matrix. (Courtesy of Dr. Kevin J. Doody.)

Luteal or Postovulatory Ovarian Phase

Following ovulation, the corpus luteum develops from the re-
 mains of the dominant or Graafian follicle in a process referred to
as luteinization. Rupture of the follicle initiates a series of mor-
phological and chemical changes leading to transformation into
the corpus luteum (Browning, 1973). 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. The rapid neovascularization of
the once avascular granulosa may be due to angiogenic factors
that include vascular endothelial growth factor (VEGF) and oth-
ers produced in response to LH by theca-lutein and granulosa-

Estrogen levels follow a more complex pattern of secretion.
Specifically, just after ovulation, estrogen levels decrease fol-
lowed by a secondary rise that reaches a peak production of
0.25 mg/day of 17β-estradiol at the midluteal phase. Toward
the end of the luteal phase, there is a secondary decrease in
estradiol production.

Ovarian progesterone production peaks at 25 to 50 mg/day
during the midluteal phase. With pregnancy, the corpus luteum
continues progesterone production in response to embryonic
hCG, which will bind and activate luteal cell LH receptors (see
Fig. 3-3).

The human corpus luteum is a transient endocrine organ
that, in the absence of pregnancy, will rapidly regress 9 to
11 days after ovulation. The mechanisms that control luteoly-
sis remain unclear. However, in part, it results from decreased
levels of circulating LH in the late luteal phase and decreased
LH sensitivity of luteal cells (Duncan and colleagues, 1996;
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factors is less clear, however, prostaglandin F2α (PGF2α) appears
to be luteolytic in nonhuman primates (Auletta, 1987; Wenz
and Jones, 1973). Within the corpus luteum, luteolysis is char-
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levels, are critical to allow the follicular development and
ovulation during the next ovarian cycle. In addition, corpus
luteum regression and decrease in circulating steroids signal
the endometrium to initiate molecular events that lead to
menstruation.
Estrogen and Progesterone Action

Estrogen Effects

The fluctuating levels of ovarian steroids are the direct cause of the endometrial cycle. Recent advances in the molecular biology of estrogen and progesterone receptors have greatly improved our understanding of their function. The most biologically potent naturally occurring estrogen—17β-estradiol—is secreted by granulosa cells of the dominant follicle and luteinized granulosa cells of the corpus luteum (see Fig. 3-3). Estrogen is the essential hormonal signal on which most events in the normal menstrual cycle depend. Estradiol action is complex and appears to involve two classic nuclear hormone receptors designated estrogen receptor α (ERα) and β (ERβ) (Katzenellenbogen and colleagues, 2001). These isoforms are the product of separate genes and can exhibit distinct tissue expression. Both estradiol-receptor complexes act as transcriptional factors that become associated with the estrogen response element of specific genes. They share a robust activation by estradiol. However, differences in their binding affinities of other estrogens and their cell-specific expression patterns suggest that ERα and ERβ receptors may have both distinct and overlapping function (Saunders, 2005). Both receptors are expressed in the uterine endometrium (Bombail and co-workers, 2008; Lecce and colleagues, 2001).

The interaction with steroid ligands brings about estrogen receptor–specific initiation of gene transcription. This in turn promotes synthesis of specific messenger RNAs, and thereafter, the synthesis of specific proteins. Among the many proteins up-regulated in most estrogen-responsive cells are estrogen and progesterone receptors themselves. In addition, estradiol has been proposed to act at the endothelial cell surface to stimulate nitric oxide production, leading to its rapid vasoactive properties (Saunders, 2005). Both receptors are expressed in the uterine endometrium (Bombail and co-workers, 2008; Lecce and colleagues, 2001).

Progestosterone Effects

Most progesterone actions on the female reproductive tract are mediated through nuclear hormone receptors. Progesterone enters cells by diffusion and in responsive tissues becomes associated with progesterone receptors (Conneely and colleagues, 2002). There are multiple isoforms of the human progesterone receptor. The best understood isoforms are the progesterone receptor type A (PR-A) and B (PR-B). Both arise from a single gene, are members of the steroid receptor superfamily of transcription factors, and regulate transcription of target genes. These receptors have unique actions. When PR-A and PR-B receptors are co-expressed, it appears that PR-A can inhibit PR-B gene regulation. The inhibitory effect of PR-A may extend to actions on other steroid receptors, including estrogen receptors. In addition, progesterone can evoke rapid responses such as changes in intracellular free calcium levels that cannot be explained by genomic mechanisms. G-protein-coupled membrane receptors for progesterone have been identified recently, but their role in the ovarian-endometrium cycle remains to be elucidated (Peluso, 2007).

Expression patterns of PR-A and PR-B endometrial receptors have been examined using immunohistochemistry (Mote and colleagues, 1999). The endometrial glands and stroma appear to have different expression patterns for these receptors that vary over the menstrual cycle. The glands express both receptors in the proliferative phase, suggesting that both receptors are involved with subnuclear vacuole formation. After ovulation, the glands continue to express PR-B through the midluteal phase, suggesting that glandular secretion seen during the luteal phase is PR-B regulated. In contrast, the stroma and predecidual cells express only PR-A throughout the menstrual cycle, suggesting that progesterone-stimulated events within the stroma are mediated by this receptor.

Progesterone receptor expression has not been found in inflammatory cells or in endothelial cells of endometrial vessels. The role of these two receptor isoforms in the regulation of human menstruation is unclear, but they likely play distinct roles. Animal models suggest that PR-A regulates the antiproliferative effects of progesterone during the secretory phase.

The Endometrial Cycle

Proliferative or Preovulatory Endometrial Phase

Fluctuations in estrogen and progesterone levels produce striking effects on the reproductive tract, particularly the endometrium (Fig. 3-2). The growth and functional characteristics of the human endometrium are unique. Epithelial— glandular cells; stromal—mesenchymal cells; and blood vessels of the endometrium replicate cyclically in reproductive-aged women at a rapid rate. The endometrium is regenerated during each ovarian—endometrial cycle. The superficial endometrium, termed functionalis layer, is shed and regenerated from the deeper basalis layer almost 400 times during the reproductive lifetime of most women (Fig. 3-5). There is no other example in humans of such cyclical shedding and regrowth of an entire tissue.

Follicular-phase production of estradiol is the most important factor in endometrial recovery following menstruation. Although up to two thirds of the functionalis endometrium is fragmented and shed during menstruation, re-epithelialization begins even before menstrual bleeding has ceased. By the fifth day of the endometrial cycle—fifth day of menses, the epithelial surface of the endometrium has been restored, and revascularization is in progress. The preovulatory endometrium is characterized by proliferation of vascular endothelial, stromal, and glandular cells (see Fig. 3-2). During the early part of the proliferative phase, the endometrium is thin, usually less than 2 mm thick. The glands at this stage are narrow, tubular structures that pursue almost a straight and parallel course from the basalis layer toward the surface of the endometrial cavity. Mitotic figures, especially in the glandular epithelium, are identified by the fifth cycle day, and mitotic activity in both epithelium and stroma persists until day 16 to 17, or 2 to 3 days after ovulation. Although blood vessels are numerous and prominent,
there is no extravascular blood or leukocyte infiltration in the endometrium at this stage.

Clearly, re-epithelialization and angiogenesis are important to cessation of endometrial bleeding (Chennazhi and Nayak, 2009; Rogers and associates, 2009). These are dependent on tissue regrowth, which is estrogen regulated. Epithelial cell growth also is regulated in part by epidermal growth factor (EGF) and transforming growth factor \( \alpha \) (TGF\( \alpha \)). Stromal cell proliferation appears to increase through paracrine and autocrine action of estrogen and increased local levels of fibroblast growth factor-9 (Tsai and colleagues, 2002). Estrogens also increase local production of VEGF, which causes angiogenesis through vessel elongation in the basalis (Bausero and colleagues, 1998; Gargett and Rogers, 2001; Sugino and co-workers, 2002).

By the late proliferative phase, the endometrium thickens from both glandular hyperplasia and increased stromal ground substance, which is edema and proteinaceous material. The loose stroma is especially prominent, and the glands in the functionalis layer are widely separated. This is compared with those of the basalis layer, in which the glands are more crowded and the stroma is denser. At midcycle, as ovulation nears, glandular epithelium becomes taller and pseudostratified. The surface epithelial cells acquire numerous microvilli, which increase epithelial surface area, and cilia, which aid in the movement of endometrial secretions during the secretory phase (Ferenczy, 1976).

Determining the menstrual cycle day by endometrial histological criteria, termed dating, is difficult during the proliferative phase because of the considerable variation of phase length among women. Specifically, the follicular phase normally may be as short as 5 to 7 days or as long as 21 to 30 days. In contrast, the luteal or secretory postovulatory phase of the cycle is remarkably constant at 12 to 14 days.

**Secretory or Postovulatory Endometrial Phase**

During the early secretory phase, endometrial dating is based on glandular epithelium histology. After ovulation, the estrogen-primed endometrium responds to rising progesterone levels in a highly predictable manner (see Fig. 3-1). By day 17, glycogen accumulates in the basal portion of glandular epithelium, creating subnuclear vacuoles and pseudostratification. This is the first sign of ovulation that is histologically evident. It is likely the result of direct progesterone action through receptors expressed in glandular cells (Mote and colleagues, 2000). On day 18, vacuoles move to the apical portion of the secretory nonciliated cells. By day 19, these cells begin to secrete glycoprotein and mucopolysaccharide contents into the lumen (Hafez and colleagues, 1975). Glandular cell mitosis ceases with secretory activity on day 19 due to rising progesterone levels, which antagonize the mitotic effects of estrogen. Estradiol action is also decreased because of glandular expression of the type 2 isoform of 17\( \beta \)-hydroxysteroid dehydrogenase. This converts estradiol to the less active estrone (Casey and MacDonald, 1996).

Dating in the mid- to late-secretory phase relies on changes in the endometrial stroma (see Fig. 3-2). On days 21 to 24, the stroma becomes edematous. On days 22 to 25, stromal cells surrounding the spiral arterioles begin to enlarge, and stromal mitosis becomes apparent. Days 23 to 28 are characterized by predecidual cells, which surround spiral arterioles.

An important feature of secretory-phase endometrium between days 22 and 25 is striking changes associated with predecidual transformation of the upper two thirds of the functionalis layer. The glands exhibit extensive coiling and luminal secretions
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CHAPTER 3

become visible. Changes within the endometrium also can mark the so-called window of implantation seen on days 20 to 24. Epithelial surface cells show decreased microvilli and cilia but appearance of luminal protrusions on the apical cell surface (Nikas, 2003). These pinopodes are important in preparation for blastocyst implantation. They also coincide with changes in the surface glycocalyx that allow acceptance of a blastocyst (Aplin, 2003).

The secretory phase is also highlighted by the continuing growth and development of the spiral arteries. Boyd and Hamilton (1970) emphasized the extraordinary importance of the endometrial spiraling or coiled arteries. They arise from arcuate arteries, which are myometrial branches of the uterine vessels (see Fig. 3-5). The morphological and functional properties of spiral arteries are unique and essential for establishing changes in blood flow to permit either menstruation or implantation. During endometrial growth, spiral arteries lengthen at a rate appreciably greater than the rate of increase in endometrial tissue height or thickness (Fig. 3-6). This growth discordance obliges even greater coiling of the already spiraling vessels. Spiral artery development reflects a marked induction of angiogenesis, consisting of widespread vessel sprouting and extension. Perrot-Applanat and associates (1988) described progesterone and estrogen receptors in the smooth muscle cells of the uterus and spiral arteries. They further demonstrated that such rapid angiogenesis is regulated, in part, through estrogen- and progesterone-regulated synthesis of VEGF (Ancelin and colleagues, 2002; Chennazhi and Nayak, 2009). This protein is secreted by stromal cells and glandular epithelium and stimulates endothelial cell proliferation and increases vascular permeability. Thus, steroid hormone influences on growth and vasculature are directed to a large degree through the local production of growth factors.

Menstruation

The midluteal–secretory phase of the endometrial cycle is a critical branch point in endometrial development and differentiation. With corpus luteum rescue and continued progesterone secretion, the process of decidualization continues. If luteal progesterone production decreases with luteolysis, events leading to menstruation are initiated. Many molecular mechanisms involving endometrial progesterone withdrawal, as well as the subsequent inflammatory response that causes endometrial sloughing, have been defined (Critchley and colleagues, 2006).

A notable histological characteristic of late premenstrual-phase endometrium is stromal infiltration by neutrophils, giving a pseudoinflammatory appearance to the tissue. These cells infiltrate primarily on the day or two immediately preceding menses onset. The endometrial stromal and epithelial cells produce interleukin-8 (IL-8), which is a chemotactic–activating factor for neutrophils (Arici and colleagues, 1993). IL-8 may be one agent that serves to recruit neutrophils just prior to menstruation. Similarly, monocyte chemotactic protein-1 (MCP-1) is synthesized by endometrium (Arici and colleagues, 1995).
Leukocyte infiltration is considered key to extracellular matrix breakdown of the functionalis layer. Invading leukocytes secrete enzymes that are members of the matrix metalloproteinase (MMP) family. These add to the proteases already produced by endometrial stromal cells. The rising level of MMPs tips the balance between proteases and protease inhibitors, effectively initiating matrix degradation. This phenomenon has been proposed to initiate the events leading to menstruation (Dong and colleagues, 2002).

## Anatomical Events During Menstruation

The classic study by Markee (1940) described tissue and vascular changes in endometrium before menstruation. First, there were marked changes in endometrial blood flow essential for menstruation. With endometrial regression, coiling of spiral arteries becomes sufficiently severe that resistance to blood flow increases strikingly, causing hypoxia of the endometrium. Resultant stasis is the primary cause of endometrial ischemia and tissue degeneration (Fig. 3-6). A period of vasoconstriction precedes menstruation and is the most striking and constant event observed in the cycle. Intense vasoconstriction of the spiral arteries also serves to limit menstrual blood loss. Blood flow appears to be regulated in an endocrine manner by sex steroid hormone–induced modifications of a paracrine-mediated vasoactive peptide system as described subsequently.

### Prostaglandins and Menstruation

Progestosterone withdrawal increases expression of inducible cyclooxygenase 2 (COX-2) enzyme to synthesize prostaglandins and decreases expression of 15-hydroxyprostaglandin dehydrogenase (PGDH), which degrades prostaglandins (Casey and colleagues, 1980, 1989). The net result is increased prostaglandin production by stromal cells along with increased prostaglandin receptor density on blood vessels and surrounding cells.

A role for prostaglandins—especially vasoconstricting prostaglandin F2α (PGF2α)—in initiation of menstruation has been suggested (Abel, 2002). Large amounts of prostaglandins are present in menstrual blood. PGF2α administration prompts symptoms that mimic dysmenorrhea, which is commonly associated with normal menses and likely caused by myometrial contractions and uterine ischemia. PGF2α administration to non-pregnant women also will cause menstruation. This response is believed to be mediated by PGF2α-induced vasoconstriction of spiral arteries, causing the uppermost endometrial zones to become hypoxic. This is a potent inducer of angiogenesis and vascular permeability factors such as VEGF. Prostaglandins play an important role in the cascade of events leading to menstruation that include vasoconstriction, myometrial contractions, and up-regulation of proinflammatory responses.

### Vasoactive Peptides and Menstruation

A number of peptides may comprise a hormone-responsive paracrine system in the endometrium to regulate spiral artery blood flow. One is the endothelin–enkephalinase system (Casey and MacDonald, 1996). The endothelins—ET-1, ET-2, and ET-3—are small, 21-amino-acid peptides. Endothelin-1 (ET-1) is a potent vasoconstrictor first identified as a product of vascular endothelial cells (Yanagisawa and colleagues, 1988). Endothelins are degraded by enkephalinase, which is localized in endometrial stromal cells. Its specific activity in these cells increases strikingly and in parallel with the increase in progesterone blood levels after ovulation. The specific activity of enkephalinase is highest during the midluteal phase and declines steadily thereafter as progesterone plasma levels decrease (Casey and colleagues, 1991).

### Activation of Lytic Mechanisms

Following vasoconstriction and endometrial cytokine changes, activation of proteases within stromal cells and leukocyte invasion is required to degrade the endometrial interstitial matrix. And matrix metalloproteases—MMP-1 and MMP-3—are released from stromal cells and may activate other neutrophilic proteases such as MMP-8 and MMP-9.

### Origin of Menstrual Blood

Menstrual bleeding is from both systems, but arterial bleeding is appreciably greater than venous. Endometrial bleeding appears to follow rupture of an arteriole of a coiled artery, with consequent hematoma formation. With a hematoma, the superficial endometrium is distended and ruptures. Subsequently, fissures develop in the adjacent functionalis layer, and blood, as well as tissue fragments of various sizes, are sloughed. Hemorrhage stops with arteriolar constriction. Changes that accompany partial tissue necrosis also serve to seal vessel tips.

The endometrial surface is restored by growth of flanges, or collars, that form the everted free ends of the endometrial glands (Markee, 1940). These flanges increase in diameter very rapidly, and epithelial continuity is reestablished by fusion of the edges of these sheets of migrating thin cells.

### Interval between Menses

The modal interval of menstruation is considered to be 28 days, but there is considerable variation among women, as well as in the cycle lengths of a given woman. Marked differences in the intervals between menstrual cycles are not necessarily indicative of infertility. Arey (1939) analyzed 12 studies comprising about 20,000 calendar records from 1500 women. He concluded that there is no evidence of perfect menstrual cycle regularity. Among average adult women, a third of cycles departed by more than 2 days from the mean of all cycle lengths. In his analysis of 5322 cycles in 485 normal women, an average interval of 28.4 days was estimated. Average cycle length in pubertal girls was 33.9 days. Haman (1942) surveyed 2460 cycles in 150 women, and the distribution curve for cycle length is shown in Figure 3-7.

### The Decidua

The decidua is a specialized, highly modified endometrium of pregnancy and is a function of hemochorial placentation. The latter has in common the process of trophoblast invasion, and considerable research has focused on the interaction between decidual cells and invading trophoblasts. Decidualization—transformation of secretory endometrium to decidua—is dependent on estrogen and progesterone and factors secreted by the implanting blastocyst. The special relationship that exists between the decidua and the invading trophoblast seemingly defies the laws of transplantation immunology (Beer and
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Billingham, 1971). The success of this unique semiallograft not only is of great scientific interest but may involve processes that harbor insights leading to more successful transplantation surgery and perhaps even immunological treatment of neoplasia (Billingham and Head, 1986; Lala and colleagues, 2002).

### Decidual Structure

The first scientific description of the membrana decidua was in the 18th century by William Hunter. According to Damjanov (1985), membrana denoted its gross anatomical appearance, whereas decidua was an analogy to deciduous leaves to indicate that it is shed after childbirth. The decidua is classified into three parts based on anatomical location. Decidua directly beneath blastocyst implantation is modified by trophoblast invasion and becomes the decidua basalis. The decidua capsularis overlies the enlarging blastocyst, and initially separates it from the rest of the uterine cavity (Fig. 3–8). This portion is most prominent during the second month of pregnancy, consisting of decidual cells covered by a single layer of flattened epithelial cells. Internally, it contacts the avascular, extraembryonic fetal membrane—the chorion laeve. The remainder of the uterus is lined by decidua parietalis—sometimes called decidua vera when decidua capsularis and parietalis are joined.

During early pregnancy, there is a space between the decidua capsularis and parietalis because the gestational sac does not fill the entire uterine cavity. By 14 to 16 weeks, the expanding sac has enlarged to completely fill the uterine cavity. With fusion of the decidua capsularis and parietalis, the uterine cavity is functionally obliterated. 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, like the secretory endometrium, are composed of three layers. There is a surface, or compact zone—zona compacta; a middle portion, or spongy zone—zona spongiosa—with 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.

### Decidual Reaction

In human pregnancy, 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, they spread in waves throughout the uterine endometrium and then from the site of implantation. The endometrial stromal cells enlarge to form polygonal or round decidual cells. The nuclei become round and vesicular, and the cytoplasm becomes clear, slightly basophilic, and surrounded by a translucent membrane. Each mature decidual cell becomes surrounded by a pericellular membrane. Thus, the human decidual cells clearly build walls around themselves and possibly around the fetus. The pericellular matrix surrounding the decidual cells may allow attachment of cytotrophoblasts through

**FIGURE 3-7.** Duration of menstrual cycle. (Based on distribution data of Arey, 1939, and Haman, 1942.)

**FIGURE 3-8** Decidualized endometrium covers the early embryo. Three portions of the decidua (basalis, capsularis, and parietalis) also are illustrated.
cellular adhesion molecules. The cell membrane also may provide decidual cell protection against selected cytotrophoblastic proteases.

### Decidual Blood Supply

As a consequence of implantation, the blood supply to the decidua capsularis is lost as the embryo-fetus grows. Blood supply to the decidua parietalis through spiral arteries persists, as in the endometrium during the luteal phase of the cycle. The spiral arteries in the decidua parietalis retain a smooth muscle wall and endothelium and thereby remain responsive to vasoactive agents that act on their smooth muscle or endothelial cells.

The spiral arterial system supplying the decidua basalis directly beneath the implanting blastocyst, and ultimately the intervillous space, is altered remarkably. These spiral arterioles and arteries are invaded by cytotrophoblasts. During this process, the walls of vessels in the basalis are destroyed. Only a shell without smooth muscle or endothelial cells remains. Importantly, as a consequence, these vascular conduits of maternal blood—which become the uteroplacental vessels—are not responsive to vasoactive agents. By contrast, 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

The decidua contains numerous cell types, whose composition varies with the stage of gestation (Loke and King, 1995). The primary cellular components are the true decidual cells, which differentiated from the endometrial stromal cells, and numerous maternal bone marrow–derived cells. The zona compacta consists of large, closely packed, epithelioid, polygonal, light-staining cells with round nuclei. Many stromal cells appear stellate, with long protoplasmic processes that anastomose with those of adjacent cells. This is particularly so when the decidua is edematous.

A striking abundance of large, granular lymphocytes termed decidual natural killer cells (NK) are present in the decidua early in pregnancy. In peripheral blood, there are two subsets of NK cells. About 90 percent are highly cytolytic and 10 percent show less cytolytic ability but increased secretion of cytokines. In contrast to peripheral blood, 95 percent of NK cells in decidua secrete cytokines. About half of these unique cells also express angiogenic factors. These decidua NK cells likely play an important role in trophoblast invasion and vasculogenesis.

Early in pregnancy, zona spongiosa of the decidua 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 nourishment of the blastocyst. As pregnancy progresses, the epithelium gradually becomes cuboidal or even flattened, later degenerating and sloughing to a greater extent into the gland lumens. Later in pregnancy, the glandular elements largely disappear. In comparing the decidua parietalis at 16 weeks with the early proliferative endometrium of a nonpregnant woman, it is clear that there is marked hyperplasty but only slight hyperplasia of the endometrial stroma during decidual transformation.

The decidua basalis contributes to the formation of the basal plate of the placenta (Fig. 3-9). It differs histologically from the decidua parietalis in two important respects. First, the spongy zone of the basalis consists mainly of arteries and widely dilated veins, and by term, the glands have virtually disappeared. Second, the decidua basalis is invaded by large numbers of interstitial trophoblast cells and trophoblastic giant cells. Although most abundant in the decidua, the giant cells commonly penetrate the upper myometrium. Their number and invasiveness may be so extensive as to resemble choriocarcinoma.

The Nitabuch layer is a zone of fibrinoid degeneration in which invading trophoblasts meet the decidua. If the decidua is defective, as in placenta accreta, the Nitabuch layer is usually absent (see Chap. 35, p. 776). 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. McCombs and Craig (1964) found that decidual necrosis is a normal phenomenon in the first and probably second trimesters. Thus, necrotic decidua obtained through curettage after spontaneous abortion in the first trimester should not necessarily be interpreted as either a cause or an effect of the pregnancy loss.

### Decidual Prolactin

Convincing evidence has been presented that the decidua is the source of prolactin that is present in enormous amounts in amnionic fluid (Golander and colleagues, 1978; Riddick...
and co-workers, 1979). Decidual prolactin is not to be confused with placent al lactogen (hPL), which is produced only by the syncytiotrophoblast. Rather, decidual prolactin is a product of the same gene that encodes for anterior pituitary prolactin. And although the amino acid sequence of prolactin in both tissues is identical, an alternative promoter is used within the prolactin gene to initiate transcription in decidua (Telmann and Gellersen, 1998). The latter is thought to explain the different mechanisms that regulate expression in the decidua versus pituitary (Christian and colleagues, 2002a, 2000b).

The protein preferentially enters amniotic fluid, and little enters maternal blood. Consequently, prolactin levels in amniotic fluid are extraordinarily high and may reach 10,000 ng/mL during weeks 20 to 24 (Tyson and colleagues, 1972). This compares with fetal serum levels of 350 ng/mL and maternal serum levels of 150 to 200 ng/mL. As a result, decidual prolactin is a classic example of paracrine function between maternal and fetal tissues.

**Role(s) of Decidual Prolactin**

The exact physiological roles of decidual prolactin are still unknown. Its action is mediated by relative expression of two unique prolactin receptors as well as the amount of intact or full-length prolactin protein compared with the truncated 16-kDa form (Jabbour and Critchley, 2001). Receptor expression has been demonstrated in decidua, chorionic cytotrophoblasts, amniotic epithelium, and placental syncytiotrophoblast (Maaskant and colleagues, 1996). There are a number of possible roles for decidual prolactin. First, because most or all decidual prolactin enters amniotic fluid, there may be a role for this hormone in transmembrane solute and water transport, and thus, in maintenance of amniotic fluid volume. Second, there are prolactin receptors in a number of bone marrow-derived immune cells, and prolactin may stimulate T cells in an autocrine or paracrine manner (Pellegrini and colleagues, 1992). This raises the possibility that decidual prolactin may act in regulating immunological functions during pregnancy. Prolactin may play a role in regulation of angiogenesis during implantation. In this regard, intact prolactin protein enhances angiogenesis, whereas the proteolytic fragment can inhibit new vessel growth. Lastly, decidual prolactin has been shown in the mouse to have a protective function by repressing expression of genes detrimental to pregnancy maintenance (Bao and colleagues, 2007).

**Regulation of Decidual Prolactin**

Factors that regulate decidual prolactin production are not clearly defined. Most agents known to inhibit or stimulate pituitary prolactin secretion—including dopamine, dopamine agonists, and thyrotropin-releasing hormone—do not alter decidual prolactin secretion either in vivo or in vitro. Brosens and colleagues (2000) demonstrated that prostaglandins act synergistically with cyclic adenosine monophosphate on endometrial stromal cells in culture to increase prolactin expression. This suggests that the level of progesterone receptor expression may determine the decidualization process, at least as marked by prolactin production. And arachidonic acid, but not PGF2α or PGE2, attenuates the rate of decidual prolactin secretion (Handwerger and colleagues, 1981). Conversely, a variety of cytokines and growth factors—ET-1, IL-1, IL-2, and epidermal growth factor—decrease decidual prolactin secretion (Chao and colleagues, 1994; Frank and associates, 1995).

**Implantation, Placental Formation, and Fetal Membrane Development**

Human placental development is as uniquely intriguing as fetal embryology. During its brief intrauterine passage, the fetus is dependent on the placenta for pulmonary, hepatic, and renal functions. These are accomplished through the unique placental anatomical association with the maternal interface. The placenta links mother and fetus by indirect interaction with maternal blood that spurts into the intervillous space from uteroplacental vessels. Maternal blood bathes the outer syncytiotrophoblast to allow exchange of gases and nutrients with fetal capillary blood within connective tissue at the villous core. Fetal and maternal blood are not normally mixed in this hemochorial placenta. There is also a paracrine system that links mother and fetus through the anatomical and biochemical juxtaposition of extraembryonic chorion laeve of fetal origin and maternal decidua parietalis. This is an extraordinarily important arrangement for communication between fetus and mother and for maternal immunological acceptance of the conceptus (Guzeloglu-Kayisli and associate, 2009).

### Fertilization and Implantation

**Ovum Fertilization and Zygote Cleavage**

The union of egg and sperm at fertilization represents one of the most important and fascinating processes in biology. Ovulation frees the secondary oocyte and adherent cells of the cumulus-oocyte complex from the ovary. Although technically this mass of cells is released into the peritoneal cavity, the oocyte is quickly engulfed by the infundibulum of the fallopian tube. Further transport through the oviduct is accomplished by directional movement of cilia and tubal peristalsis. Fertilization normally occurs in the oviduct, and it is generally agreed that it must take place within a few hours, and no more than a day after ovulation.

Because of this narrow window of opportunity, spermatozoa must be present in the 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. Thus, the postovulatory and postfertilization developmental ages are similar.

Steps involved with fertilization are highly complex. Molecular mechanisms allow passage of spermatozoa between follicular cells, through the zona pellucida, and into the oocyte cytoplasm leading to the formation of the zygote. These are reviewed by Primakoff and Myles (2002).

The timing of events in early human development is described as days or weeks postfertilization, that is, postconceptional. By contrast, in most chapters of this book, clinical pregnancy dating is calculated from the start of the last menstrual period. As discussed earlier, the length of the follicular phase of the cycle is subject to more variability than the luteal phase. Thus, 1 week postfertilization corresponds to approximately 3 weeks from the last menstrual period in women with regular 28-day cycles.
After fertilization in the fallopian tube, the mature ovum becomes a zygote—a diploid cell with 46 chromosomes—that then undergoes cleavage into blastomeres (Fig. 3-10). In the two-cell zygote, the blastomeres and polar body are free in the perivitelline fluid and are surrounded by a thick zona pellucida. The zygote undergoes slow cleavage for 3 days while still within 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 about 3 days after fertilization. Gradual accumulation of fluid between the cells of the morula results in the formation of the early blastocyst.

### The Blastocyst

In the earliest stages of the human blastocyst, the wall of the primitive blastodermic vesicle consists of a single layer of ectoderm. As early as 4 to 5 days after fertilization, the 58-cell blastula differentiates into five embryo-producing cells—the inner cell mass, and 53 cells destined to form trophoblasts (Hertig, 1962). In a 58-cell blastocyst, the outer cells, called the trophectoderm, can be distinguished from the inner cell mass that forms the embryo (see Fig. 3-10).

Interestingly, the 107-cell blastocyst is found to be no larger than the earlier cleavage stages, despite the accumulated fluid. It measures about 0.155 mm in diameter, which is similar to the size of the initial postfertilization zygote. At this stage, the eight formative, or embryo-producing, cell, are surrounded by 99 trophoblastic cells. It is at this stage that the blastocyst is released from the zona pellucida as a result of secretion of specific proteases from the secretory-phase endometrial glands (O’Sullivan and colleagues, 2002).

Release from the zona pellucida allows blastocyst-produced cytokines and hormones to directly influence endometrial receptivity (Lindhard and colleagues, 2002). Evidence has accumulated that IL-1α and IL-1β are secreted by the blastocyst and that these cytokines can directly influence the endometrium. Embryos also have been shown to secrete human chorionic gonadotropin (hCG), which may influence endometrial receptivity (Licht and co-workers, 2001; Lobo and colleagues, 2001). The receptive endometrium is thought to respond by producing leukemia inhibitory factor (LIF) and colony-stimulating factor-1 (CSF-1). These serve to increase trophoblast protease production that degrades selected maternal extracellular matrix proteins and allows trophoblast invasion. Thus, embryo “hatching” is a critical step toward successful pregnancy as it allows association of trophoblasts with endometrial epithelial cells and permits release of trophoblast-produced hormones into the uterine cavity.

### Blastocyst Implantation

Implantation of the embryo into the uterine wall is a common feature of all mammals. In women, it takes place 6 or 7 days after fertilization. This process can be divided into three phases: (1) apposition—initial adhesion of the blastocyst to the uterine wall; (2) adhesion—increased physical contact between the blastocyst and uterine epithelium; and (3) invasion—penetration and invasion of syncytiotrophoblast and cytotrophoblast into the endometrium, inner third of the myometrium, and uterine vasculature.

Successful implantation requires receptive endometrium appropriately primed with estrogen and progesterone. As shown in Figure 3-1, uterine receptivity is limited to days 20 to 24 of the cycle (Bergh and Navot, 1992). Adherence to epithelium is mediated by cell-surface receptors at the implantation site that interact with receptors on the blastocyst (Carson, 2002; Lessey and Castelbaum, 2002; Lindhard and associates, 2002; Paria and colleagues, 2002). Development of a receptive epithelium results from the postovulatory production of estrogen and progesterone by the corpus luteum. If the blastocyst approaches the endometrium after cycle day 24, the potential for adhesion is diminished because synthesis of antiadhesive glycoproteins prevents receptor interactions (Navot and Bergh, 1991).
At the time of its interaction with the endometrium, the blastocyst is composed of 100 to 250 cells. The blastocyst loosely adheres to the endometrial epithelium by apposition. This most commonly occurs on the upper posterior uterine wall. In women, syncytiotrophoblast has not been distinguished prior to implantation. Attachment of the trophectoderm of the blastocyst to the endometrial surface by apposition and adherence appears to be closely regulated by paracrine interactions between these two tissues.

Successful endometrial blastocyst adhesion involves modification in expression of cellular adhesion molecules (CAMs). The integrins—one of four families of CAMs—are cell-surface receptors that mediate adhesion of cells to extracellular matrix proteins (Lessey and Castelbaum, 2002). Great diversity of cell binding to a host of different extracellular matrix proteins is possible by differential regulation of the integrin receptors. Endometrial integrins are hormonally regulated, and a specific set of integrins expressed at implantation (Lessey and colleagues, 1996). Specifically, $\alpha V\beta 3$ and $\alpha 4\beta 1$ integrins expressed on endometrial epithelium are considered a marker of receptivity for blastocyst attachment. Aberrant expression of $\alpha V\beta 3$ has been associated with infertility (Lessey and colleagues, 1995).

**Biology of the Trophoblast**

The formation of the human placenta begins with the trophectoderm, which is first to differentiate at the morula stage. It gives rise to the layer of trophoblast cells encircling the blastocyst. And then until term, the trophoblast plays critical roles at the fetal-maternal interface. Trophoblast exhibits the most variable structure, function, and developmental pattern of all placental components. Its invasiveness provides for implantation, its role in nutrition of the conceptus is reflected in its name, and its function as an endocrine organ is essential to maternal physiological adaptations and to maintenance of pregnancy.

**Trophoblast Differentiation**

By the eighth day postfertilization, after initial implantation, the trophoblast has differentiated into an outer multinucleated syncytiotrophoblast, and an inner layer of primitive mononuclear cells—cytotrophoblast (Fig. 3-11). The latter are germinal cells for the syncytiotum and are the primary secretory component within the placenta. Although the ability to undergo DNA synthesis and mitosis, a well-demarcated cell border, and a single nucleus characterize each cytotrophoblast, these characteristics are lacking in the syncytiotrophoblast (Arnholdt and colleagues, 1991). It is so named because it has no individual cells. Instead, it has an amorphous cytoplasm without cell borders, nuclei that are multiple and diverse in size and shape, and a continuous syncytial lining. This configuration aids transport across the syncytiotrophoblast, because control of transport is not dependent on the participation of individual cells.

After implantation is complete, the trophoblast further differentiates along two main pathways, giving rise to villous and extravillous trophoblast. As shown in Figure 3-12, both pathways give rise to populations of trophoblast cells that have distinct functions when in contact with maternal tissues (Loke and King, 1995). The villous trophoblast gives rise to the chorionic villi, which primarily transport oxygen and nutrients between the fetus and mother. The extravillous trophoblast gives rise to the chorionic villi, which primarily transport oxygen and nutrients between the fetus and mother. The extravillous trophoblast migrates into the decidua and myometrium and also penetrates maternal vasculature, thus coming into contact with a variety of maternal cell types (Pijnenborg, 1994). The extravillous trophoblast is thus further classified as interstitial trophoblast and endovascular trophoblast. The interstitial trophoblast invades the decidua and eventually penetrates the myometrium to form placental bed.
giant cells. These trophoblasts also surround spiral arteries. The endovascular trophoblast penetrates the lumen of the spiral arteries (Pijnenborg and colleagues, 1983). These are both discussed in greater detail in sections that follow.

■ Embryonic Development after Implantation

Early Trophoblast Invasion

After gentle erosion between epithelial cells of the surface endometrium, invading trophoblasts burrow deeper, and by the 10th day, the blastocyst becomes totally encased within endometrium (Fig. 3-13). The mechanisms leading to trophoblast invasion into the endometrium are similar to the characteristics of metastasizing malignant cells. They are discussed further on page 53.

At 9 days of development, the blastocyst wall facing the uterine lumen is a single layer of flattened cells (Figs. 3-11 and 3-14). The opposite, thicker wall comprises two zones—the trophoblasts and the embryo-forming inner cell mass. As early as 7½ days after fertilization, the inner cell mass or embryonic disc is differentiated into a thick plate of
Implantation, Embryogenesis, and Placental Development

CHAPTER 3

primitive ectoderm and an underlying layer of endoderm. Some small cells appear between the embryonic disc and the trophoblast and enclose a space that will become the amnionic cavity.

Embryonic mesenchyme first appears as isolated cells within blastocyst cavity. When the cavity is completely lined with mesoderm, it is termed the chorionic vesicle, and its membrane, now called the chorion, is composed of trophoblasts and mesenchyme. The amnion and yolk sac are illustrated in Figure 3-15. Mesenchymal cells within the cavity are the most numerous and 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.

Lacunae Formation within the Syncytiotrophoblast

Beginning about 12 days after conception, the syncytiotrophoblast of the trophoblast shell is permeated by a system of intercommunicating channels called trophoblastic lacunae. As the embryo enlarges, more maternal decidua basalis is invaded by basal syncytiotrophoblast. After invasion of superficial decidual capillary walls, lacunae become filled with maternal blood (see Fig. 3-11). At the same time, the decidual reaction intensifies in the surrounding stroma, which is characterized by enlargement of the decidual stromal cells and glycogen storage.

Development of Primary Villous Stalks

With deeper blastocyst invasion into the decidua, the extravillous cytotrophoblasts give rise to solid primary villi composed of a cytotrophoblastic core covered by syncytium. These arise from buds of cytotrophoblast that begin to protrude into the primitive syncytiotrophoblast before 12 days postfertilization. As the lacunae join, a complicated labyrinth is formed that is partitioned by these solid cytotrophoblastic columns. The trophoblast-lined labyrinthine channels form the intervillous space, and the solid cellular columns form the primary villous stalks. The villi initially are located over the entire blastocyst surface. They later disappear except over the most deeply implanted portion, which is destined to form the placenta.

Placental Organization

The term hemochorial is used to describe human placentation. It derives from hemo referring to maternal blood, which directly bathes the syncytiotrophoblast, and chorio for chorion (placenta). The older term hemochorioendothelial takes into consideration that chorionic tissue is separated from fetal blood by the endothelial wall of the fetal capillaries that traverse the villous core.

Chorionic Villi

Beginning on approximately the 12th day after fertilization, chorionic villi can first be distinguished. Mesenchymal cords derived from extraembryonic mesoderm invade the solid trophoblast columns. These form secondary villi. After angiogenesis begins in the mesenchymal cores, the resulting villi are termed tertiary. Although maternal venous sinuses are tapped early in implantation, maternal arterial blood does not enter the intervillous space until around day 15. By approximately the 17th day, however, fetal blood vessels are functional, and a placental circulation is established. The fetal–placental circulation is completed when embryonic blood vessels are connected with chorionic vessels. In some villi, there is failure of angiogenesis from lack of circulation. They can be seen normally, but the
most striking exaggeration of this process is seen with hydatidi-
form mole (see Chap. 11, p. 257).

Villi are covered by the outer layer of syncytium and inner
layer of cytotrophoblasts, which are also known as Langhans
cells (see Fig. 3-12). Cytotrophoblast proliferation at the villous
tips produce the trophoblastic cell columns that form anchor-
ing villi. They are not invaded by fetal mesenchyme, and they
are anchored to the decidua at the basal plate. Thus, the base of
the intervillous space faces the maternal side and consists of cy-
totrophoblasts from cell columns, the covering shell of syncy-
tiotrophoblast, and maternal decidua of the basal plate. The
base of the chorionic plate forms the roof of the intervillous
space and consists of two layers of trophoblasts externally and
fibrous mesoderm internally. The “definitive” chorionic plate is
formed by 8 to 10 weeks as the amnionic and primary chori-
onic plate mesenchyme fuse together. This formation is ac-
complished by expansion of the amnionic sac, which also sur-
rounds the connective stalk and the allantois and joins these
structures to form the umbilical cord (Kaufmann and Scheffen,

Villus Ultrastructure

Interpretation of the fine structure of the placenta came from
electron microscopic studies of Wislocki and Dempsey (1955).
There are prominent microvilli on the syncytial surface that
 correspond to the so-called brush border described by light mi-
croscopy (Fig. 3-16). Associated pinocytotic vacuoles and ves-
icles are related to absorptive and secretory placental functions.
Microvilli act to increase surface area in direct contact with ma-
ternal blood. This contact between the trophoblastic surface
and maternal blood is the defining characteristic of the hemo-
chorial placenta.

The human hemochorial placenta can be subdivided into
hemodichorial or hemomonochorial (Enders, 1965). The di-

chorial type is more prominent during the first trimester of ges-
tation. It consists of the inner layer of the cytotrophoblasts with
the associated basal lamina, covered by a layer of syncytiotro-
phoblasts (see Fig. 3-16). Later in gestation the inner layer of
cytotrophoblasts is no longer continuous, and by term there are
only scattered cells present (Fig. 3-17). These create a narrower
hemomonochorial barrier that aids nutrient and oxygen trans-
port to the fetus.

Placental Development

Development of the Chorion and Decidua

In early pregnancy, the villi are distributed over the entire periph-
ery of the chorionic membrane. A blastocyst dislodged from the
endometrium at this stage of development appears shaggy (Fig.
3-18). As the blastocyst with its surrounding trophoblasts grows
and expands into the decidua, one pole extends outward toward
the endometrial cavity. The opposite pole will form the placenta
from villous trophoblasts and anchoring cytotrophoblasts. Chori-
onic villi in contact with the decidua basalis proliferate to form
the chorion frondosum—or leafy chorion—which is the fetal com-
ponent of the placenta. As growth of embryonic and extrabry-
onic tissues continues, the blood supply of the chorion facing the
endometrial cavity is restricted. Because of this, villi in contact
with the decidua capsularis cease to grow and degenerate. This
portion of the chorion becomes the avascular fetal membrane
that abuts the decidua parietalis, that is, the chorion laeve—or

FIGURE 3-16 Electron micrograph of first-trimester human placenta
showing well-differentiated syncytiotrophoblast (S) with numerous
mitochondria (black arrows). Cytotrophoblast (C) has large mito-
chondria (M) but few other organelles. At the top, there is a promi-
nent border of microvilli (red arrows) arising from the syncytium.

FIGURE 3-17 Electron micrograph of term human placenta villus. A
villus capillary filled with red blood cells (asterisks) is seen in close
proximity to the microvilli border. (From The Human Placenta; JD
Sons, Ltd. Reproduced with permission of Blackwell Publishing Ltd.)
smooth chorion. The chorion laeve is generally more translucent than the amnion and rarely exceeds 1-mm thickness. The chorion is composed of cytotrophoblasts and fetal mesodermal mesenchyme that survives in a relatively low-oxygen atmosphere.

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 an 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.

With continued expansion of the embryo–fetus, the uterine lumen is obliterated, and the chorion laeve becomes contiguous with the entire maternal decidua parietalis that is not occupied by the placenta. As the fetus grows, the decidua capsularis merges with the parietalis. The capsularis then is largely lost by pressure and the attendant loss of blood supply. The area of decidua where decidua capsularis and decidua parietalis merge is referred to as the decidua vera.

**Maternal Regulation of Trophoblast Invasion and Vascular Growth.** Decidual natural killer cells (dNK) accumulate in the decidua during the first half of pregnancy and are found in direct contact with trophoblasts. As described on page 46, these cells lack cytotoxic functions as well as other unique properties that distinguish them from circulating natural killer cells and from natural killer cells in the endometrium prior to pregnancy (Manaster and co-workers, 2008). This is important because it prevents them from recognizing and destroying fetal cells as “foreign.” Hanna and associates (2006) have elucidated the ability of dNK cells to attract and promote invasion of trophoblast into the decidua and promote vascular growth. Decidual NK cells express both interleukin-8 and interferon-inducible protein-10, which bind to receptors on invasive trophoblast cells to promote their invasion into the decidua toward the spiral arteries. Decidual NK cells also produce proangiogenic factors, including VEGF and placental growth factor (PIGF), which promote vascular growth in the decidua. In addition, trophoblasts secrete specific chemokines that attract the dNK cells to the maternal-fetal interface. Thus, both cell types simultaneously attract each other to promote decidual population.

**Trophoblast Invasion of the Endometrium.**

The extravillous trophoblast of the first-trimester placenta are highly invasive. They form columns of cells that extend from the endometrium to the inner third of the myometrium. Recall that hemochorial placentation requires invasion of endometrium and spiral arteries. The invasive ability of trophoblasts results from their ability to secrete numerous proteolytic enzymes capable of digesting the extracellular matrix as well as activating proteases already present in the endometrium. 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 matrix metalloproteinases (MMPs), which are a family of structurally similar enzymes. One member of the family, matrix metalloproteinase-9 (MMP-9), appears to be critical for human trophoblast invasion. MMP-9 production is increased by trophoblast factors such as IL-1 and hCG as well as paracrine uterine factors such as leukemia inhibiting factor and colony-stimulating factor-1 (Bischof, 2002; Fitzgerald, 2008; Librach, 1991, and all their colleagues).

The relative ability to invade maternal tissue in early pregnancy compared with limited invasiveness in late pregnancy is controlled by autocrine and paracrine trophoblastic and endometrial factors. Trophoblasts secrete insulin-like growth factor II, which acts in an autocrine manner. It promotes invasion into the endometrium, whereas decidual cells secrete insulin-like growth factor binding protein type 4, which blocks this autocrine loop. Thus, the degree of trophoblast invasion is controlled by regulation of matrix degradation as well as by factors that cause trophoblast migration.

Integrin subunits expression also appears important to control trophoblast invasion and adhesive interactions between trophoblast cells during column formation. Recall that the decidual cell becomes completely encased by a pericellular extracellular matrix membrane. This “wall” around the decidual cell provides a scaffolding for attachment of the cytotrophoblasts of the anchoring villi. The cytotrophoblast first elaborate selected proteases that degrade decidual extracellular matrix. Thereafter, expression of a specific group of integrins enables the docking of these cells. There are also integrin-mediated adhesive interactions of trophoblast cells with each other. In particular, the interaction of L-selectin with its carbohydrate ligands in the cytotrophoblast is important in formation and maintenance of cell columns (Prakobphol and colleagues, 2006). Trophoblasts are further secured by fetal fibronectin (Feinberg and colleagues, 1991). Fetal-specific fibronectin (fFN) is a unique glycopeptide of the
Invasion of Spiral Arteries

One of the most remarkable features of human placental development is the extensive modification of maternal vasculature by trophoblasts, which are by definition of fetal origin. These events occur in the first half of pregnancy and are considered in detail because of their importance to uteroplacental blood flow. They are also integral to some pathological conditions such as preeclampsia and fetal-growth restriction (see Chap. 34, p. 710). Modifications of spiral arteries are carried out by two populations of extravillous trophoblast—interstitial trophoblast, which surrounds the arteries, and endovascular trophoblast, which penetrates the spiral artery lumen (see Fig. 3-12). Although earlier work has focused on the role of the endovascular trophoblast, function of the interstitial trophoblast has more recently been investigated (Benirschke and Kaufmann, 2000; Pijnenborg and colleagues, 1983). These interstitial cells are now recognized to constitute a major portion of the placental bed, penetrating the decidua and adjacent myometrium. They aggregate around spiral arteries, and their functions may include vessel preparation for endovascular trophoblast invasion.

Endovascular trophoblast enters the lumen of the spiral arteries and initially forms cellular plugs. It then destroys vascular endothelium via an apoptosis mechanism and invades and modifies vascular media. Thus, fibrinoid material replaces smooth muscle and connective tissue of the vessel media. Spiral arteries later regenerate endothelium. Hamilton and Boyd (1966) report that Friedlander in 1870 first described structural changes in spiral arteries. Invading endovascular trophoblast can extend several centimeters along the vessel lumen, and they must migrate against arterial flow. These vascular changes are not observed in the decidua parietalis, that is, in decidual sites removed from the chorionic plate. The invading cytotrophoblasts of note, invasion by trophoblasts involves only the decidual spiral arteries and not decidual veins.

In their summary of anatomical studies of the uteroplacental vasculature, Ramsey and Donner (1980) described that development of these uteroplacental vessels proceeds in two waves or stages. The first wave occurs before 12 weeks postfertilization and consists of invasion and modification of spiral arteries up to the border between deciduas and myometrium. The second wave is between 12 and 16 weeks and involves some invasion of the intramyometrial segments of spiral arteries. The remodeling by this two-phase invasion converts narrow-lumen, muscular spiral arteries into dilated, low-resistance uteroplacental vessels. Molecular mechanisms of these crucial events, and their significance in the pathogenesis of preeclampsia and fetal-growth restriction, have been reviewed by Kaufmann (2003) and Red-Horse (2006) and their associates.

Establishment of Maternal Blood Flow

About 1 month after conception, maternal blood enters the intervillus space in fountain-like bursts from the spiral arteries. Blood is propelled outside of the maternal vessels and sweeps over and directly bathes the syncytiotrophoblast. The apical surface of the syncytiotrophoblast consists of a complex microvillous structure that undergoes continual shedding and reformation during pregnancy.

Villus Branching

Although certain villi of the chorion frondosum extend from the chorionic plate to the decidua to serve as anchoring villi, most arborize and end freely in the intervillus space. As gestation proceeds, the short, thick, early stem villi branch to form progressively finer subdivisions and greater numbers of increasingly smaller villi (Fig. 3-19). Each of the truncal or main stem villi and their ramifications (rami) constitute a placental lobule, or cotyledon. Each lobule is supplied with a single truncal branch of the chorionic artery. And each lobule has a single vein so that lobules constitute functional units of placental architecture.

Placental Growth and Maturation

Placental Growth

In the first trimester, placental growth is more rapid than that of the fetus. But by approximately 17 postmenstrual weeks, placental and fetal weights are approximately equal. By term, placental weight is approximately one sixth of fetal weight. According to Boyd and Hamilton (1970), the average placenta at term is 185 mm in diameter and 23 mm in thickness, with a volume of 497 mL and a weight of 508 g. These measurements vary widely, and there are multiple variant placental forms and several types of umbilical cord insertions. These are discussed in detail in Chapter 27 (p. 577).

Viewed from the maternal surface, the number of slightly elevated convex areas, called lobes, varies from 10 to 38. Lobes are incompletely separated by grooves of variable depth that overlie placental septa, which arise from folding of the basal plate. Although grossly visible lobes are commonly referred to as cotyledons, this is not accurate. Correctly used, lobules or cotyledons are the functional units supplied by each primary villus.

The total number of placental lobes remains the same throughout gestation, and individual lobes continue to grow—although less actively in the final weeks (Crawford, 1959).

Placental Maturation

As villi continue to branch and the terminal ramifications become more numerous and smaller, the volume and prominence of cytotrophoblasts decrease. As the syncytiotrophoblast thins, the fetal vessels become more prominent and lie closer to the surface. The villous stroma also exhibits changes as gestation progresses. In early pregnancy, the branching connective-tissue cells are separated by an abundant loose intercellular matrix. Later, the stroma becomes denser and the cells more spindly and more closely packed.

Another change in the stroma involves the infiltration of Hofbauer cells, which are fetal macrophages. These are nearly round with vesicular, often eccentric nuclei and very granular or vacuolated cytoplasm. Hofbauer cells are characterized histochemically by intracytoplasmic lipid and by phenotypic markers specific for macrophages. They increase in numbers and...
maturation state throughout pregnancy. These macrophages are phagocytic, have an immunosuppressive phenotype, can produce a variety of cytokines, and are capable of paracrine regulation of trophoblast functions (Cervar and colleagues, 1999; Vince and Johnson, 1996).

Some of the histological changes that accompany placental growth and maturation provide an increased efficiency of transport and exchange to meet increasing fetal metabolic requirements. Among these changes are decreased syncytiotrophoblastic thickness, significant cytotrophoblast reduction, decreased stroma, and increased number of capillaries with their approximation to the syncytial surface. By 16 weeks the apparent continuity of the cytotrophoblasts is lost. At term, the covering of the villi may be focally reduced to a thin layer of syncytium with minimal connective tissue in which thin-walled fetal capillaries abut the trophoblast and dominate the villi.

There are some changes in placental architecture that can cause decreased efficiency of placental exchange if they are substantive. These include thickening of basal lamina of trophoblast or capillaries, obliteration of certain fetal vessels, and fibrin deposition on the villi surface.

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**Fetal and Maternal Blood Circulation in the Mature Placenta**

Because the placenta is functionally an intimate approximation of the fetal capillary bed to maternal blood, its gross anatomy primarily concerns vascular relations. 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. 3-20, 3-21, 3-22). The maternal surface is divided into irregular lobes by furrows produced by septa, which consist of fibrous tissue with sparse vessels. The broad-based septa ordinarily do not reach the chorionic plate, thus providing only incomplete partitions (Fig. 3-23).
Maternal and Fetal Anatomy and Physiology

SECTION 2

Before 10 weeks, there is no end-diastolic flow pattern within the umbilical artery at the end of the fetal cardiac cycle (Cole, 1991; Fisk, 1988; Loquet, 1988, and all their colleagues). After 10 weeks, end-diastolic flow appears and is maintained throughout normal pregnancy (Maulik, 1997). Clinically, these are studied with Doppler sonography to assess fetal well-being (see Chap. 16, p. 363).

Maternal Circulation

Because an efficient maternal–placental circulation is requisite, many investigators have sought to define factors that regulate blood flow into and from the intervillous space. An adequate mechanism must explain how blood can: (1) leave maternal circulation; (2) flow into an amorphous space lined by syncytiotrophoblast, rather than capillary endothelium; and (3) return through maternal veins without producing arteriovenous-like shunts that would prevent maternal blood from remaining in contact with villi long enough for adequate exchange. Early studies of Ramsey and Davis (1963) and Ramsey and Harris (1966) help to provide a physiological explanation of placental circulation. These investigators demonstrated, by careful, low-pressure injections of radiocontrast material, that arterial entrances as well as venous exits are scattered randomly over the entire base of the placenta.

The physiology of maternal-placental circulation is depicted in Figure 3-24. Maternal blood enters through the basal plate and is driven high up toward the chorionic plate by arterial

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 and again within the dividing villi, finally forming capillary networks in the terminal divisions. 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 fetal surface of the placenta in the chorionic plate are referred to as the placental surface or chorionic vessels. These vessels are responsive 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 interesting relationship, but they are difficult to distinguish by histological criteria. In 65 percent of placentas, chorionic arteries form a fine network supplying the cotyledons—a pattern of disperse-type branching. The remaining 35 percent radiate to the edge of the placenta without narrowing. Both types are end arteries that supply one cotyledon as each branch turns downward to pierce the chorionic plate.

Truncal arteries are perforating branches of the surface arteries that pass through the chorionic plate. Each truncal artery supplies one cotyledon. There is a decrease in smooth muscle of the vessel wall and an increase in the caliber of the vessel as it penetrates through the chorionic plate. The loss in muscle continues as the truncal arteries and veins branch into their rami.

Before 10 weeks, there is no end-diastolic flow pattern within the umbilical artery at the end of the fetal cardiac cycle (Cole, 1991; Fisk, 1988; Loquet, 1988, and all their colleagues). After 10 weeks, end-diastolic flow appears and is maintained throughout normal pregnancy (Maulik, 1997). Clinically, these are studied with Doppler sonography to assess fetal well-being (see Chap. 16, p. 363).

Maternal Circulation

Because an efficient maternal–placental circulation is requisite, many investigators have sought to define factors that regulate blood flow into and from the intervillous space. An adequate mechanism must explain how blood can: (1) leave maternal circulation; (2) flow into an amorphous space lined by syncytiotrophoblast, rather than capillary endothelium; and (3) return through maternal veins without producing arteriovenous-like shunts that would prevent maternal blood from remaining in contact with villi long enough for adequate exchange. Early studies of Ramsey and Davis (1963) and Ramsey and Harris (1966) help to provide a physiological explanation of placental circulation. These investigators demonstrated, by careful, low-pressure injections of radiocontrast material, that arterial entrances as well as venous exits are scattered randomly over the entire base of the placenta.

The physiology of maternal-placental circulation is depicted in Figure 3-24. Maternal blood enters through the basal plate and is driven high up toward the chorionic plate by arterial
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Arrangement aids closure of veins during a uterine contraction and prevents entry of maternal blood from the intervillous space. The number of arterial openings into the intervillous space becomes gradually reduced by cytotrophoblast invasion. According to Brosens and Dixon (1963), there are about 120 spiral arterial entries into the intervillous space at term. These discharge blood in spurts that bathes the adjacent villi (Borell and co-workers, 1958). After the 30th week, a prominent venous plexus separates the decidua basalis from the myometrium, thus participating in providing a plane of cleavage for placental separation.

Pressure before laterally dispersing. After bathing the external microvillous surface of chorionic villi, 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. The previously described trophoblast invasion of the spiral arteries creates low-resistance vessels that can accommodate massive increase in uterine perfusion over 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 entry of maternal blood from the intervillous space. The number of arterial openings into the intervillous space becomes gradually reduced by cytotrophoblast invasion. According to Brosens and Dixon (1963), there are about 120 spiral arterial entries into the intervillous space at term. These discharge blood in spurts that bathes the adjacent villi (Borell and co-workers, 1958). After the 30th week, a prominent venous plexus separates the decidua basalis from the myometrium, thus participating in providing a plane of cleavage for placental separation.

FIGURE 3-21 Photomicrograph of a histological section through amnion, chorion, and decidua basalis depicted in Figure 3-20A. $C =$ chorionic plate with fetal blood vessels; $P =$ placental villi; $D =$ decidua basalis; $M =$ myometrium.

FIGURE 3-22 Photomicrograph of early implanted blastocyst. Trophoblasts are seen invading the decidua basalis. (Used with permission from Dr. Kurt Benirschke.)

FIGURE 3-23 Photograph of the maternal surface of the placenta. Placenta lobes are formed by clefts on the surface that originate from placental septa. (Used with permission from Dr. Judith J. Head.)
Maternal and Fetal Anatomy and Physiology

As discussed, 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 increased during contractions. They attributed this to distension of the intervillous space as the consequence of relatively greater 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. Subsequently, by use of Doppler velocimetry, it was shown that diastolic flow velocity in spiral arteries is diminished during uterine contractions.

From these observations, it can be seen that principal factors regulating blood flow in the intervillous space are arterial blood pressure, intrauterine pressure, the pattern of uterine contractions, 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. There are numerous examples of trafficking cells between mother and fetus in both directions. This situation is best exemplified clinically by erythrocyte D-antigen isoinmunization and erythroblastosis fetalis (see Chap. 29, p. 618). Desai and Cregger (1963) found that, even under normal conditions, labeled maternal leukocytes and platelets crossed the placenta from mother to fetus. Although this likely is a small amount in most cases, occasionally the fetus exsanguinates into the maternal circulation. Indeed, in their recent review, Silver and colleagues (2007) found that fetomaternal hemorrhage accounted for 3 to 14 percent of stillbirths.

It is indisputable that fetal cells can become engrafted in the mother during pregnancy and can be identified decades later. Fetal lymphocytes and CD34+ mesenchymal stem cells reside in maternal blood or bone marrow (Nguyen and co-workers, 2006; Piper and colleagues, 2007). Termed microchimerism, such residual stem cells may participate in maternal tissue regeneration and have been implicated to explain the disparate female:male ratio of autoimmune disorders (Gleicher and Barad, 2007; Stevens, 2006). As discussed in Chapter 53 (p. 1127), they are associated with lymphocytic thyroiditis, scleroderma, and systemic lupus erythematosus.

Immunological Considerations of the Fetal-Maternal Interface

For more than 50 years, there have been many attempts to explain survival of the semiallogenic fetal graft. One of the earliest explanations was based on the theory of antigenic immaturity of the embryo-fetus. This was disproved by Billingham (1964), who showed that transplantation (HLA) antigens are demonstrable very early in embryonic life. Another theory posited diminished immunological responsiveness of the pregnant woman, but there is little evidence for this to be other than ancillary. In another explanation, the uterus (decidua) is proposed to be an immunologically privileged tissue site. However, this theory is challenged by cases of advanced ectopic pregnancies (see Chap. 10, p. 240). Thus, the enigma continues.

Clearly, there is no doubt that the lack of uterine transplantation immunity is unique compared with that of other tissues. Survival of the conceptus in the uterus can be attributed to an immunological peculiarity of cells involved in implantation and fetal-placental development. These include decidual natural killer cells with their inefficient cytotoxic abilities, decidual stromal cells, and invasive trophoblasts that populate the decidua (Hanna, 2006; Santoni, 2007; Staun-Ram, 2005, and all their co-workers). The trophoblasts are the only fetal-derived cells in direct contact with maternal tissues. Previous studies have suggested that maternal natural killer cells act to control the invasion of trophoblast cells, which have adapted to survive in an immunologically hostile environment (Thellin and associates, 2000). More recently Hanna and colleagues (2006) have reported a “peaceful” model of trophoblast invasion and maternal vascular remodeling. In this scheme, decidual natural killer cells work in concert with stromal cells. They mediate angiogenesis through production of proangiogenic factors such as VEGF and control trophoblast chemoattraction toward spiral arteries by production of interleukin-8 and interferon inducible protein-10.
Immunogenicity of the Trophoblasts

More than 50 years ago, Sir Peter Medawar (1953) suggested that survival of the fetal semiallograft might be explained by immunological neutrality. The placenta was considered immunologically inert and therefore unable to create a maternal immune response. Subsequently, research was focused on defining expression of the major histocompatibility complex (MHC) antigens on trophoblasts. Human leukocyte antigens (HLA) are the human analogue of the MHC. And indeed, MHC class I and II antigens are absent from villous trophoblasts, which appear to be immunologically inert at all stages of gestation (Weetman, 1999). But invasive extravillous trophoblasts do express MHC class I molecules, which have been the focus of considerable study.

Trophoblast HLA (MHC) Class I Expression

The HLA genes are the products of multiple genetic loci of the MHC located within the short arm of chromosome 6 (Hunt and Orr, 1992). There are 17 HLA class I genes, including 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. The remaining DNA sequences appear to be pseudogenes or partial gene fragments.

Moffett-King (2002) reasoned that normal implantation depends on controlled trophoblastic invasion of maternal endometrium–decidua and spiral arteries. Such invasion must proceed far enough to provide for normal fetal growth and development, but there must be a mechanism for regulating its depth. She suggested that uterine decidual natural killer cells (uNK cells) combined with unique expression of three specific HLA class I genes in extravillous cytotrophoblasts act in concert to permit and subsequently limit trophoblast invasion.

Class I antigens in extravillous cytotrophoblasts are accounted for by the expression of classic HLA-C and nonclassical class Ib molecules of HLA-E and HLA-G. To elucidate the importance of HLA-C, HLA-E, and HLA-G expression, it is important to understand the unusual lymphocyte population of the decidua.

Uterine Natural Killer Cells (uNK)

These distinctive lymphocytes are believed to originate in bone marrow and belong to the natural killer cell lineage. They are by far the predominant population of leukocytes present in mid-luteal phase endometrium at the expected time of implantation (Johnson and colleagues, 1999). These uNKs have a distinct phenotype characterized by a high surface density of CD56 or neural cell adhesion molecule (Loke and King, 1995; Manaster and associates, 2008; Moffett-King, 2002). Their infiltration is increased by progesterone and by stromal cell production of IL-15 and decidual prolactin (Dunn and co-workers, 2002; Gubbay and colleagues, 2002).

Near the end of the luteal phase of nonfertile ovulatory cycles, the nuclei of the uterine NK cell begin to disintegrate. But if implantation proceeds, they persist in large numbers in the decidua during early pregnancy. By term, however, there are relatively few uNK cells in the decidua. In first-trimester decidua, there are many uNK cells in close proximity to extravillous trophoblast where it is speculated that they serve to regulate trophoblast invasion. These uNK cells secrete large amounts of granulocyte-macrophage–colony-stimulating factor (GM-CSF), which suggests that they are in an activated state. Jokhi and co-workers (1999) speculate that GM-CSF may function primarily to fore-stall trophoblast apoptosis and not to promote trophoblast replication. Expression of angiogenic factors by uNK cells also suggests a role in decidual vascular remodeling (Li and colleagues, 2001). In this case, it is uNKs, rather than the T lymphocytes, that are primarily responsible for decidual immunosurveillance.

HLA-G Expression in Trophoblasts

This antigen is expressed only in humans, and it has a highly restricted tissue distribution. It is expressed in cytotrophoblasts contiguous with maternal tissues, that is, decidual and uNK cells. Indeed, HLA-G antigen expression is identified only in extravillous cytotrophoblasts in the decidua basalis and in the chorion laeve (McMaster and colleagues, 1995). During pregnancy, a soluble major isoform—HLA-G2—is increased (Hunt and colleagues, 2000a, b). Embryos used for in vitro fertilization do not implant if they do not express this soluble HLA-G isoform (Fuzzi and colleagues, 2002). Thus, HLA-G may be immunologically permissive of the maternal-fetal antigen mismatch (LeBouteiller and colleagues, 1999). Finally, Goldman-Wohl and associates (2000) have provided evidence for abnormal HLA-G expression in extravillous trophoblasts from women with preeclampsia.

The Amnion

At term, the amnion is a tough and tenacious but pliable membrane. This innermost avascular fetal membrane is contiguous with amnionic fluid and occupies a role of incredible importance in human pregnancy. The amnion provides almost all tensile strength of the fetal membranes. Thus, development of its components that protect against its rupture or tearing is vitally important to successful pregnancy outcome. Indeed, preterm rupture of fetal membranes is a major cause of preterm delivery (see Chap. 36, p. 817).

Structure

Bourne (1962) described five separate layers of amnion. The inner surface, which is bathed by amnionic fluid, is an uninterrupted, single layer of cuboidal epithelium believed to be derived from embryonic ectoderm (Fig. 3-25). This epithelium is attached firmly to a distinct basement membrane that is connected to the acellular compact layer, which is composed primarily of interstitial collagens. On the outer side of the compact layer, there is a row of fibroblast-like mesenchymal cells, which are widely dispersed at term. These are probably derived from embryonic disc mesoderm. There also are a few fetal macrophages in the amnion. The outermost layer of amnion is the relatively acellular zona spongiosa, which is contiguous with the second fetal membrane, the chorion laeve. The human amnion lacks smooth muscle cells, nerves, lymphatics, and importantly, blood vessels.

Development

Early during implantation, a space develops between the embryonic cell mass and adjacent trophoblasts (see Fig. 3-11). Small cells that line this inner surface of trophoblasts have been called
Early in pregnancy, amnionic epithelium replicates at a rate appreciably faster than mesenchymal cells. At term, these cells form a continuous uninterrupted epithelium on the fetal amnionic surface. Conversely, mesenchymal cells are widely dispersed, being connected by a fine lattice network of extracellular matrix with the appearance of long slender fibrils.

**Amnion Epithelial Cells.** The apical surface of amnionic epithelium is replete with highly developed microvilli that are consistent with a major site of transfer between amnionic fluid and amnion. This epithelium is active metabolically, and these cells synthesize tissue inhibitor of metalloproteinase-1, PGE₂ and fetal fibronectin (Rowe and colleagues, 1997). In term pregnancies, amnionic expression of prostaglandin endoperoxide H synthase correlates with elevated fetal fibronectin (Mijovic and co-workers, 2000). By prostaglandin production, amnionic epithelium participates in the “final common pathway” of labor initiation. Epithelial cells may respond to signals derived from the fetus or the mother, and they are responsive to a variety of endocrine or paracrine modulators. Examples include oxytocin and vasopressin, both of which increase PGE₂ production in vitro (Moore and associates, 1988). They may also produce cytokines such as IL-8 during initiation of labor (Elliott and colleagues, 2001).

Amnionic epithelium also synthesizes vasoactive peptides, including endothelin and parathyroid hormone-related protein (Economos and associates, 1992; Germain and colleagues, 1992). The tissue produces brain natriuretic peptide and corticotropin-releasing hormone (CRH), which are peptides that smooth muscle relaxants (Riley and colleagues, 1991; Warren and Silverman, 1995). It seems reasonable that vasoactive peptides produced in amnion gain access to adventitial surface of chorionic vessels. Thus, amnion may be involved in modulating chorionic vessel tone and blood flow. Amnion-derived vasoactive peptides function in other tissues in diverse physiological processes. After their secretion, these bioactive agents enter amnionic fluid and thereby are available to the fetus by swallowing and inhalation.

**Amnion Mesenchymal Cells.** Mesenchymal cells of the amnionic fibroblast layer are responsible for other major functions. Synthesis of interstitial collagens that comprise the compact layer of the amnion—the major source of its tensile strength—takes place in mesenchymal cells (Casey and MacDonald, 1996). These cells also synthesize cytokines that include IL-6, IL-8, and monocyte chemoattractant protein-1 (MCP-1). Cytokine synthesis increases in response to bacterial toxins and IL-1. This functional capacity of amnion mesenchymal cells is an important consideration in the study of amnionic fluid for evidence of labor-associated accumulation of inflammatory mediators (Garcia-Velasco and Atrici, 1999). Finally, mesenchymal cells may be a greater source of PGE₂ than epithelial cells (Whittle and colleagues, 2000).

**Anatomy of the Amnion**

Reflected amnion is fused to the chorion laeve. Placental amnion covers the placenta surface and thereby is in contact with the adventitial surface of chorionic vessels. Umbilical amnion covers the umbilical cord. In the conjoined portion of membranes of diamnionic-dichorionic twin placentas, fused amnions are separated by fused chorion laeve. Thus, aside from the small area of
the membranes immediately over the cervical os, this is the only site at which the reflected chorion laeve is not contiguous with decidua. With diamnionic-monochorionic placentas, there is no intervening tissue between the fused amnions.

**Amnion Tensile Strength**

More than 135 years ago, Matthew Duncan examined the forces involved in fetal membrane rupture. During tests of tensile strength—resistance to tearing and rupture—he found that the decidua and then the chorion laeve gave way long before the amnion ruptured. Indeed, the membranes are quite elastic and can expand to twice normal size during pregnancy (Benirschke and Kaufmann, 2000). The amnion provides the major strength of the membranes. Its 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.

**Interstitial Collagens.** Collagens are the major macromolecules of most connective tissues and the most abundant proteins in the body. Collagen I is the major interstitial collagen in tissues characterized by great tensile strength, such as bone and tendon. In other tissues, collagen III is believed to make a unique contribution to tissue integrity, serving to increase tissue extensibility and tensile strength. For example, the ratio of collagen III to collagen I in the walls of a number of highly extensible tissues—amnionic sac, blood vessels, urinary bladder, bile ducts, intestine, and gravid uterus—is greater than that in nonelastic tissues (Jeffrey, 1991). Although collagen III provides some of the extensibility of this membrane, elastin microfibrils have also been identified (Bryant-Greenwood, 1998).

The tensile strength of amnion is regulated in part by interaction of fibrillar collagen with proteoglycans such as decorin, which promote tissue strength. Compositional changes at the time of labor include a decline in decorin and increase in hyaluronan resulting in loss of tensile strength (Chap. 6, p. 140)(Meinert and associates, 2007). Fetal membranes overlying the cervix have a reported regional decline in expression of matrix proteins such as fibulins. This change is suggested to contribute to tissue remodeling and loss of tensile strength (Moore and co-workers, 2009).

**Metabolic Functions**

From the foregoing, it is apparent that the amnion is clearly more than a simple avascular membrane that contains amnionic fluid. It is metabolically active, 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 (Nemeth and colleagues, 2000). This in turn may trigger both autocrine and paracrine responses to include production of matrix metalloproteinases, IL-8, and collagenase (Bryant-Greenwood, 1998; Maradny and colleagues, 1996). Such factors may modulate changes in membrane properties during labor.

**Amnionic Fluid**

The normally clear fluid that collects within the amnionic cavity increases as pregnancy progresses until about 34 weeks, when there is a decrease in volume. At term, the average volume is about 1000 mL, although this may vary widely in abnormal conditions. The origin, composition, circulation, and function of amnionic fluid are discussed further in Chapter 21 (p. 490).

### Umbilical Cord and Related Structures

#### Cord Development

The yolk sac and the umbilical vesicle into which it develops are prominent early in pregnancy. At first, the embryo is a flattened disc interposed between amnion and yolk sac (see Fig. 3-15). Because its dorsal surface grows faster than the ventral surface, in association with the elongation of the neural tube, the embryo bulges into the amnionic sac and the dorsal part of the yolk sac is incorporated into the body of the embryo to form the gut. The allantois projects into the base of the body stalk from the caudal wall of the yolk sac and later, from the anterior wall of the hindgut.

As pregnancy advances, the yolk sac becomes smaller and its pedicle relatively longer. By about the middle of the third month, the expanding amnion obliterates the exocoelom, fuses with the chorion laeve, and covers the bulging placental disc and the lateral surface of the body stalk. The latter is then called the *umbilical cord*—or *funis*. Remnants of the exocoelom in the anterior portion of the cord may contain loops of intestine, which continue to develop outside the embryo. Although the loops are later withdrawn into the peritoneal cavity, the apex of the midgut loop retains its connection with the attenuated vitelline duct.

The cord at term normally has two arteries and one vein (Fig. 3-26). The right umbilical vein usually disappears early during fetal development, leaving only the original left vein. In sections of any portion of the cord near the center, the small
duct of the umbilical vesicle can usually be seen. The vesicle is lined by a single layer of flattened or cuboidal epithelium. In sections just beyond the umbilicus, another duct representing the allantoic remnant is occasionally found. The intra-abdominal portion of the duct of the umbilical vesicle, which extends from umbilicus to intestine, usually atrophies and disappears, but occasionally it remains patent, forming the Meckel diverticulum. The most common vascular anomaly is the absence of one umbilical artery which may be associated with fetal anomalies (see Chap. 27, p. 582).

Cord Structure and Function
The umbilical cord, or funis, extends from the fetal umbilicus to the fetal surface of the placenta or chorionic plate. Its exterior is dull white, moist, and covered by amnion, through which three umbilical vessels may be seen. Its diameter is 0.8 to 2.0 cm, with an average length of 55 cm and a range of 30 to 100 cm. Generally, cord length less than 30 cm is considered abnormally short (Benirschke and Kaufmann, 2000). Folding and tortuosity of the vessels, which are longer than the cord itself, frequently create nodulations on the surface, or false knots, which are essentially varices. The extracellular matrix is a specialized connective tissue referred to as Wharton jelly. After fixation, the umbilical vessels appear empty, but normally the vessels are not emptied of blood. The two arteries are smaller in diameter than the vein. The mesoderm of the cord, which is of allantoic origin, fuses with that of the amnion.

Blood flows from the umbilical vein and 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 (see Fig. 4-12, p. 90). The other route consists of numerous smaller openings into the hepatic circulation. Blood from the liver flows into the inferior vena cava via the hepatic vein. Resistance in the ductus venosus is controlled by a sphincter situated at the origin of the ductus at the umbilical recess and innervated by a branch of the vagus nerve.

Blood exits the fetus via the two umbilical arteries. These are anterior branches of the internal iliac artery and become obliterated after birth. Remnants can be seen as the medial umbilical ligaments.

Anatomically, the umbilical cord can be regarded as a component of the fetal membranes. Vessels contained in the cord spiral or twist. Spiraling may occur in a clockwise (dextral) or anticlockwise (sinistral) direction. Anticlockwise spiral is present in 50 to 90 percent of fetuses. It is believed that the spiraling serves to prevent crimping, which occurs in all hollow cylinders subjected to torsion. Boyd and Hamilton (1970) note that these twists are not true spirals, but rather they are cylindrical helices in which a constant curvature is maintained equidistant from the central axis. Benirschke and Kaufmann (2000) reported that there is an average of 11 helices in a cord.

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. A compendium of average production rates for various steroid hormones in nonpregnant and in near-term pregnant women is given in Table 3-1. It is apparent that alterations in steroid hormone production that accompany normal human pregnancy are incredible. The human placenta also synthesizes an enormous amount of protein and peptide hormones. This includes nearly 1 gram of placental lactogen (hPL) every 24 hours, massive quantities of chorionic gonadotropin (hCG), adrenocorticotropin (ACTH), growth hormone variant (hGH-V), parathyroid hormone–related protein (PTH-rP), calcitonin, relaxin, inhibins, activins, and atrial natriuretic peptide. In addition, there are various hypothalamic-like releasing and inhibiting hormones such as thyrotropin-releasing hormone (TRH), gonadotropin-releasing hormone (GnRH), corticotropin-releasing hormone (CRH), somatostatin, and growth hormone–releasing hormone (GHRH).

<table>
<thead>
<tr>
<th>Steroida</th>
<th>Nonpregnant</th>
<th>Pregnant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estradiol-17β</td>
<td>0.1–0.6</td>
<td>15–20</td>
</tr>
<tr>
<td>Estriol</td>
<td>0.02–0.1</td>
<td>50–150</td>
</tr>
<tr>
<td>Progesterone</td>
<td>0.1–40</td>
<td>250–600</td>
</tr>
<tr>
<td>Aldosterone</td>
<td>0.05–0.1</td>
<td>0.250–0.600</td>
</tr>
<tr>
<td>Deoxycorticosterone</td>
<td>0.05–0.5</td>
<td>1–12</td>
</tr>
<tr>
<td>Cortisol</td>
<td>10–30</td>
<td>10–20</td>
</tr>
</tbody>
</table>

aEstrogens 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.
It is understandable, therefore, that yet another remarkable feature of human pregnancy is the successful physiological adaptations of pregnant women to the unique endocrine milieu as discussed throughout Chapter 6.

**Human Chorionic Gonadotropin (hCG)**

This so-called pregnancy hormone is a glycoprotein with biological activity similar to luteinizing hormone (LH). Both act via the plasma membrane LH-hCG receptor. Although hCG is produced almost exclusively in the placenta, it also is synthesized in fetal kidney. Other fetal tissues produce either the β-subunit or intact hCG molecule (McGregor and associates, 1981, 1983).

Various malignant tumors also produce hCG, sometimes in large amounts—especially trophoblastic neoplasms (Chap. 11, p. 257). Chorionic gonadotropin is produced in very small amounts in tissues of men and nonpregnant women, perhaps primarily in the anterior pituitary gland. Nonetheless, the detection of hCG in blood or urine is almost always indicative of pregnancy (see Chap. 8, p. 192).

**Chemical Characteristics**

Chorionic gonadotropin is a glycoprotein with a molecular weight of 36,000 to 40,000 Da. It has the highest carbohydrate content of any human hormone—30 percent. The carbohydrate component, and especially the terminal sialic acid, protects the molecule from catabolism. The 36-hour plasma half-life of intact hCG is much longer than the 2 hours for LH. The hCG molecule is composed of two dissimilar subunits. One is designated α and is composed of 92 amino acids, whereas the β subunit contains 145 amino acids. These are noncovalently linked and are held together by electrostatic and hydrophobic forces. Isolated subunits are unable to bind the LH receptor and thus lack biological activity.

This hormone is structurally related to three other glycoprotein hormones—LH, FSH, and TSH. The amino-acid sequence of the α-subunits of all four glycoproteins is identical. The β-subunits, although sharing certain similarities, are characterized by distinctly different amino-acid sequences. Recombination of an α- and a β-subunit of the four glycoprotein hormones gives a molecule with biological activity characteristic of the hormone from which the β-subunit was derived.

**Biosynthesis**

Both α- and β-chain synthesis of hCG are regulated separately. A single gene located on chromosome 6 encodes the α-subunit for hCG, LH, FSH, and TSH. There are seven separate genes on chromosome 19 for the β-hCG–β-LH family. Six genes code for β-hCG and one for β-LH (Miller-Lindholm and colleagues, 1997). Both subunits are synthesized as larger precursors, which are then cleaved by endopeptidases. Intact hCG is then assembled and rapidly released by exocytosis of secretory granules (Morrish and colleagues, 1987).

**Site of hCG Synthesis**

Before 5 weeks, hCG is expressed in both syncytiotrophoblast and cytotrophoblast (Maruo and colleagues, 1992). Later, when maternal serum levels peak, hCG is produced almost solely in syncytiotrophoblasts (Beck and associates, 1986; Kurman and colleagues, 1984). At this time, hCG mRNAs for both α- and β-subunits in syncytiotrophoblast are greater than at term (Hoshina and co-workers, 1982). This may be an important consideration when hCG is used as a screening procedure to identify abnormal fetuses.

**Molecular Forms of hCG in Plasma and Urine**

There are multiple forms of hCG in maternal plasma and urine. Some result from enzymatic degradation, and others by modifications during molecular synthesis and processing. These multiple forms of hormone vary enormously in bioactivity and immunoreactivity.

**Free Subunits.** Circulating free β-subunit levels are low to undetectable throughout pregnancy. In part, this is the result of its rate-limiting synthesis. Free α-subunits that do not combine with the β-subunit are found in placental tissue and maternal plasma. These levels increase gradually and steadily until they plateau at about 36 weeks. At this time, they account for 30 to 50 percent of hormone (Cole, 1997). Thus, α-hCG secretion roughly corresponds to placental mass, whereas secretion of complete hCG molecules is maximal at 8 to 10 weeks.

**Concentrations of hCG in Serum and Urine**

The intact hCG molecule is detectable in plasma of pregnant women 7 to 9 days after the midcycle surge of LH that precedes ovulation. Thus, it is likely that hCG enters maternal blood at the time of blastocyst implantation. Plasma levels increase rapidly, doubling every 2 days, with maximal levels being attained at 8 to 10 weeks (Fig. 3-27). Appreciable fluctuations in levels for a given patient are observed on the same day—evidence that trophoblast secretion

![FIGURE 3-27 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.](image-url)

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of protein hormones is episodic (Barnea and Kaplan, 1989; Diaz-Cueto and colleagues, 1994).

Because hCG circulates as multiple highly related isoforms with variable cross-reactivity between commercial assays, there is considerable variation in calculated serum hCG levels among the more than 100 assays. Peak maternal plasma levels reach about 100,000 mIU/mL between the 60th and 80th days after menses (see Fig. 3-27). At 10 to 12 weeks, plasma levels begin to decline, and a nadir is reached by about 16 weeks. Plasma levels are maintained at this lower level for the remainder of pregnancy.

The pattern of hCG appearance in fetal blood is similar to that in the mother. Fetal plasma levels, however, are only about 3 percent of those in maternal plasma. Amniotic fluid hCG concentration early in pregnancy is similar to that in maternal plasma. As pregnancy progresses, hCG concentration in amniotic fluid declines, and near term the levels are about 20 percent of those in maternal plasma.

Maternal urine contains the same variety of hCG degradation products as maternal plasma. The principal urinary form is the terminal degradation hCG product—the β-core fragment. Its concentrations follow the same general pattern as that in maternal plasma, peaking at about 10 weeks. It is important to recognize that the so-called 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 forms found in urine.

**Significance of Abnormally High or Low hCG Levels.**

There are a number of clinical circumstances in which substantively higher maternal plasma hCG levels are found. Some examples are multifetal pregnancy, erythroblastosis fetalis associated with fetal hemolytic anemia, and gestational trophoblastic disease. Relatively higher hCG levels may be found at midtrimester in women carrying a fetus with Down syndrome—an observation used in biochemical screening tests (see Chap. 13, p. 293). The reason for this is not clear, but it has been speculated that it is due to reduced placental maturity. Relatively lower hCG plasma levels are found in women with early pregnancy wastage, including ectopic pregnancy (see Chap. 10, p. 245).

**Regulation of hCG Synthesis.**

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

**Metabolic Clearance of hCG.**

Renal clearance of hCG accounts for 30 percent of its metabolic clearance. The remainder is likely cleared by metabolism in the liver (Wehmann and Nisula, 1980). Clearances of β- and α-subunit are about 10-fold and 30-fold, respectively, greater than that of intact hCG. By contrast, renal clearance of these subunits is considerably lower than that of dimeric hCG.

**Biological Functions of hCG.**

Both hCG subunits are required for binding to the LH-hCG receptor in the corpus luteum and the fetal testis. LH-hCG receptors are present in a variety of tissues, but their role there is less defined. The best-known biological function of hCG is the so-called rescue and maintenance of function of the corpus luteum—that is, continued progesterone production. Bradbury and colleagues (1950) found that the progesterone-producing life span of a corpus luteum of menstruation could be prolonged perhaps for 2 weeks by hCG administration. This is only an incomplete explanation for the physiological role of hCG in pregnancy. For example, maximum plasma hCG concentrations are attained well after hCG-stimulated corpus luteum secretion of progesterone has ceased. Specifically, progesterone luteal synthesis begins to decline at about 6 weeks despite continued and increasing hCG production.

It is also known that hCG stimulates fetal testicular testosterone secretion, which is maximum approximately when peak levels of hCG are attained. Thus, at a critical time in sexual differentiation of the male fetus, hCG enters fetal plasma from the syncytiotrophoblast. In the fetus, it acts as an LH surrogate to stimulate replication of Leydig cells and testosterone synthesis to promote male sexual differentiation (see Chap. 4, p. 101). Before about 110 days, there is no vascularization of the fetal anterior pituitary from the hypophyseal system. Thus, there is little pituitary LH secretion and hCG acts as LH before this time. Thereafter, as hCG levels fall, pituitary LH maintains a modest level of testicular stimulation.

The maternal thyroid gland is also stimulated by large quantities of hCG. In some women with gestational trophoblastic disease, biochemical and clinical evidence of hyperthyroidism sometimes develops (see Chap. 11, p. 260). This once was attributed to formation of chorionic thyrotropins by neoplastic trophoblasts. It was subsequently, however, shown that some forms of hCG bind to TSH receptors on thyrocytes (Hershman, 1999). And treatment of men with exogenous hCG increases thyroid activity. 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. For example, acidic isoforms stimulate thyroid activity, and some more basic isoforms stimulate iodine uptake (Kraiem, 1994; Tsuruta, 1995; Yoshimura, 1994, and all their colleagues). Finally, the LH-hCG receptor is expressed by thyrocytes, which suggests that hCG stimulates thyroid activity via the LH-hCG receptor and by the TSH receptor (Tomer and colleagues, 1992).

Other hCG functions include promotion of relaxin secretion by the corpus luteum (Duffy and co-workers, 1996). LH-hCG receptors are found in myometrium and in uterine vascular tissue. It has been hypothesized that hCG may act to promote uterine vascular vasodilatation and myometrial smooth muscle relaxation (Kurtzman and colleagues, 2001).

**Human Placental Lactogen (hPL)**

Prolactin-like activity in the human placenta was first described by Ehrhardt (1936). The responsible protein was
isolated from placental extracts and retroplacental blood (Ito and Higashi, 1961; Josimovich and MacLaren, 1962). Because of its potent lactogenic and growth hormone-like bioactivity, as well as an immunochemical resemblance to human growth hormone (hGH), it was called human placental lactogen or chorionic growth hormone. It also has been referred to as chorionic somatomammotropin. Currently, human placental lactogen (hPL) is used by most. Grumbach and Kaplan (1964) showed that this hormone, like hCG, was concentrated in syncytiotrophoblast. It is detected as early as the second or third week after fertilization. Also similar to hCG, hPL is demonstrated in cytotrophoblasts before 6 weeks (Maruo and associates, 1992).

**Chemical Characteristics**

Human placental lactogen is a single nonglycosylated polypeptide chain with a molecular weight of 22,279 Da. It is derived from a 25,000-Da precursor. There are 191 amino-acid residues in hPL compared with 188 in hCG. The sequence of each hormone is strikingly similar, with 96-percent homology. HPL also is structurally similar to human prolactin (hPRL), with a 67-percent amino-acid sequence similarity. For these reasons, it has been suggested that the genes for hPL, hPRL, and hGH evolved from a common ancestral gene—probably that for prolactin—by duplication (Ogren and Talamantes, 1994).

**Gene Structure and Expression**

There are five genes in the growth hormone–placental lactogen gene cluster that are linked and located on chromosome 17. Two of these—hPL2 and hPL3—both encode hPL, and the amount of mRNA in the term placenta is similar for each. In contrast, the prolactin gene is located on chromosome 6 (Owerbach and colleagues, 1980, 1981). The production rate of hPL near term—approximately 1 g/day—is by far the greatest of any known hormone in humans.

**Serum Concentration**

HPL is demonstrable in the placenta within 5 to 10 days after conception and can be detected in maternal serum as early as 3 weeks. Maternal plasma concentrations are linked to placental mass, and they rise steadily until 34 to 36 weeks. Serum concentrations reach levels in late pregnancy of 5 to 15 μg/mL—higher than those of any other protein hormone (see Fig. 3-27). The half-life of hPL in maternal plasma is between 10 and 30 minutes (Walker and co-workers, 1991).

Very little hPL is detected in fetal blood or in the urine of the mother or newborn. Amniotic fluid levels are somewhat lower than in maternal plasma. Because hPL is secreted primarily into the maternal circulation, with only very small amounts in cord blood, it appears that its role in pregnancy, if any, is mediated through actions in maternal rather than in fetal tissues. Nonetheless, there is continuing interest in the possibility that hPL serves select functions in fetal growth.

**Regulation of hPL Biosynthesis**

Levels of mRNA for hPL in syncytiotrophoblast remain relatively constant throughout pregnancy. This finding is supportive of the idea that the rate of hPL secretion is proportional to placental mass. There are very high plasma levels of hCG in women with trophoblastic neoplasms, but only low levels of hPL in these same women.

Prolonged maternal starvation in the first half of pregnancy leads to an increase in the plasma concentration of hPL. 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 PGE2 and PGF2α (Bhaumick and associates, 1987; Genbacev and colleagues, 1977).

**Metabolic Actions**

HPL has putative actions in a number of important metabolic processes. These include:

1. Maternal lipolysis with increased levels of circulating free fatty acids. This provides a source of energy for maternal metabolism and fetal nutrition. In vitro studies suggest that hPL inhibits leptin secretion by term trophoblast (Coya and associates, 2005).

2. An anti-insulin or “diabetogenic” action that leads to increased maternal insulin levels. This favors protein synthesis and provides a readily available source of amino acids to the fetus.

3. A potent angiogenic hormone that may play an important role in the formation of fetal vasculature (Corbacho and co-workers, 2002).

### Other Placental Protein Hormones

**Chorionic Adrenocorticotropicin**

ACTH, lipotropin, and β-endorphin—all proteolytic products of proopiomelanocortin—are recovered from placental extracts (Genazzani and associates, 1975; Odagiri and colleagues, 1979). The physiological role of placental ACTH is unclear. Although maternal plasma levels of ACTH increase during pregnancy, they remain lower than those in men and nonpregnant women, except during labor (Carr and colleagues, 1981a). Placental ACTH is secreted into both maternal and fetal circulations, however, maternal ACTH is not transported to the fetus. Importantly, placental ACTH is not under feedback regulation by glucocorticoids, which may explain maternal partial resistance to dexamethasone suppression (Nolten and Rueckert, 1981). Placental corticotropin-releasing hormone (CRH) stimulates synthesis and release of chorionic ACTH. Placental CRH production is positively regulated by cortisol, producing a novel positive feedback loop. As discussed later, this system may be important for controlling fetal lung maturation and timing of parturition.

**Relaxin**

Relaxin expression has been demonstrated in human corpus luteum, decidua, and placenta (Bogic and colleagues, 1995). This peptide 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. Two of the three relaxin genes—H2 and H3—are transcribed in the corpus luteum (Bathgate and associates, 2002; Hudson and colleagues, 1983, 1984). Other tissues, including decidua, placenta, and membranes, express H1 and H2 (Hansell and colleagues, 1991).
The rise in maternal circulating relaxin levels seen in early pregnancy is attributed to secretion by the corpus luteum, and levels parallel those seen for hCG. The uterine relaxin receptor was cloned by Hsu and colleagues (2002). It has been proposed that relaxin, along with rising progesterone levels, acts on myometrium to promote relaxation and the quiescence observed in early pregnancy (see Chap. 6, p. 153). In addition, the production of relaxin and relaxin-like factors within the placenta and fetal membranes is believed to play an autocrine-paracrine role in postpartum regulation of extracellular matrix degradation (Qin and colleagues, 1997a, b).

**Parathyroid Hormone-Related Protein (PTH-rP)**

Circulating levels of PTH-rP are significantly elevated in pregnancy within maternal but not fetal circulation (Bertelloni and colleagues, 1994; Saxe and associates, 1997). Although not clear, many potential functions of this hormone have been proposed. 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. Placental-derived PTH-rP may have an important autocrine-paracrine role within the fetal–maternal unit as well as on the adjacent myometrium. It may activate trophoblast receptors to promote calcium transport for fetal bone growth and ossification.

**Growth Hormone Variant (hGH-V)**

The placenta expresses a growth hormone variant that is not expressed in the pituitary. 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. Placental hGH-V presumably is synthesized in the syncytiotrophoblast, but its pattern of synthesis and secretion during gestation is not precisely known because antibodies against hGH-V cross-react with hGH. It is believed that hGH-V is present in maternal plasma by 21 to 26 weeks, increases in concentration until approximately 36 weeks, and remains relatively constant thereafter. There is a correlation between the levels of hGH-V in maternal plasma and those of insulin-like growth factor-1. Also, the secretion of hGH-V by trophoblasts in vitro is inhibited by glucose in a dose-dependent manner (Patel and colleagues, 1995). Overexpression of hGH-V in mice causes severe insulin resistance, and thus it is a likely candidate to mediate insulin resistance of pregnancy (Barbour and associates, 2002).

**Hypothalamic-Like Releasing Hormones**

For each of the known hypothalamic-releasing or -inhibiting hormones described—GnRH, TRH, CRH, GHRH, and somatostatin—there is an analogous hormone produced in human placenta (Petraglia and colleagues, 1992; Siler-Khodr, 1988). Many investigators have proposed that this is indicative of a hierarchy of control in the synthesis of chorionic trophic agents.

**Gonadotropin-Releasing Hormone (GnRH).** There is a reasonably large amount of immunoreactive GnRH in the placenta (Siler-Khodr, 1988; Siler-Khodr and Khodr, 1978). Interestingly, it is found in cytotrophoblasts, but not syncytiotrophoblast. Gibbons and co-workers (1975) and Khodr and Siler-Khodr (1980) demonstrated that the human placenta could synthesize both GnRH and TRH in vitro. Placental-derived GnRH functions to regulate trophoblast hCG production, hence the observation that GnRH levels are higher early in pregnancy. Placental-derived GnRH is also the likely cause of elevated maternal GnRH levels in pregnancy (Siler-Khodr and colleagues, 1984).

**Corticotropin-Releasing Hormone (CRH).** This hormone is a member of a larger family of CRH-related peptides that includes CRH, urocortin, urocortin II, and urocortin III (Dautzenberg and Hauger, 2002). CRH produced in nonpregnant women has relatively low serum levels of 5 to 10 pmol/L. During pregnancy, these increase to about 100 pmol/L in the early third trimester and to almost 500 pmol/L abruptly during the last 5 to 6 weeks (see Fig. 3-27). Urocortin also is produced by the placenta and secreted into the maternal circulation, but at much lower levels than seen for CRH (Florio and co-workers, 2002). After labor begins, maternal plasma CRH levels increase further by two- to threefold (Petraglia and colleagues, 1989, 1990).

The biological function of CRH synthesized in the placenta, membranes, and decidua has been somewhat defined. CRH receptors are present in many tissues: placenta, adrenal gland, sympathetic ganglia, lymphocytes, gastrointestinal tract, pancreas, gonads, and myometrium. Some findings suggest that CRH can act through two major families—the type 1 and type 2 CRH receptors (CRH-R1 and CRH-R2). Trophoblast, amnion, chorion, and decidua express both CRH-R1 and CRH-R2 receptors, as well as several variant receptors (Florio and colleagues, 2000). Both CRH and urocortin increase trophoblast ACTH secretion, supporting an autocrine-paracrine role (Petraglia and co-workers, 1999). Large amounts of CRH from trophoblast enter maternal blood, but there also is a large concentration of a specific CRH-binding protein in maternal plasma, and the bound CRH seems to be biologically inactive.

Other 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 levels of CRH seen near the end of gestation. One hypothesis suggests that CRH may be involved with parturition initiation (Wadhwa and colleagues, 1998). Prostaglandin formation in the placenta, amnion, chorion laeve, and decidua is increased with CRH treatment (Jones and Challis, 1989b). This latter observation further supports a potential role in the timing of parturition.

Glucocorticoids act in the hypothalamus to inhibit CRH release, but in the trophoblast, glucocorticoids stimulate CRH gene expression (Jones and colleagues, 1989a; Robinson and co-workers, 1988). Thus, there may be a novel positive feedback loop in the placenta by which placental CRH stimulates placental ACTH to stimulate fetal and maternal adrenal glucocorticoid production with subsequent stimulation of placental CRH expression (Nicholson and King, 2001; Riley and colleagues, 1991).

**Growth Hormone-Releasing Hormone (GHRH).** The role of placental GHRH is not known (Berry and associates, 1992). Ghrelin is another regulator of hGH secretion that is produced by...
placental tissue (Horvath and colleagues, 2001). Trophoblast ghrelin expression peaks at midpregnancy and is a potential regulator of hGh-V production or a paracrine regulator of differentiation (Fuglsang and associates, 2005; Gualillo and co-workers, 2001).

Other Placental Peptide Hormones

Leptin
This hormone is normally secreted by adipocytes. It functions as an anti-obesity hormone that decreases food intake through its hypothalamic receptor. It also regulates bone growth and immune function (Cock and Auwerx, 2003; La Cava and colleagues, 2004). Leptin also is synthesized by both cytotoxic and syncytial trophoblasts (Henson and Castracane, 2002). Relative contributions of leptin from maternal adipose tissue versus placenta are currently not well defined. Maternal serum levels are significantly higher than those in nonpregnant women. Fetal leptin levels are correlated positively with birthweight and likely play an important role in fetal development and growth. Recent studies suggest that leptin inhibits apoptosis and promotes trophoblast proliferation (Magarinos and associates, 2007).

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 and colleagues, 1989). There are receptors for neuropeptide Y on trophoblast, and treatment of placental cells with neuropeptide Y causes CRH release (Robidoux and colleagues, 2000).

Inhibin and Activin
Inhibin is a glycoprotein hormone that acts preferentially to inhibit pituitary FSH release. It is produced by human testis and by ovarian granulosa cells, including the corpus luteum. Inhibin is a heterodimer made up of an α-subunit and one of two distinct β-subunits, βA or βB. All three are produced by trophoblast, and maternal serum levels peak at term (Petraglia and co-workers, 1991). One function may be to act in concert with the large amounts of sex steroid hormones to inhibit FSH secretion and thereby inhibit ovulation during pregnancy. Inhibin may act via GnRH to regulate placental hCG synthesis (Petraglia and colleagues, 1987).

Activin is closely related to inhibin and is formed by the combination of the two β-subunits. Its receptor is expressed in the placenta and amnion. Activin A is not detectable in fetal blood before labor but is present in umbilical cord blood after labor begins. Petraglia and colleagues (1994) found that serum activin A levels decline rapidly after delivery. It is not clear if chorionic activin and inhibin are involved in placental metabolic processes other than GnRH synthesis.

Placental Progesterone Production
After 6 to 7 weeks’ gestation, little progesterone is produced in the ovary (Diczfalusy and Troen, 1961). Surgical removal of the corpus luteum or even bilateral oophorectomy during the 7th to 10th week does not cause a decrease in excretion of urinary pregnanediol, the principal urinary metabolite of progesterone. Before this time, however, removal of the corpus luteum will result in miscarriage unless an exogenous progesterin is given (see Chap. 40, p. 906). After approximately 8 weeks, the placenta assumes progesterone secretion, which continues to increase such that there is a gradual increase in maternal serum levels throughout pregnancy (Fig. 3-28). By the end of pregnancy, these levels are 10 to 5000 times those found in nonpregnant women, depending on the stage of the ovarian cycle.

Progesterone Production Rates
The daily production rate of progesterone in late, normal, singleton pregnancies is about 250 mg. In multifetal pregnancies, the daily production rate may exceed 600 mg/day. 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 through a process of diffusion.

Even though the placenta produces a prodigious amount of progesterone, there is limited capacity for trophoblast cholesterol biosynthesis. Radiolabeled acetate is incorporated into cholesterol by placental tissue at a slow rate. The rate-limiting enzyme in cholesterol biosynthesis is 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase. Because of this, the placenta must rely on exogenous cholesterol for progesterone formation. Bloch (1945) and Werbin and co-workers (1957) found that after intravenous administration of radiolabeled cholesterol to pregnant women, the amount of radioactivity of urinary pregnanediol was...
similar to that of plasma cholesterol. Hellig and associates (1970) also found that maternal plasma cholesterol was the principal precursor—as much as 90 percent—of progesterone biosynthesis. The trophoblast preferentially uses LDL cholesterol for progesterone biosynthesis (Simpson and Burkhart, 1980; Simpson and colleagues, 1979). In studies of pregnant baboons, when maternal serum LDL levels were reduced, there was a significant drop in placental progesterone production (Henson and associates, 1997). Thus, placental progesterone is formed through the uptake and use of a maternal circulating precursor. This mechanism is unlike the placental production of estrogens, which relies principally on fetal adrenal precursors.

**Progestosterone Synthesis and Fetal Relationships**

Although there is a relationship between fetal well-being and placental production of estrogen, this is not the case for placental progesterone. Fetal demise, ligature of the umbilical cord with the fetus and placenta remaining in situ, and anencephaly are all conditions associated with very low maternal plasma levels and low urinary excretion of estrogens. In these circumstances, there is not a concomitant decrease in progesterone levels until some indeterminate time after fetal death. Thus, placental endocrine function, including the formation of protein hormones such as hCG and progesterone biosynthesis, may persist for long periods (weeks) after fetal demise.

**Progestosterone Metabolism During Pregnancy**

The metabolic clearance rate of progesterone in pregnant women is similar to that found in men and nonpregnant women. This is an important consideration in evaluating the role of progesterone in initiation of parturition (see Chap. 6, p. 154). During pregnancy, there is a disproportionate increase in the plasma concentration of 5α-dihydroprogesterone as a result of synthesis in syncytiotrophoblast from both placenta-produced progesterone and fetal-derived precursor (Dombroski and co-workers, 1997). Thus, the concentration ratio of this progesterone metabolite to progesterone is increased in pregnancy. The mechanisms for this are not defined completely but may be relevant to the resistance to pressor agents that normally develops in pregnant women (see Chap. 5, p. 120). Progesterone also is converted to the potent mineralocorticoid deoxycorticosterone in pregnant women and in the fetus. The concentration of deoxycorticosterone is increased strikingly in both maternal and fetal compartments (see Table 3-1). The extra-adrenal formation of deoxycorticosterone from circulating progesterone accounts for most of its production in pregnancy (Casey and MacDonald, 1982a, 1982b).

**Placental Estrogen Production**

The placenta produces huge amounts of estrogens using blood-borne steroid precursors from the maternal and fetal adrenal glands. Near-term, normal human pregnancy is a hyperestrogenic state. The amount of estrogen produced each day by syncytiotrophoblast during the last few weeks of pregnancy is equivalent to that produced in 1 day by the ovaries of no fewer than 1000 ovulatory women. The hyperestrogenic state of human pregnancy is one of continually increasing magnitude as pregnancy progresses, terminating abruptly after delivery.

During the first 2 to 4 weeks of pregnancy, rising hCG levels maintain production of estradiol in the maternal corpus luteum. Production of both progesterone and estrogens in the maternal ovaries decreases significantly by the seventh week of pregnancy. At this time, there is a luteal-placental transition. By the seventh week, more than half of estrogen entering maternal circulation is produced in the placenta (MacDonald, 1965; Siiteri and MacDonald, 1963, 1966). These studies support the transition of a steroid milieu dependent on the maternal corpus luteum to one dependent on the developing placenta.

**Placental Estrogen Biosynthesis**

The pathways of estrogen synthesis in the placenta differ from those in the ovary of nonpregnant women. Estrogen production in the ovary takes place during the follicular and luteal phase through the interaction of theca and granulosa cells. Specifically, androstenedione is synthesized in ovarian theca and then transferred to adjacent granulosa cells for estradiol synthesis. Estradiol production within the corpus luteum of nonpregnant women as well as in early pregnancy continues to require interaction between the luteinized theca and granulosa cells. In human trophoblast, neither cholesterol nor progesterone can serve as precursor for estrogen biosynthesis. A crucial enzyme necessary for sex steroid synthesis—steroid 17α-hydroxylase/17,20-lyase (CYP17)—is not expressed in the human placenta. Consequently, the conversion of C21-steroids to C19-steroids—the latter being the immediate and obligatory precursors of estrogens—is not possible.

Although C19-steroids—dehydroepiandrosterone (DHEA) and its sulfate (DHEA-S)—often are called adrenal androgens, these steroids can also serve as estrogen precursors (Fig. 3-29). Ryan (1959a) found that there was an exceptionally high capacity of placenta to convert appropriate C19-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 and colleagues, 2000; Salido and co-workers, 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 (3BHSD) to produce androstenedione. Cytochrome P450 aromatase (CYP19) then converts androstenedione to estrone, which is then converted to estradiol by 17β-hydroxysteroid dehydrogenase type 1 (17BHSD1).

**Plasma C19-Steroids as Estrogen Precursors**

Frandsen and Stakemann (1961) found that levels of urinary estrogens in women pregnant with an anencephalic fetus were only about 10 percent found in normal pregnancy. The adrenal glands of anencephalic fetuses are atrophic because of absent hypothalamic-pituitary function, which precludes ACTH stimulation. Thus, it seemed reasonable that fetal adrenal glands might provide substance(s) used for placental estrogen formation.

In subsequent studies, DHEA-S was found to be a major precursor of estrogens in pregnancy (Baulieu and Dray, 1963; Siiteri and MacDonald, 1963). The large amounts of DHEA-S in plasma and its much longer half-life uniquely qualify it as
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the principal precursor for placental estradiol synthesis. There is a 10- to 20-fold increase in the metabolic clearance rate of plasma DHEA-S in women at term compared with that in men and nonpregnant women (Gant and co-workers, 1971). This rapid use results in a progressive decrease in plasma DHEA-S concentration as pregnancy progresses (Milewich and co-workers, 1978). 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. A schematic representation of the pathways of estrogen formation in the placenta is presented in Figure 3-29. As shown, the estrogen products released from the placenta are dependent on the substrate available. Thus, estrogen production during pregnancy reflects the unique interactions between fetal adrenal glands, fetal liver, placenta, and maternal adrenal glands.

Directional Secretion of Steroids from Syncytiotrophoblast

More than 90 percent of estradiol and estriol formed in syncytiotrophoblast enters maternal plasma (Gurpide and co-workers, 1966) (see Table 3-1). And 85 percent or more of placental progesterone enters maternal plasma, with little maternal progesterone crossing the placenta to the fetus (Gurpide and co-workers, 1972).

The major reason for directional movement of newly formed steroid into the maternal circulation is the nature of hemochorial placentation. In this system, steroids secreted from syncytiotrophoblast can enter maternal blood directly. Steroids that leave the syncytiotium do not enter fetal blood directly. They must first traverse the cytotrophoblasts and then enter connective tissue of the villous core and then fetal capillaries. From either of these spaces, steroids can reenter the syncytiotium. The net result of this hemochorial arrangement is that there is substantially greater entry of steroids into the maternal circulation compared with the amount that enters fetal blood.

FETAL ADRENAL GLAND HORMONES

Morphologically, functionally, and physiologically, the fetal adrenal glands are remarkable organs. At term, the fetal adrenal glands weigh the same as those of the adult. More than 85 percent of the fetal gland is composed of a unique fetal zone, which has a great capacity for steroid biosynthesis. Daily steroid production of fetal adrenal glands near term is 100 to 200 mg/day. This compares with resting adult steroid secretion of 30 to 40 mg/day. Thus, the fetal adrenal gland is a truly prodigious steroidogenic tissue.

The fetal zone is lost in the first year of life and is not present in the adult. In addition to ACTH, fetal adrenal gland growth is influenced by factors secreted by the placenta. This is exemplified by the continued growth of the fetal glands throughout gestation, but rapid involution immediately after birth when placenta-derived factors dissipate.
Placental Estriol Synthesis
The estrogen products released from the placenta are dependent on the substrate available. Estriadiol is the primary placental estrogen secretory product at term. In addition, significant levels of estradiol and estetrol are found in the maternal circulation, and they increase, particularly late in gestation (see Fig. 3-28). These hydroxylated forms of estrogen are produced in the placenta using substrates formed by the combined efforts of the fetal adrenal gland and liver.

There are important fetal-maternal interactions through the fetal liver (see Fig. 3-29). High levels of fetal hepatic 16α-hydroxylase act on adrenal derived steroids. Ryan (1959b) and MacDonald and Siiteri (1965) found that 16α-hydroxylated C19-steroids, particularly 16α-hydroxydehydroepiandrosterone (16-OH DHEA), were converted to estriol by placental tissue. Thus, the disproportionate increase in estriol formation during pregnancy is accounted for by placental synthesis of estriol principally from plasma-borne 16-OH DHEA-S. Near term, the fetus is the source of 90 percent of placental estriol and estetrol precursor in normal human pregnancy.

Thus, the placenta secretes several estrogens, including estradiol, estrone, estriol, and estetrol. Because of its hemochorial nature, most placental estrogens are released into the maternal circulation. Maternal estriol and estetrol are produced almost solely by fetal steroid precursors. Thus,levels of these steroids were used in the past as an indicator of fetal well-being. However, low sensitivity and specificity of such tests have caused them to be discarded.

Enzymatic Considerations
There is a severe deficiency in the expression of the microsomal enzyme 3α-hydroxysteroid dehydrogenase, Δ5-4-isomerase (3BHSD) in adrenal fetal zone cells (Doody and co-workers, 1990; Rainey and colleagues, 2001). This limits the conversion of pregnenolone to progesterone and of 17α-hydroxyprogrenenolone to 17α-hydroxyprogesterone, an obligatory step in cortisol biosynthesis. There is, however, very active steroid sulfotransferase activity in the fetal adrenal glands. As a consequence, the principal secretory products of the fetal adrenal glands are pregnenolone sulfate and DHEA-S. Comparatively, cortisol, which likely arises primarily in the neocortex and transitional zone of the fetal adrenal glands and not in the fetal zone, is a minor secretory product until late in gestation.

Fetal Adrenal Steroid Precursor
The precursor for fetal adrenal steroidogenesis is cholesterol. The rate of steroid biosynthesis in the fetal gland 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. All enzymes involved in cholesterol biosynthesis are elevated compared with that of the adult adrenal gland (Rainey and colleagues, 2001). Thus, the rate of de novo cholesterol synthesis by fetal adrenal tissue is extremely high. Even so, it is insufficient to account for the steroids produced by these glands. Therefore, cholesterol must be assimilated from the fetal circulation. Plasma cholesterol and its esters are present in the form of very-low-density lipoprotein (VLDL), low-density lipoprotein (LDL), and high-density lipoprotein (HDL).

Simpson and colleagues (1979) found that fetal glands take up lipoproteins as a source of cholesterol for steroidogenesis. LDL was most effective, HDL was much less, and VLDL was devoid of stimulatory activity. They also evaluated relative contributions of cholesterol synthesized de novo and that of cholesterol derived from LDL uptake. These authors confirmed that fetal adrenal glands are highly dependent on circulating LDL as a source of cholesterol for optimum steroidogenesis (Carr and colleagues, 1980, 1982; Carr and Simpson, 1981).

Most fetal plasma cholesterol arises by de novo synthesis in the fetal liver (Carr and Simpson, 1984). The low level of LDL cholesterol in fetal plasma is not the consequence of impaired fetal LDL synthesis, but instead, it results from the rapid use of LDL by the fetal adrenal glands for steroidogenesis (Parker and colleagues, 1980, 1983). As expected, in the anencephalic newborn with atrophic adrenal glands, the LDL cholesterol levels in umbilical cord plasma are high.

Fetal Conditions That Affect Estrogen Production
Several fetal disorders alter the availability of substrate for placental steroid synthesis. A schematic representation of the pathways of placental estrogen formation is presented in Figure 3-29.

Fetal Demise
It has been known for many decades that fetal death is followed by a striking reduction in levels of urinary estrogens. It was also known that there was an abrupt and striking decrease in the production of placental estrogens after ligation of the umbilical cord with the fetus and placenta left in situ (Cassmer, 1959). These findings led to at least two interpretations. The first was that maintenance of the fetal placental circulation is essential to the functional integrity of the placenta. This was unlikely to be correct because placental production of progesterone was maintained after occlusion of the umbilical cord. A second explanation was that after umbilical cord ligation, an important source of precursors of placental estrogen—but not progesterone—biosynthesis was eliminated upon fetal death.

Fetal Anencephaly
In the absence of the fetal zone of the adrenal cortex, as in anencephaly, the formation rate of placental estrogens—especially estriol—is severely limited because of diminished availability of C19-steroid precursors. Therefore, almost all estrogens produced in women pregnant with an anencephalic fetus arise by placental use of maternal plasma DHEA-S. Furthermore, in such pregnancies, the production of estrogens can be increased by the maternal administration of ACTH, which stimulates the rate of DHEA-S secretion by the maternal adrenal gland. Because ACTH does not cross the placenta, there is no fetal adrenal stimulation. Finally, placental estrogen production is decreased in women pregnant with an anencephalic fetus when a potent glucocorticoid is given to the mother. This suppresses ACTH secretion and thus decreases the rate of DHEA-S secretion from the maternal adrenal cortex (MacDonald and Siiteri, 1965).
Fetal Adrenal Hypoplasia

Congenital adrenal cortical hypoplasia occurs in perhaps 1 in 12,500 births (McCabe, 2001). There appear to be two primary forms. In the *miniature adult form*, which results from anencephaly or abnormal pituitary function, there is a very small adrenal cortical zone. The *cytomegalic form* is so called because of nodular formation of eosinophilic cells in the fetal zone. Estrogen production in pregnancies with either form is limited and suggests the absence of C19-precursors. The cytomegalic form results from disruptive mutations in the gene known as the dosage-sensitive sex reversal–adrenal hypoplasia congenita critical region on the X chromosome, gene 1(DAX1) (McCabe, 2001).

Fetal-Placental Sulfatase Deficiency

Placental estrogen formation is generally regulated by the availability of C19-steroid prohormones in fetal and maternal plasma. Specifically, there is no rate-limiting enzymatic reaction in the placental pathway from C19-steroids to estrogen biosynthesis. An exception to this generalization is placental sulfatase deficiency, which is associated with very low estrogen levels in otherwise normal pregnancies (France and Liggins, 1969). Sulfatase deficiency precludes the hydrolysis of C19-steroid sulfates, the first enzymatic step in the placental use of these circulating prohormones for estrogen biosynthesis. This deficiency is an X-linked disorder, and all affected fetuses are male. Its estimated frequency is 1 in 2000 to 5000 births and is associated with delayed onset of labor. It also is associated with the development of ichthyosis in affected males later in life (Bradshaw and Carr, 1986).

Fetal-Placental Aromatase Deficiency

There are a few well-documented examples of aromatase deficiency (Simpson, 2000). Fetal adrenal DHEA-S, which is produced in large quantities, 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, causing virilization of the mother and the female fetus (Harada and colleagues, 1992; Shozu and associates, 1991). Although pregnancies with aromatase deficiency and a male fetus may be uneventful, these estrogen-deficient males have delayed epiphyseal closure during puberty. As a consequence, affected men continue to grow during adulthood, becoming very tall and displaying deficient bone mineralization (Morishima and colleagues, 1995).

Trisomy 21—Down Syndrome

Second-trimester maternal serum screening for abnormal levels of hCG, alpha-fetoprotein, and other analytes has become universal (see Chap. 13, p. 292). As a result, it was discovered that serum unconjugated estriol levels were low in women with Down syndrome fetuses (Benn, 2002). The likely reason for this is inadequate formation of C19-steroids in the adrenal glands of these trisomic fetuses. This supposition is supported by reduced DHEA-S levels in both amniotic fluid and maternal serum in Down syndrome pregnancies (Newby and colleagues, 2000).

Deficiency in Fetal LDL Cholesterol Biosynthesis

A successful pregnancy in a woman with β-lipoprotein deficiency has been described (Parker and co-workers, 1986). The absence of LDL in the maternal serum restricted progesterone formation in both the corpus luteum and placenta. In addition, levels of estriol were lower than normal. Presumably, the diminished estrogen production was the result of decreased fetal LDL formation, which limited fetal adrenal production of estrogen precursor.

Fetal Erythroblastosis

In some cases of severe fetal D-antigen isoimmunization, estrogen levels in maternal plasma are elevated above normal. This is likely due to an increased placental mass from hypertrophy. This is seen with other causes of hyperplacentosis with a fetal hemolytic anemia, which occurs in such pregnancies (see Chap. 29, p. 618).

Maternal Conditions That Affect Placental Estrogen Production

Glucocorticoid Treatment

The administration of glucocorticoids in moderate to high doses to pregnant women causes a striking reduction in placental estrogen formation. Glucocorticoids act to inhibit ACTH secretion by the maternal and fetal pituitary glands, resulting in decreased maternal and fetal adrenal secretion of the placental estrogen precursor, DHEA-S.

Maternal Adrenal Dysfunction

In pregnant women with Addison disease, maternal urinary estrogen levels are decreased (Baulieu and colleagues, 1956). The decrease principally affects estrone and estradiol, because the fetal adrenal contribution to the synthesis of estriol, particularly in the latter part of pregnancy, is quantitatively much more important.

Maternal Ovarian Androgen-Producing Tumors

The extraordinary efficiency of the placenta in the aromatization of C19-steroids may be exemplified by two considerations. First, Edman and associates (1981) found that virtually all of the androstenedione entering the intervillous space is taken up by syncytiotrophoblast and converted to estradiol, and none of this C19-steroid enters the fetus. Second, it is relatively rare that a female fetus is virilized when there is a maternal androgen-secreting ovarian tumor. This finding also indicates that the placenta efficiently converts aromatizable C19-steroids, including testosterone, to estrogens, thus precluding transplacental passage. Indeed, it may be that virilized female fetuses of women with an androgen-producing tumor are cases in which a nonaromatizable C19-steroid androgen is produced by the tumor—for example, 5α-dihydrotestosterone. Another explanation is that testosterone is produced very early in pregnancy in amounts that exceed the capacity of placental aromatase.

Gestational Trophoblastic Disease

In the case of complete hydatidiform mole or choriocarcinoma, there is no fetal adrenal source of C19-steroid precursor for implantation, embryogenesis, and placental development.
trophoblast estrogen biosynthesis. Consequently, placental estrogen formation is limited to the use of C_{17,20}-steroids in the maternal plasma, and therefore the estrogen produced is principally estradiol (MacDonald and Siiteri, 1964, 1966). Great variation is observed in the rates of both estradiol and progesterone formation in molar pregnancies.

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Contemporary obstetrical research focuses on the physiology and pathophysiology of the fetus, its development, and its environment. An important result is that the status of the fetus has been elevated to that of a patient who, in large measure, can be given the same meticulous care that obstetricians provide for pregnant women. In the course of these studies, it has become apparent that the conceptus is a dynamic force in the pregnancy unit. Normal fetal development is considered in this chapter. Anomalies, injuries, and diseases that affect the fetus and newborn are addressed in Chapter 29.

**DETERMINATION OF GESTATIONAL AGE**

Several terms are used to define the duration of pregnancy, and thus fetal age, but these are somewhat confusing. They are shown schematically in Figure 4-1. Gestational age or menstrual age is the time elapsed since the first day of the last menstrual period, a time that actually precedes conception. This starting time, which is usually about 2 weeks before ovulation and fertilization and nearly 3 weeks before implantation of the blastocyst, has traditionally been used because most women know their last period. Embryologists describe embryofetal development in ovulation age, or the time in days or weeks from ovulation. Another term is postconceptional age, nearly identical to ovulation age.

Clinicians customarily calculate gestational age as menstrual age. About 280 days, or 40 weeks, elapse on average between the first day of the last menstrual period and the birth of the fetus. This corresponds to 9 and 1/3 calendar months. A quick estimate of the due date of a pregnancy 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 July 5, the due date is 07-05 minus 3 (months) plus 7 (days) = 04-12, or April 12 of the following year. This calculation has been termed Naegele’s rule. Many women undergo first- or early second-trimester sonographic examination to confirm gestational age. In these cases, the sonographic estimate is usually a few days later than that determined by the last period. To rectify this inconsistency—and to reduce the number of pregnancies diagnosed as postterm—some have suggested assuming that the average pregnancy is actually 283 days long and that 10 days be added to the last menses instead of 7 (Olsen and Clausen, 1998).

The period of gestation can also be divided into three units of three calendar months (13 weeks) each. These three trimesters have become important obstetrical milestones.

**MORPHOLOGICAL GROWTH**

Ovum, Zygote, and Blastocyst

During the first 2 weeks after ovulation, development phases include: (1) fertilization, (2) blastocyst formation, and (3) blastocyst implantation. Primitive chorionic villi are formed soon after implantation. With the development of chorionic villi, it is conventional to refer to the products of conception as an embryo. The early stages of preplacental development and formation of the placenta are described in Chapter 3 (p. 47).
Embryonic Period

The embryonic period commences at the beginning of the third week after ovulation and fertilization, which coincides in time with the expected day that the next menstruation would have started. The embryonic period lasts 8 weeks and is when organogenesis takes place (see Fig. 4-1). The embryonic disc is well defined, and most pregnancy tests that measure human chorionic gonadotropin (hCG) become positive by this time (see Chap. 8, p. 192). As shown in Figure 4-2, the body stalk is now differentiated, and the chorionic sac is approximately 1 cm in diameter. There is a true intervillous space that contains maternal blood and villous cores in which angioblastic chorionic mesoderm can be distinguished.

The schematic timeline is shown in Figure 4-3. During the third week, fetal blood vessels in the chorionic villi appear (Fig. 4-4). In the fourth week a cardiovascular system has formed, and thereby, a true circulation is established both within the embryo and between the embryo and the chorionic villi. By the end of the fourth week, the chorionic sac is 2 to 3 cm in diameter, and the embryo is 4 to 5 mm in length (Figs. 4-5, 4-6, and 4-7). Partitioning of the primitive heart begins in the middle of the fourth week. Arm and leg buds are present, and the amnion is beginning to unsheathe the body stalk, which thereafter becomes the umbilical cord.

At the end of the sixth week, the embryo is 22 to 24 mm in length, and the head is large compared with the trunk. The heart is completely formed. 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.

Fetal Period

The end of the embryonic period and the beginning of the fetal period is arbitrarily designated by most embryologists to begin 8 weeks after fertilization—or 10 weeks after onset of last menses. At this time, the embryofetus is nearly 4 cm long (Fig. 4-8).

Referring back to Figure 4-3, development during the fetal period consists of growth and maturation of structures that were formed during the embryonic period. Because of the variability in the length of the legs and the difficulty of maintaining them in extension, crown-to-rump measurements, which correspond to the sitting height, are more accurate than those corresponding to the standing height (Table 4-1).

12 Gestational Weeks

The uterus usually is just palpable above the symphysis pubis, and the fetal crown-rump length is 6 to 7 cm. Centers of ossification have appeared in most of the fetal bones, and the fingers and toes have become differentiated. Skin and nails have developed 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

The fetal crown-rump length is 12 cm, and the weight is 110 g. Gender can be determined by experienced observers by inspection of the external genitalia by 14 weeks.
20 Gestational Weeks

This is the midpoint of pregnancy as estimated from the beginning of the last menses. The fetus now weighs somewhat more than 300 g, and weight begins to increase in a linear manner. From this point onward, the fetus moves about every minute and is active 10 to 30 percent of the time (DiPietro, 2005). The fetal skin has become less transparent, a downy lanugo covers its entire body, and some scalp hair has developed.

24 Gestational Weeks

The fetus now weighs about 630 g. The skin is characteristically wrinkled, and fat deposition begins. The head is still comparatively large, and eyebrows and eyelashes are usually recognizable. The canalicular period of lung development, during which the bronchi and bronchioles enlarge and alveolar ducts develop, is nearly completed. 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.

28 Gestational Weeks

The crown-rump length is approximately 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. The otherwise normal neonate born at this age has a 90-percent chance of survival without physical or neurological impairment.

32 Gestational Weeks

The fetus has attained a crown-rump length of about 28 cm and a weight of approximately 1700 g. The skin surface is still red and wrinkled.
36 Gestational Weeks
The average crown-rump length of the fetus is about 32 cm, and the weight is approximately 2500 g. Because of the deposition of subcutaneous fat, the body has become more rotund, and the previous wrinkled appearance of the face has been lost.

40 Gestational Weeks
This is considered term from the onset of the last menstrual period. The fetus is now fully developed. The average crown-rump length is about 36 cm, and the weight is approximately 3400 g.

Fetal Head
From an obstetrical viewpoint, the fetal head size is important because an essential feature of labor is the adaptation between the head and the maternal bony pelvis. Only a comparatively small part of the head at term is represented by the face. The rest of the head is composed of the firm skull, which is made up of two frontal, two parietal, and two temporal bones, along with the upper portion of the occipital bone and the wings of the sphenoid. These bones are separated by membranous spaces that are termed sutures (Fig. 4-9).

The most important sutures are the frontal, between the two frontal bones; the sagittal, between the two parietal bones; the two coronal, between the frontal and parietal bones; and the two lambdoid, between the posterior margins of the parietal bones and upper margin of the occipital bone. Where several sutures meet, an irregular space forms, which is enclosed by a membrane and designated as a fontanel (see Fig. 4-9). The greater, or anterior, fontanel is a lozenge-shaped space that is situated at the junction of the sagittal and the coronal sutures. The lesser, or posterior, fontanel is represented by a small triangular area at the intersection of the sagittal and lambdoid sutures. The localization of these fontanels gives important information concerning the presentation and position of the fetus during labor.

It is customary to measure certain critical diameters and circumferences of the newborn head (see Fig. 4-9). The diameters include:

1. The occipitofrontal (11.5 cm), which follows a line extending from a point just above the root of the nose to the most prominent portion of the occipital bone.
2. The biparietal (9.5 cm), the greatest transverse diameter of the head, which extends from one parietal boss to the other.
3. The bitemporal (8.0 cm), which is the greatest distance between the two temporal sutures.
4. The occipitomental (12.5 cm), which extends from the chin to the most prominent portion of the occiput.
5. The suboccipitobregmatic (9.5 cm), which follows a line drawn from the middle of the large fontanel to the undersurface of the occipital bone just where it joins the neck.

The greatest circumference of the head, which corresponds to the plane of the occipitofrontal diameter, averages 34.5 cm, a size too large to fit through the pelvis without flexion. The smallest circumference, corresponding to the plane of the suboccipitobregmatic diameter, is 32 cm. The bones of the cranium are normally connected only by a thin layer of fibrous tissue. This allows considerable shifting or sliding of each bone to accommodate the size and shape of the maternal pelvis. This process is termed molding. The head position and degree of skull ossification result in a spectrum of cranial plasticity from minimal to great. In some cases, this undoubtedly contributes to fetopelvic disproportion, a leading indication for cesarean delivery (see Chap. 20, p. 472).

### Fetal Brain

There is a steady gestational age-related change in the appearance of the fetal brain so that it is possible to identify fetal age from its external appearance (Dolman, 1977). Neuronal proliferation and migration proceed along with gyral growth and maturation (Fig. 4-10). Manganaro and colleagues (2007) have provided sequential maturation studies of the developing fetal brain imaged with magnetic resonance imaging. Myelination of the ventral roots of the cerebrospinal nerves and brainstem begins at
to chimerism from entrance of allogeneic fetal cells, including trophoblasts, into maternal blood. These are estimated to range from 1 to 6 cells/mL around midpregnancy, and some are “immortal” (Lissauer and colleagues, 2007). A clinical corollary is that some maternal autoimmune diseases may be provoked by such chimerism (see Chap. 54, p. 1146).

### The Intervillous Space

Maternal blood in the extravascular compartment, that is, the intervillous space, is the primary biologic unit of maternal–fetal transfer. Blood from the maternal spiral arteries directly bathes the trophoblasts. Substances transferred from mother to fetus first enter the intervillous space and are then transported to the syncytiotrophoblast. Substances transported from the fetus to the mother are transferred from the syncytium into the same space. Thus, the chorionic villi and the intervillous space function together as the fetal lung, gastrointestinal tract, and kidney.

Circulation within the intervillous space is described in Chapter 3 (p. 55). Intervillous and uteroplacental blood flow increases throughout the first trimester of normal pregnancies (Mercé and associates, 2009). At term, the residual volume of

### TABLE 4-1. Criteria for Estimating Age During the Fetal Period

<table>
<thead>
<tr>
<th>Age (weeks)</th>
<th>Menstrual Fertilization</th>
<th>Crown-Rump Length (mm)a</th>
<th>Foot Length (mm)a</th>
<th>Fetal Weight (g)b</th>
<th>Main External Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>11</td>
<td>9</td>
<td>50</td>
<td>7</td>
<td>8</td>
<td>Eyes closing or closed. Head more rounded. External genitalia still not distinguishable as male or female. Intestines are in the umbilical cord.</td>
</tr>
<tr>
<td>12</td>
<td>10</td>
<td>61</td>
<td>9</td>
<td>14</td>
<td>Intestines in abdomen. Early fingernail development.</td>
</tr>
<tr>
<td>14</td>
<td>12</td>
<td>87</td>
<td>14</td>
<td>45</td>
<td>Sex distinguishable externally. Well-defined neck.</td>
</tr>
<tr>
<td>16</td>
<td>14</td>
<td>120</td>
<td>20</td>
<td>110</td>
<td>Head erect. Lower limbs well developed.</td>
</tr>
<tr>
<td>18</td>
<td>16</td>
<td>140</td>
<td>27</td>
<td>200</td>
<td>Ears stand out from head.</td>
</tr>
<tr>
<td>20</td>
<td>18</td>
<td>160</td>
<td>33</td>
<td>320</td>
<td>Vernix caseosa present. Early toenail development.</td>
</tr>
<tr>
<td>22</td>
<td>20</td>
<td>190</td>
<td>39</td>
<td>460</td>
<td>Head and body (lanugo) hair visible.</td>
</tr>
<tr>
<td>24</td>
<td>22</td>
<td>210</td>
<td>45</td>
<td>630</td>
<td>Skin wrinkled and red.</td>
</tr>
<tr>
<td>26</td>
<td>24</td>
<td>230</td>
<td>50</td>
<td>820</td>
<td>Fingernails present. Lean body.</td>
</tr>
<tr>
<td>28</td>
<td>26</td>
<td>250</td>
<td>55</td>
<td>1000</td>
<td>Eyes partially open. Eyelashes present.</td>
</tr>
<tr>
<td>30</td>
<td>28</td>
<td>270</td>
<td>59</td>
<td>1300</td>
<td>Eyes open. Good head of hair. Skin slightly wrinkled.</td>
</tr>
<tr>
<td>34</td>
<td>32</td>
<td>300</td>
<td>68</td>
<td>2100</td>
<td>Fingernails reach fingertips. Skin pink and smooth.</td>
</tr>
<tr>
<td>40</td>
<td>38</td>
<td>360</td>
<td>83</td>
<td>3400</td>
<td>Prominent chest; breasts protrude. Testes in scrotum or palpable in inguinal canals. Fingernails extend beyond fingertips.</td>
</tr>
</tbody>
</table>

aThese measurements are average and so may not apply to specific cases; dimensional variations increase with age. 
bThese weights refer to fetuses that have been fixed for about 2 weeks in 10-percent formalin. Fresh specimens usually weigh approximately 5 percent less.

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approximately 6 months, but the major portion of myelination occurs after birth. The lack of myelin and the incomplete ossification of the fetal skull permit the structure of the brain to be seen with sonography throughout gestation.

### THE PLACENTA AND FETAL GROWTH

The placenta is the organ of transfer between mother and fetus. At the maternal-fetal interface, there is transfer of oxygen and nutrients from the mother to the fetus and carbon dioxide and metabolic wastes from fetus to mother. There are no direct communications between fetal blood, which is contained in the fetal capillaries of the chorionic villi, and maternal blood, which remains in the intervillous space. Bidirectional transfer depends on the processes that permit or aid the transport through the syncytiotrophoblast of the intact chorionic villi.

That said, there are occasional breaks in the chorionic villi, which permit escape of various numbers of fetal cells 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 (see Chap. 29, p. 618). It can also lead to chimerism from entrance of allogeneic fetal cells, including trophoblasts, into maternal blood. These are estimated to range from 1 to 6 cells/mL around midpregnancy, and some are “immortal” (Lissauer and colleagues, 2007). A clinical corollary is that some maternal autoimmune diseases may be provoked by such chimerism (see Chap. 54, p. 1146).

#### The Intervillous Space

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Circulation within the intervillous space is described in Chapter 3 (p. 55). Intervillous and uteroplacental blood flow increases throughout the first trimester of normal pregnancies (Mercé and associates, 2009). At term, the residual volume of
the intervillous space measures about 140 mL. Before delivery, however, the volume of this space may be twice this value (Aherne and Dunnill, 1966). Uteroplacental blood flow near term has been estimated to be 700 to 900 mL/min, with most of the blood apparently going to the intervillous space.

Active labor contractions reduce blood flow into the intervillous space, the degree of which depends on the intensity of the contraction. Blood pressure within the intervillous space is significantly less than uterine arterial pressure, but somewhat greater than venous pressure. The latter, in turn, varies depending on several factors, including maternal position. When supine, for example, pressure in the lower part of the inferior vena cava is elevated, and consequently, pressure in the uterine and ovarian veins, and in turn in the intervillous space, is increased.

### Placental Transfer

**Chorionic Villus**

Substances that pass from maternal blood to fetal blood must first traverse the syncytiotrophoblast, then stroma of the intervillous space, and finally the fetal capillary wall. Although this histological barrier separates the blood in the maternal and fetal
circulations, it does not function like a simple physical barrier. In fact, throughout pregnancy, syncytiotrophoblast actively or passively permits, facilitates, and adjusts the amount and rate of transfer of a wide range of substances to the fetus.

**Regulation of Placental Transfer**

The syncytiotrophoblast is the fetal tissue interface. Its maternal-facing surface is characterized by a complex microvillus structure. The fetal-facing basal cell membrane of the trophoblast is the site of transfer to the intravillous space through which the fetal capillaries traverse. These 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, at least 10 variables are important.

1. The concentration of the substance in maternal plasma, and the extent to which it is bound to another compound, such as a carrier protein.
2. The rate of maternal blood flow through the intervillous space.
3. The area available for exchange across the villous trophoblast epithelium.
4. If the substance is transferred by simple diffusion, the physical properties of the trophoblastic tissue.
5. For any substance actively transported, the capacity of the biochemical machinery of the placenta for effecting active transfer, for example, specific receptors on the plasma membrane of the trophoblast.
6. The amount of the substance metabolized by the placenta during transfer.
7. The area for exchange across the fetal intervillous capillaries.
8. The concentration of the substance in the fetal blood.
9. Specific binding or carrier proteins in the fetal or maternal circulation.
10. The rate of fetal blood flow through the villous capillaries.

**FIGURE 4-10** 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 listed. A. 20 weeks. B. 35 Weeks. C. 40 Weeks.
Mechanisms of Transfer

Most substances with a molecular mass less than 500 Da pass readily through placental tissue by simple diffusion. Also, some low-molecular-weight compounds undergo transfer facilitated by syncytiotrophoblast. These are usually those that are in low concentration in maternal plasma but are essential for normal fetal development. Simple diffusion appears to be the mechanism involved in the transfer of oxygen, carbon dioxide, water, and most electrolytes. Anesthetic gases also pass through the placenta rapidly by simple diffusion.

Insulin, steroid hormones, and thyroid hormones cross the placenta, but at very slow rates. The hormones synthesized in situ in the trophoblasts enter both the maternal and fetal circulation, but not equally (see Chap. 3, p. 62). Examples are concentrations of chorionic gonadotropin and placental lactogen, which are much lower in fetal plasma than in maternal plasma. Substances of high molecular weight usually do not traverse the placenta, but there are important exceptions, such as immunoglobulin G—molecular weight 160,000 Da—which is transferred by way of a specific trophoblast receptor-mediated mechanism.

Transfer of Oxygen and Carbon Dioxide

It has long been recognized that the placenta serves as the fetal lung. As early as 1674, Mayow suggested that the placenta served as the fetal lung (Morriss and associates, 1994). In 1796, Erasmus Darwin, only 22 years after the discovery of oxygen, observed that the color of blood passing through lungs and gills became bright red. He deduced, from the structure as well as the position of the placenta, that it likely was the source of fetal oxygen.

Placental oxygen transfer is blood-flow limited. Using estimated uteroplacental blood flow, Longo (1991) calculated oxygen delivery to be about 8 mL O2/min/kg of fetal weight. And because fetal blood oxygen stores are sufficient for only 1 to 2 minutes, this supply must be continuous. Normal values for oxygen, carbon dioxide, and pH in fetal blood are presented in Figure 4-11. Because of the continuous passage of oxygen from maternal blood in the intervillous space to the fetus, its oxygen saturation resembles that in the maternal capillaries. The average oxygen saturation of intervillous blood is estimated to be 65 to 75 percent, with a partial pressure (PO2) of 30 to 35 mm Hg. The oxygen saturation of umbilical vein blood is similar, but with a somewhat lower oxygen partial pressure.

In general, transfer of fetal carbon dioxide is accomplished by diffusion. The placenta is highly permeable to carbon dioxide, which traverses the chorionic villus more rapidly than oxygen. Near term, the partial pressure of carbon dioxide (PCO2) in the umbilical arteries averages about 50 mm Hg, or approximately 5 mm Hg more than in the maternal intervillous blood. Fetal blood has less affinity for carbon dioxide than does maternal blood, thereby favoring the carbon dioxide transfer from fetus to mother. Also, mild maternal hyperventilation results in a fall in PCO2 levels, favoring a transfer of carbon dioxide from the fetal compartment to maternal blood (see Chap. 5, p. 122).

Selective Transfer and Facilitated Diffusion

Although simple diffusion is an important method of placental transfer, the trophoblast and chorionic villus unit demonstrate enormous selectivity in transfer. This results in different concentrations of a variety of metabolites on the two sides of the villus. The concentrations of a number of substances that are not synthesized by the fetus are several times higher in fetal than in maternal blood. Ascorbic acid is a good example. This relatively low-molecular-weight substance resembles pentose and hexose sugars and might be expected to traverse the placenta by simple diffusion. The concentration of ascorbic acid, however, is two to four times higher in fetal plasma than in maternal plasma (Morriss and associates, 1994). Another example is the unidirectional transfer of iron across the placenta. 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.
Fetal 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, the nutrition of the blastocyst 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 5 and summarized here. The maternal diet is transferred into storage forms to meet her demands for energy, tissue repair, and new growth, including maternal needs for pregnancy. Three major maternal storage depots—the liver, muscle, and adipose tissue—and the storage hormone insulin are intimately involved in the metabolism of the nutrients absorbed from the maternal gut.

Insulin secretion is sustained by increased serum levels of glucose and amino acids. The net effect is storage of glucose as glycogen primarily in liver and muscle, retention of some amino acids as protein, and storage of the excess as fat. Storage of maternal fat peaks in the second trimester, and then declines as fetal demands increase in late pregnancy (Pipe and colleagues, 1979). Interestingly, the placenta appears to act as a nutrient sensor, altering transport based on the maternal supply and environmental stimuli (Fowden and colleagues, 2006; Jansson and Powell, 2006).

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 result in free fatty acids. Lipolysis is activated, directly or indirectly, by hormones that include glucagon, norepinephrine, placental lactogen, glucocorticosteroids, and thyroxine.

Glucose and Fetal Growth

Although dependent on the mother for nutrition, the fetus also actively participates in providing for its own nutrition. At midpregnancy, fetal glucose concentration is independent of and may exceed maternal levels (Bozzetti and colleagues, 1988). Glucose is the major nutrient for fetal growth and energy. It is logical that mechanisms exist during pregnancy to minimize maternal glucose use so that the limited maternal supply is available to the fetus. It is believed that placental lactogen (hPL), a hormone normally present in abundance in the mother but not the fetus, blocks the peripheral uptake and use of glucose, while promoting the mobilization and use of free fatty acids by maternal tissues (see Chap. 3, p. 65).

Glucose Transport

The transfer of D-glucose across cell membranes is accomplished by a carrier-mediated, stereospecific, nonconcentrating process of facilitated diffusion. At least 14 separate glucose transport proteins (GLUTs) have been discovered (Leonce and colleagues, 2006). They belong to the 12-transmembrane segment transporter superfamily and are characterized further by tissue-specific distribution. GLUT-1 and GLUT-3 primarily facilitate glucose uptake by the placenta and are located in the plasma membrane of the microvilli of the syncytiotrophoblast (Korgun and colleagues, 2005). GLUT-1 expression increases as pregnancy advances and is induced by almost all growth factors (Sakata and colleagues, 1995).

Glucose, Insulin, and Fetal Macrosomia

The precise biomolecular events in the pathophysiology of fetal macrosomia are not defined. Nonetheless, it seems clear that fetal hyperinsulinemia is one driving force (Schwartz and colleagues, 1994). As discussed in Chapter 38 (p. 842), insulin-like growth factor, as well as fibroblast growth factor, also is involved (Giudice and associates, 1995; Hill and colleagues, 1995). Therefore, a hyperinsulinemic state with increased levels of selected growth factors, together with increased expression of GLUT proteins in syncytiotrophoblast, may promote excessive fetal growth.

Leptin

Leptin was originally identified as a product of adipocytes and a regulator of energy homeostasis. However, this polypeptide also contributes to angiogenesis, hematopoiesis, osteogenesis, pulmonary maturation, and neuroendocrine, immune, and reproductive functions (Henson and Castracane, 2006; Maymo and colleagues, 2009).

During pregnancy, leptin is produced by the mother, fetus, and placenta. It is expressed in syncytiotrophoblasts and fetal vascular endothelial cells. Of placental production, 5 percent enters fetal circulation, whereas 95 percent is transferred to the mother (Hauguel de Mouzon and associates, 2006). As a result, the placenta greatly contributes to maternal leptin levels.

Fetal levels begin rising approximately at 34 weeks and are correlated with fetal weight. Abnormal levels have been associated with growth disorders and preeclampsia. Postpartum, leptin levels decline in both the newborn and mother (Grisaru-Granovsky and co-workers, 2008).

Lactate

Lactate is transported across the placenta by facilitated diffusion. By way of co-transport with hydrogen ions, lactate is probably transported as lactic acid.

Free Fatty Acids and Triglycerides

The human newborn has a large proportion of fat, which averages 15 percent of body weight (Kimura, 1991). This indicates that late in pregnancy, a substantial part of the substrate transferred to the human fetus is stored as fat. Neutral fat in the form of triacylglycerols does not cross the placenta, but glycerol does, and fatty acids are synthesized in the placenta. 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 while preserving these neutral lipids in fetal blood. Fatty acids transferred to the fetus can be converted to triacylglycerols in the fetal liver.

The placental uptake and use of low-density lipoprotein (LDL) is an alternative mechanism for fetal assimilation of essential fatty acids and amino acids (see Chap. 3, p. 67). The LDL particles from maternal plasma bind to specific LDL receptors in the coated-pit regions of the microvilli on the maternal-facing side of the syncytiotrophoblast. The large—about 250,000
Maternal and Fetal Anatomy and Physiology

SECTION 2

Amino Acids

The placenta concentrates a large number of amino acids (Leblanc, 1979). Neutral amino acids from maternal plasma are taken up by trophoblasts by at least three specific processes. Presumably, amino acids are concentrated in the syncytiotrophoblasts and thence transferred to the fetal side by diffusion. Based on data from cordocentesis blood samples, the concentration of amino acids in umbilical cord plasma is greater than in maternal venous or arterial plasma (Morriss and associates, 1994). Activity of the transport systems is influenced by gestational age and environmental factors including heat stress, hypoxia, under- and overnutrition, as well as hormones such as glucocorticoids, growth hormone, and leptin (Fowden and colleagues, 2006). Recent in vivo studies suggest an upregulation of transport for certain amino acids and an increased fetal delivery in women with gestational diabetes associated with fetal overgrowth (Jansson and colleagues, 2006).

Proteins

Generally, there is very limited placental transfer of larger proteins. There are important exceptions, for example, immunoglobulin G (IgG) crosses the placenta in large amounts via endocytosis via trophoblast Fc receptors. IgG is present in approximately the same concentrations in cord and maternal sera, but IgA and IgM of maternal origin are effectively excluded from the fetus (Gitlin and colleagues, 1972).

Ions and Trace Metals

Iodide transport is clearly attributable to a carrier-mediated, energy-requiring active process. And indeed, the placenta concentrates iodide. 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.

The most common source of cadmium in the environment is cigarette smoke. Cadmium levels in maternal blood and placenta are increased with maternal smoking, but there is no increase in cadmium transfer into the fetus. Presumably, the low levels of cadmium in the fetus are attributable to the sequestration of cadmium by metallothionein(s) in trophoblast. This comes about because cadmium acts to increase the transcription of the metallothionein gene(s). Thus, cadmium-induced increases in trophoblast metallothionein levels result in placental cadmium accumulation by sequestration. In the rat, data suggest that cadmium reduces the number of trophoblast cells, leading to poor placental growth (Lee and co-workers, 2009).

Metallothionein also binds and sequesters copper (Cu²⁺) in placental tissue, thus accounting for the low levels of Cu²⁺ in cord blood (Iyengar and Rapp, 2001). A number of enzymes require Cu²⁺, and its deficiency results in inadequate collagen cross-linking and in turn, diminished tensile strength of tissues. This may be important because the concentration of cadmium in amniotic fluid is similar to that in maternal blood. The incidence of preterm membrane rupture is increased in women who smoke. It is possible that cadmium provokes metallothionein synthesis in amnion, causing sequestration of Cu²⁺ and a pseudocopper deficiency.

Calcium and Phosphorus

These minerals also are actively transported from mother to fetus. A calcium-binding protein is present in placenta. Parathyroid hormone-related protein (PTH-rP), as the name implies, acts as a surrogate PTH in many systems, including the activation of adenylate cyclase and the movement of calcium ions (see also Chap. 3, p. 66, and Chap. 6, p. 149). PTH-rP is produced by the placenta as well as in fetal parathyroid glands, kidney, and other fetal tissues. Moreover, PTH is not demonstrable in fetal plasma, but PTH-rP is present. For these reasons, some refer to PTH-rP as the fetal parathormone (Abbás and associates, 1990). There is a Ca²⁺-sensing receptor in trophoblast, as there is in the parathyroid glands (Juulén and colleagues, 1990). The expression of PTH-rP in cytotrophoblasts is modulated by the extracellular concentration of Ca²⁺ (Hellman and co-workers, 1992). It seems possible, therefore, that PTH-rP synthesized in decidua, placenta, and other fetal tissues is important in fetal Ca²⁺ transfer and homeostasis.

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 syncytiotum. The transport of vitamin C—ascorbic acid—from mother to fetus is accomplished by an energy-dependent, carrier-mediated process. The levels of the principal vitamin D—cholecalciferol—metabolites, including 1,25-dihydroxycholecalciferol, are greater in maternal plasma than those in fetal plasma. The 1β-hydroxylation of 25-hydroxyvitamin D₃ is known to take place in placenta and in decidua.

FETAL PHYSIOLOGY

Amnionic Fluid

In early pregnancy, amnionic fluid is an ultrafiltrate of maternal plasma. By the beginning of the second trimester, it consists largely of extracellular fluid that diffuses through the fetal skin and thus reflects the composition of fetal plasma (Gilbert and Brace, 1993). After 20 weeks, the cornification of fetal skin prevents this diffusion, and amnionic fluid is composed largely of fetal urine. Fetal kidneys start producing urine at 12 weeks, and
by 18 weeks, they are producing 7 to 14 mL per day. Fetal urine contains more urea, creatinine, and uric acid than fetal plasma. Amnionic fluid also contains desquamated fetal cells, vernix, lanugo, and various secretions. Because these are hypotonic, the net effect is that amnionic fluid osmolality decreases with advancing gestation. Pulmonary fluid contributes a small proportion of the amnionic volume, and fluid filtering through the placenta accounts for the rest.

The volume of amnionic fluid at each week is quite variable. In general, the volume increases by 10 mL per week at 8 weeks and increases up to 60 mL per week at 21 weeks, then declines gradually back to a steady state by 33 weeks (Brace and Wolf, 1989).

Amnionic fluid serves to cushion the fetus, allowing musculoskeletal development and protecting it from trauma. It also maintains temperature and has a minimal nutritive function. Epidermal growth factor (EGF) and EGF-like growth factors, such as transforming growth factor-β, are present in amnionic fluid. Ingestion of fluid into the gastrointestinal tract and inhalation into the lung may promote growth and differentiation of these tissues. Animal studies have shown that pulmonary hypoplasia can be produced by draining off amnionic fluid, by chronically draining pulmonary fluid through the trachea, and by physically preventing the prenatal chest excursions that mimic breathing (Adzick and associates, 1984; Alcorn and colleagues, 1977). Thus, the formation of intrapulmonary fluid and, at least as important, the alternating egress and retention of fluid in the lungs by breathing movements are essential to normal pulmonary development. Clinical implications of oligohydramnios and pulmonary hypoplasia are discussed in Chapter 21 (p. 496).

### Fetal Circulation

The fetal circulation is substantially different from that of the adult and functions until the moment of birth, when it is required to change dramatically. For example, because fetal blood does not need to enter the pulmonary vasculature to be oxygenated, most of the right ventricular output bypasses the lungs. In addition, the fetal heart chambers work in parallel, not in series, which effectively supplies the brain and heart with more highly oxygenated blood than the rest of the body.

Oxygen and nutrient materials required for fetal growth and maturation are delivered from the placenta by the single umbilical vein (Fig. 4.12). 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 where oxygen is extracted. The relatively deoxygenated blood from the liver then flows back into the inferior vena cava, which also receives less oxygenated 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.

In contrast to postnatal life, the ventricles of the fetal heart work in parallel, not in series. Well-oxygenated blood enters the left ventricle, which supplies the heart and brain, and less oxygenated blood enters the right ventricle, which supplies the rest of the body. The two separate circulations are maintained by the structure of the right atrium, 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 medial aspect of the inferior vena cava and the less oxygenated blood stays 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—is such that it preferentially shunts the well-oxygenated blood from the medial side of the inferior vena cava and the ductus venosus through the foramen ovale into the left heart and then to the heart and brain (Dawes, 1962). After these tissues have extracted needed oxygen, the resulting less oxygenated blood returns to the right heart through the superior vena cava.

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 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 15 percent of right ventricular output—8 percent of the combined ventricular output—goes to the lungs (Teitel, 1992). 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, which distally become the umbilical arteries. In the placenta, this blood picks up oxygen and other nutrients and is recirculated through 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. 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, which course from the level of the bladder along the abdominal wall to the umbilical ring and into the cord as the umbilical arteries, undergo atrophy and obliteration within 3 to 4 days after birth. These become the umbilical ligaments, whereas the intra-abdominal 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, resulting in the formation of the ligamentum venosum (Clymann and Heymann, 1981).
Fetal Blood

Hemopoiesis

In the very early embryo, hemopoiesis is demonstrable first in the yolk sac. The next major site is the liver, and finally the bone marrow. The contributions made by each site are depicted in Figure 4-13.

The first erythrocytes released into the fetal circulation are nucleated and macrocytic. Mean cell volumes are expressed in femtoliters (fL), and one femtoliter equals one cubic micrometer. The mean cell volume is at least 180 fL in the embryo and decreases to 105 to 115 fL at term. The erythrocytes of aneuploid fetuses generally do not undergo this maturation and maintain high mean cell volumes—130 fL on average (Sipes and associates, 1991). As fetal development progresses, more and more of the circulating erythrocytes are smaller and nonnucleated. As the fetus grows, both the volume of blood in the common fetoplacental circulation and hemoglobin concentration increase. Hemoglobin content of fetal blood increases to about 12 g/dL at midpregnancy and to 18 g/dL at term (Walker and Turnbull, 1953). 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 production is increased. Reticulocytes are initially present at high levels, but decrease to 4 to 5 percent of the total at term. The fetal erythrocytes differ structurally and metabolically from those of the adult. They are more deformable, which serves to offset their higher viscosity, and contain several enzymes with appreciably different activities (Smith and co-workers, 1981).

Erythropoiesis

This process is controlled primarily by fetal erythropoietin because maternal erythropoietin does not cross the placenta. Fetal erythropoietin production is influenced by testosterone, estrogen, prostaglandins, thyroid hormone, and lipoproteins (Stockman and deAlarcon, 1992). Serum levels of erythropoietin increase with fetal maturity, as do the numbers of responsive erythrocytes. The exact site of erythropoietin production is disputed, but the fetal liver appears to be an important source until renal production begins. There is a close correlation between the concentration of erythropoietin in amniotic fluid and that in umbilical venous blood obtained by cordocentesis. After birth, erythropoietin normally may not be detectable for up to 3 months.

Fetal Blood Volume

Although precise measurements of human fetoplacental 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 the volume of fetal blood contained in the placenta after prompt cord clamping to average 45 mL/kg of fetal weight. Thus, fetoplacental blood volume at term is approximately 125 mL/kg of fetal weight.

Fetal Hemoglobin

This tetrameric protein is composed of two copies of two different peptide chains, which determine the type of hemoglobin produced. Normal adult hemoglobin A is made of α and β chains. During embryonic and fetal life, a variety of α and β chain

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**FIGURE 4-13** Chronological appearance of hemopoietic stem cells in the human embryo. (Modified from Tavian and Péault, 2005.)
precursors are produced, resulting in the serial production of several different embryonic hemoglobins. The genes that direct production of the various embryonic versions of these chains are arranged in the order in which they are temporally activated. Genes for β-type chains are on chromosome 11 and for α-type chains on chromosome 16. This sequence is shown in Figure 4-14. Each of these genes is turned on and then off during fetal life, until the α and β genes, which direct the production of hemoglobin A, are permanently activated.

The timing of the production of each of these early hemoglobin versions corresponds to changes in the site of hemoglobin production. As Figure 4-13 illustrates, 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 erythropoiesis finally moves to the bone marrow, adult-type hemoglobin A appears in fetal red blood cells and is present in progressively greater amounts as the fetus matures (Pataryas and Stamatoyannopoulos, 1972).

The final adult version of the α chain is produced exclusively by 6 weeks. After this, there are no functional alternative versions. If an α-gene mutation or deletion occurs, there is no alternate α-type chain that could substitute 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. In the case of a β-gene mutation or deletion, these two other versions of the β chain can often continue to be produced, resulting in hemoglobin A2 or hemoglobin F, which substitute for the abnormal or missing hemoglobin.

Genes are turned off by methylation of the control region, which is discussed in Chapter 12 (p. 278). In some situations, methylation does not occur, and in newborns of diabetic women, there may be persistence of hemoglobin F from hypomethylation of the γ gene (Perrine and associates, 1988). With sickle cell anemia, the γ gene remains unmethylated, and large quantities of fetal hemoglobin continue to be produced (see Chap. 51, p. 1085). Increased hemoglobin F levels are associated with fewer sickle-cell disease symptoms, and pharmacological modification of these levels by hemoglobin F-inducing drugs is one approach to disease treatment (Trompeter and Roberts, 2009).

There is a functional difference between hemoglobins A and F. 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 (see Fig. 42-3, p. 931). This is because hemoglobin A binds 2,3-diphosphoglycerate (2,3-DPG) more avidly than does hemoglobin F, thus lowering the affinity of hemoglobin A for oxygen (De Verdier and Garby, 1969). During pregnancy, maternal 2,3-DPG levels are increased, and because fetal erythrocytes have lower concentrations of 2,3-DPG, the latter has increased oxygen affinity.

The amount of hemoglobin F in fetal erythrocytes begins to decrease in the last weeks of pregnancy so that at term, about three fourths of total hemoglobin is hemoglobin F. During the first 6 to 12 months of life, the proportion of hemoglobin F continues to decrease and eventually reaches the low levels found in adult erythrocytes. Glucocorticosteroids mediate the switch from fetal to adult hemoglobin, and the effect is irreversible (Zitnik and associates, 1995).

Fetal Coagulation Factors

There are no embryonic forms of the various hemostatic proteins. With the exception of fibrinogen, 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, XI, and of prekallikrein, Protein S, Protein C, antithrombin, and plasminogen are all approximately 50 percent of adult levels. In contrast, levels of factors V, VIII, XIII, and fibrinogen are closer to adult values (Saracco and colleagues, 2009). Without prophylactic treatment, the vitamin K-dependent coagulation factors usually decrease even further during the first few days after birth. This decrease is amplified in breast-fed infants and may lead to hemorrhage in the newborn (see Chap. 29, p. 629).

Fetal fibrinogen, which appears as early as 5 weeks, has the same amino acid composition as adult fibrinogen but has different properties (Klagsbrun, 1988). It forms a less compressible clot, and the fibrin monomer has a lower degree of aggregation (Heimark and Schwartz, 1988). Plasma fibrinogen levels at birth are less than those in nonpregnant adults.

Levels of functional fetal factor XIII—fibrin-stabilizing factor—are significantly reduced compared with those in adults (Henriksen and co-workers, 1974). Severe deficiencies of factors VIII, IX, XI, or XIII are usually suspected after observing a continuous ooze from the umbilical stump. Nielsen (1969) described low levels of plasminogen and increased fibrinolytic activity in cord plasma compared with that of maternal plasma. Platelet counts in cord blood are in the normal range for nonpregnant adults.

**Figure 4-14** Schematic drawing of the arrangement of the α and β gene precursors on chromosomes 11 and 16 and the types of hemoglobin made from them. (Modified after Thompson and colleagues, 1991.)
Despite this relative reduction in procoagulants, the fetus appears to be protected from hemorrhage because fetal bleeding is a rare event. Excessive bleeding does not usually occur even after invasive fetal procedures such as cordocentesis. Nye and colleagues (1989) have shown that amniotic fluid thromboplastins and some factor in Wharton jelly combine to aid coagulation at the umbilical cord puncture site.

A variety of thrombophilias, such as protein C, S, antithrombin III deficiency, or the factor V Leiden mutation, may cause thromboses and pregnancy complications in adults (see Chap. 47, p. 1014). If the fetus inherits one of these mutations, thrombosis and infarction can develop. This is usually seen with homozygous inheritance, but Thorarensen and colleagues (1997) described three newborns with ischemic infarction or hemorrhagic stroke who were heterozygous for factor V Leiden mutation.

**Fetal Plasma Proteins**
Liver enzymes and other plasma proteins are produced by the fetus, and these levels do not correlate with maternal levels (Weiner and colleagues, 1992). Concentrations of plasma protein, albumin, lactic dehydrogenase, aspartate aminotransferase, γ-glutamyl transpeptidase, and alanine transferase all increase, whereas levels of prealbumin decrease with gestational age (Fryer and colleagues, 1993). At birth, mean total plasma protein and albumin concentrations in fetal blood are similar to maternal levels (Foley and associates, 1978).

**Ontogeny of the Fetal Immune Response**
Infections in utero have provided an opportunity to examine some of the mechanisms of the fetal immune response. Evidence of immunological competence has been reported as early as 13 weeks. Altschuler (1974) described infection of the placenta and fetus by cytomegalovirus with characteristic severe inflammatory cell proliferation as well as cellular viral inclusions. Fetal synthesis of complement late in the first trimester has been demonstrated by Kohler (1973) and confirmed by Stabile and co-workers (1988). In cord blood at or near term, the average level for most components is about half that of the adult values (Adinolfi, 1977).

**Fetal Immunocompetence**
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 are most often reflective of maternal immunological experiences.

**Immunoglobulin M**
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. In contrast, very little IgM is produced by normal fetuses, and that produced may include antibody to maternal T lymphocytes (Hayward, 1983). With infection, the IgM response is dominant in the fetus 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. Increased levels of IgM are found in newborns with congenital infection such as rubella, cytomegalovirus infection, or toxoplasmosis. Serum IgM levels in umbilical cord blood and identification of specific antibodies may be useful in the diagnosis of intrauterine infection. Adult levels of IgM are normally attained by 9 months of age.

**Immunoglobulin A**
Differing from many mammals, the human newborn does not acquire significant passive immunity from the absorption of humoral antibodies ingested in colostrum. Nevertheless, immunoglobulin A (IgA) ingested in colostrum provides mucosal protection against enteric infections. This may also explain the small amount of fetal secretory IgA found in amniotic fluid (Quan and colleagues, 1999).

**Lymphocytes**
The immune system begins to develop early and B lymphocytes appear in fetal liver by 9 weeks, and in blood and spleen by 12 weeks. T lymphocytes begin to leave the thymus at about 14 weeks (Hayward, 1983). Despite this, the newborn responds poorly to immunization, and especially poorly to bacterial capsular polysaccharides. This immature response may be due to either deficient response of newborn B cells to polyclonal activators, or lack of T cells that proliferate in response to specific stimuli (Hayward, 1983).

**Monocytes**
In the newborn, monocytes are able to process and present antigen when tested with maternal antigen-specific T cells.

**Nervous System and Sensory Organs**
The spinal cord extends along the entire length of the vertebral column in the embryo, but after that it grows more slowly. By 24 weeks, the spinal cord extends to S1, at birth to L3, and in the adult to L1. Myelination of the spinal cord 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 (Temiras and co-workers, 1968). At 10 weeks, local stimuli may evoke squinting, opening of the mouth, incomplete finger closure, and flexion of the toes. Swallowing begins at about 10 weeks, and respiration is evident at 14 to 16 weeks (Miller, 1982). Rudimentary taste buds are present at 7 weeks, and mature receptors are present by 12 weeks (Mistretta and Bradley, 1975). The ability to suck is not present until at least...
24 weeks (Lebenthal and Lee, 1983). During the third trimester, integration of nervous and muscular function proceeds rapidly. The internal, middle, and external components of the ear are well developed by midpregnancy (see Fig. 4-3). The fetus apparently hears some sounds in utero as early as 24 to 26 weeks. By 28 weeks, the eye is sensitive to light, but perception of form and color is not complete until long after birth.

## Gastrointestinal System

Swallowing begins at 10 to 12 weeks, coincident with the ability of the small intestine to undergo peristalsis and transport glucose actively (Koldovsky and colleagues, 1965; Miller, 1982). Much of the water in swallowed fluid is absorbed, and unabsorbed matter is propelled to the lower colon (Fig. 4-15). It is not clear what stimulates swallowing, 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. Late in pregnancy, however, the volume appears to be regulated substantially by fetal swallowing, for when swallowing is inhibited, hydramnios is common (see Chap. 21, p. 492). Term fetuses swallow between 200 and 760 mL per day—an amount comparable to that of the neonate (Pritchard, 1966).

Hydrochloric acid and some digestive enzymes are present in the stomach and small intestine in very small amounts in the early fetus. Intrinsic factor is detectable by 11 weeks, and pepsinogen by 16 weeks. The preterm neonate, depending on the gestational age when born, may have transient deficiencies of these enzymes (Lebenthal and Lee, 1983).

Stomach emptying appears to be stimulated primarily by volume. Movement of amnionic fluid through the gastrointestinal system may enhance growth and development of the alimentary canal. However, other regulatory factors likely are involved because anencephalic fetuses, in whom swallowing is limited, often have normal amnionic fluid volumes and normal-appearing gastrointestinal tracts. Gitlin (1974) demonstrated that late in pregnancy, about 800 mg of soluble protein is ingested daily by the fetus.

Several anomalies can affect normal fetal gastrointestinal function. Hirschsprung disease—known also as congenital aganglionic megacolon, prevents the bowel from undergoing parasympathetic-mediated relaxation and thus from emptying normally (Watkins, 1992). It may be recognized prenatally by grossly enlarged bowel during sonography. Obstructions such as duodenal atresia, megacystis-microcolon syndrome, or imperforate anus can also prevent the bowel from emptying normally. Meconium ileus, commonly found with fetal cystic fibrosis, is bowel obstruction caused by thick, viscid meconium that blocks the distal ileum (see Chap. 13, p. 298).

## 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 appearance is caused by 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 the smooth muscle of the colon to contract, resulting in intra-amnionic defecation (DeVane and co-workers, 1982; Rosenfeld and Porter, 1985). Small bowel obstruction may lead to vomiting in utero (Shrand, 1972). Fetuses who suffer from congenital chloride diarrhea may have diarrrhea in utero, which leads to hydramnios and preterm delivery (Holmberg and associates, 1977).

## Liver

Serum liver enzyme levels increase with gestational age but in reduced amounts. The fetal liver has a gestational-age related diminished capacity for converting free unconjugated bilirubin to conjugated bilirubin (see Chap. 29, p. 625). Because the life span of normal fetal macrocytic erythrocytes is brief, relatively more unconjugated bilirubin is produced. The fetal liver conjugates only a small fraction, which is excreted into the intestine and ultimately oxidized to biliverdin. Most of the unconjugated bilirubin is excreted into the amnionic fluid after 12 weeks and is then transferred across the placenta (Bashore and colleagues, 1969).
Importantly, placental transfer is bidirectional. Thus, a pregnant woman with severe hemolysis from any cause has excess unconjugated bilirubin that readily passes to the fetus and then into the amniotic fluid. Conversely, conjugated bilirubin is not exchanged to any significant degree between mother and fetus.

Most fetal cholesterol is from hepatic synthesis, which satisfies the large demand for LDL cholesterol by the fetal adrenal glands. Hepatic glycogen is present in low concentration during the second trimester, but near term there is a rapid and marked increase to levels two to three times those in the adult liver. After birth, glycogen content falls precipitously.

**Pancreas**

The discovery of insulin by Banting and Best (1922) came in response to its extraction from the fetal calf pancreas. Insulin-containing granules can be identified by 9 to 10 weeks, and insulin in fetal plasma is detectable at 12 weeks (Adam and associates, 1969). The pancreas responds to hyperglycemia by secreting insulin (Obenshain and colleagues, 1970). Serum insulin levels are unusually high in newborns of diabetic mothers and other large-for-gestational age neonates, but insulin levels are low in those small-for-gestational age (Brinsmade and Liggins, 1979). This is further described in Chapter 38 (pp. 843 and 845).

Glucagon has been identified in the fetal pancreas at 8 weeks. In the adult rhesus monkey, hypoglycemia and infused alanine cause an increase in maternal glucagon levels. Although, in the human, similar stimuli do not evoke a fetal response, by 12 hours after birth, the newborn is capable of responding (Chez and co-workers, 1975). At the same time, however, fetal pancreatic α cells do respond to L-dopa infusions (Epstein and associates, 1977). Therefore, nonresponsiveness to hypoglycemia is likely the consequence of failure of glucagon release rather than inadequate production. This is consistent with findings of the developmental expression of pancreatic genes in the fetus (Mally and associates, 1994).

Most pancreatic enzymes are present by 16 weeks. Trypsin, chymotrypsin, phospholipase A, and lipase are found in the 14-week fetus at low levels, and they increase with gestation (Werlin, 1992). Amylase has been identified in amniotic fluid at 14 weeks (Davis and associates, 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 would not be found in the fetus. Its release, however, can be stimulated experimentally. For example, Pritchard (1965) reported that radiiodine-labeled albumin injected into the amniotic sac was swallowed, digested, and absorbed from the fetal intestine.

**Urinary System**

Two primitive urinary systems—the pronephros and the mesonephros—precede the development of the metanephros (see Chap. 40, p. 890). The pronephros has involuted by 2 weeks, and the mesonephros is producing 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 development of the definitive urinary system. Between 9 and 12 weeks, the ureteric bud and the nephrogenic blastema interact to produce the metanephros. The kidney and ureter develop from intermediate mesoderm. Greater maternal anthropometrics and fetal biometrics are associated with larger fetal kidneys, whereas preferential fetal blood flow to the brain is associated with smaller kidneys (Geelhoed and colleagues, 2009). The bladder and urethra develop from the urogenital sinus. The bladder also develops in part from the allantois.

By week 14, the loop of Henle is functional and reabsorption occurs (Smith and associates, 1992). New nephrons continue to be formed until 36 weeks. 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 concentrations of electrolytes.

Renal vascular resistance is high, and the filtration fraction is low compared with values in later life (Smith and colleagues, 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 and colleagues, 1992). Hemorrhage or hypoxia generally results in a decrease in 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/day, and at term, this increases to 27 mL/hr to 650 mL/day (Wladimiroff and Campbell, 1974). Maternally administered furosemide increases fetal urine formation, whereas uteroplacental insufficiency and other types of fetal stress decrease it. Kurjak and associates (1981) found that fetal glomerular filtration rates and tubular water reabsorption were decreased in a third of growth-restricted newborns and in a sixth of those of diabetic mothers. All values were normal in anencephalic neonates and in those with hydramnios.

Obstruction of the urethra, bladder, ureters, or renal pelves can damage renal parenchyma and distort fetal anatomy. With urethral obstruction, the bladder may become sufficiently distended that it ruptures or dystocia results. Kidneys are not essential for survival in utero, but are important in the control of amniotic fluid composition and volume. Furthermore, abnormalities that cause chronic anuria are usually accompanied by oligohydramnios and pulmonary hypoplasia. Pathological correlates and prenatal therapy of urinary tract obstruction are discussed in Chapter 13 (p. 307).

**Lungs**

The timetable of lung maturation and the identification of biochemical indices of functional fetal lung maturity are of considerable interest to the obstetrician. Morphological or functional immaturity at birth leads to the development of the respiratory distress syndrome (see Chap. 29, p. 605). The presence of a
sufficient amount of surface-active materials—collectively referred to as surfactants—in the amnionic fluid is evidence of fetal lung maturity. 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 that apparently cannot be hastened by antenatal or neonatal therapy. The limits of viability, therefore, appear to be determined by the usual process of pulmonary growth. There are three essential stages of lung development as described by Moore (1983):

1. The *pseudoglandular stage* entails growth of the intrasegmental bronchial tree between the 5th and 17th weeks. During this period, the lung looks microscopically like a gland.
2. The *canalicular stage*, from 16 to 25 weeks, is when 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.
3. The *terminal sac stage* begins after 25 weeks and during this, alveoli give rise to the primitive pulmonary alveoli—the terminal sacs. Simultaneously, an extracellular matrix develops from proximal to distal lung segments until term. An extensive capillary network is built, the lymph system forms, and type II pneumonocytes begin to produce surfactant. At birth, only about 15 percent of the adult number of alveoli are present, and thus the lung continues to grow, adding more alveoli for up to 8 years.

Various insults can upset this process, and their timing determines the sequela. With fetal renal agenesis, for example, there is no amniotic fluid at the beginning of lung growth, and major defects occur in all three stages. A fetus with membrane rupture before 20 weeks and subsequent oligohydramnios usually exhibits nearly normal bronchial branching and cartilage development but has immature alveoli. Membrane rupture after 24 weeks may have little long-term effect on pulmonary structure.

**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. There are more than 200 pulmonary cell types, but surfactant is formed specifically in type II pneumonocytes 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 amniotic fluid during respiratory-like movements that are termed fetal breathing. At birth, with the first breath, an air-to-tissue interface is produced in the lung alveolus. Surfactant uncoils from the lamellar bodies, and it then spreads to line the alveoli to prevent alveolar collapse during expiration. Thus, it is the capacity for fetal lungs to produce surfactant, and not the actual laying down of this material in the lungs in utero, that establishes lung maturity.

**Surfactant Composition.** Gluck and associates (1967, 1970, 1972) and Hallman and co-workers (1976) found that about 90 percent of surfactant dry-weight is lipid. Proteins account for the other 10 percent. Approximately 80 percent of the glycerophospholipids are phosphatidylcholines (lecithins). The principal active component of surfactant is a specific lecithin—dipalmitoylphosphatidylcholine (DPPC or PC)—which accounts for nearly 50 percent. Phosphatidylglycerol (PG) accounts for another 8 to 15 percent (Keidel and Gluck, 1975). Its precise role is unclear because newborns without phosphatidylglycerol usually do well. The other major constituent is phosphatidylinositol (PI). The relative contributions of each component are shown in Figure 4-16.

**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 surface properties of the surfactant phospholipids are determined principally by the composition and degree of saturation of their long-chain fatty acids.

The major apoprotein is surfactant A (SP-A), which is a glycoprotein with a molecular weight of 28,000 to 35,000 Da (Whitsett, 1992). It is synthesized in the type II cells, and its content in amniotic fluid increases with gestational age and fetal lung maturity. SP-A may also play a role in the onset of parturition (Mendelson and Condon, 2005). Synthesis of SP-A is increased by treatment of fetal lung tissue with cyclic adenosine monophosphate (AMP) analogues, epidural growth factors, and triiodothyronine. Increased apoprotein synthesis precedes surfactant glycerocephospholipid synthesis.

SP-A gene expression is demonstrable by 29 weeks (Snyder and colleagues, 1988). There are two separate genes on chromosome 10—SP-A1 and SP-A2—and their regulation is distinctive and different (McCormick and Mendelson, 1994). Specifically,
cyclic AMP is more important in SP-A2 expression, whereas dexamethasone decreases SP-A2 expression.

Several smaller apoproteins such as SP-B and SP-C are likely important in optimizing the action of surfactant. For example, deletions in SP-B gene are incompatible with survival despite production of large amounts of surfactant.

Corticosteroids and Fetal Lung Maturation. Since Liggins (1969) first observed lung maturation in lamb fetuses given glucocorticosteroids prior to preterm delivery, many suggested that fetal cortisol stimulates lung maturation and surfactant synthesis. It is unlikely that corticosteroids are the only stimulus for augmented surfactant formation, as clearly, respiratory distress syndrome is not universal in neonates with limited cortisol production. These include those with anencephaly, adrenal hypoplasia, or congenital adrenal hyperplasia. There is evidence, however, that glucocorticosteroids administered at certain critical times during gestation effect an increase in the rate of fetal lung maturation. The use of betamethasone and dexamethasone to accelerate fetal lung maturity, as well as neonatal replacement surfactant therapy, is discussed in Chapter 36 (p. 821).

Respiration. Within a few minutes after birth, the respiratory system must provide oxygen as well as eliminate carbon dioxide. Respiratory muscles develop early, and fetal chest wall movements are detected by sonographic techniques as early as 11 weeks (Boddy and Dawes, 1975). From the beginning of the fourth month, the fetus is capable of respiratory movement sufficiently intense to move amniotic fluid in and out of the respiratory tract.

Endocrine Glands

Pituitary Gland

The fetal endocrine system is functional at some time before the central nervous system reaches maturity (Mulchahey and co-workers, 1987). The pituitary adenohypophysis develops from oral ectoderm—Rathke pouch, whereas the neurohypophysis derives from neuroectoderm.

Anterior Pituitary. The adenohypophysis, or anterior pituitary, differentiates into five cell types that secrete six protein hormones: (1) lactotropes produce prolactin—PRL; (2) somatotropes produce growth hormone—GH; (3) corticotropes produce corticotrophin—ACTH; (4) thyrotropes produce thyroid-stimulating hormone—TSH; and gonadotropes produce (5) luteinizing hormone—LH and (6) follicle-stimulating hormone—FSH.

ACTH is first detected in the fetal pituitary gland at 7 weeks, and GH and LH have been identified by 11 weeks. By the end of the 17th week, the fetal pituitary gland is able to synthesize and store all pituitary hormones. Moreover, the fetal pituitary is responsive to hormones and is capable of secreting these early in gestation (Grunbach and Kaplan, 1974). Levels of immunoreactive GH are high in cord blood, although its role in fetal growth and development is not clear. The fetal pituitary secretes β-endorphin, and cord blood levels of β-endorphin and β-lipotropin increase with fetal Pco2 (Browning and colleagues, 1983).

Neurohypophysis. The posterior pituitary gland is well developed by 10 to 12 weeks, and oxytocin and arginine vasopressin (AVP) are demonstrable. Both hormones probably function in the fetus to conserve water by actions largely at the lung and placenta rather than kidney. Levels of AVP in umbilical cord plasma are increased strikingly compared with maternal levels (Chard and associates, 1971; Polin and co-workers, 1977). Elevated fetal blood AVP appears to be associated with fetal stress (Devane and co-workers, 1982).

Intermediate Pituitary Gland. There is a well-developed intermediate lobe in the fetal pituitary gland. The cells of this structure begin to disappear before term and are absent from the adult pituitary. The principal secretory products of the intermediate lobe cells are α-melanocyte-stimulating hormone (α-MSH) and β-endorphin.

Thyroid Gland

The pituitary–thyroid system is functional by the end of the first trimester. The thyroid gland is able to synthesize hormones by 10 to 12 weeks, and TSH, thyroxine, and thyroid-binding globulin (TBG) have been detected in fetal serum as early as 11 weeks (Ballabio and colleagues, 1989). The placenta actively concentrates iodide on the fetal side, and by 12 weeks and throughout pregnancy, the fetal thyroid concentrates iodide more avidly than does the maternal thyroid. Thus, maternal administration of either radioiodide or appreciable amounts of ordinary iodide is hazardous after this time. Normal fetal levels of free thyroxine (T4), free triiodothyronine (T3), and thyroxine-binding globulin increase steadily throughout gestation (Ballabio and associates, 1989). Compared with adult levels, by 36 weeks, fetal serum concentrations of TSH are higher, total and free T3 concentrations are lower, and T4 is similar. This suggests that the fetal pituitary may not become sensitive to feedback until late in pregnancy (Thorpe-Beeston and co-workers, 1991; Wenstrom and colleagues, 1990).

Fetal thyroid hormone plays a role in the normal development of virtually all fetal tissues, but especially the brain. Its influence is illustrated by congenital hyperthyroidism, which occurs when maternal thyroid-stimulating antibody crosses the placenta to stimulate the fetal thyroid. These fetuses develop tachycardia, hepatosplenomegaly, hematological abnormalities, craniosynostosis, and growth restriction. As children, they have perceptual motor difficulties, hyperactivity, and reduced growth (Wenstrom and colleagues, 1990). Neonatal effects of fetal thyroid deficiency are discussed in Chapter 53 (p. 1126).

The placenta prevents substantial passage of maternal thyroid hormones to the fetus by rapidly deiodinating maternal T4 and T3 to form reverse T3, a relatively inactive thyroid hormone (Vulsma and colleagues, 1989). A number of antithyroid antibodies—immunoglobulin G—cross the placenta when present in high concentrations. Those include the long-acting thyroid stimulators (LATS), LATS-protector (LATS-P), and thyroid-stimulating immunoglobulin (TSI). It was previously believed that normal fetal growth and development, which occurred despite fetal hypothyroidism, provided evidence that T4 was not essential for fetal growth. It is now known, however, that growth proceeds normally because small quantities of maternal T4 prevent antenatal cretinism in fetuses with thyroid
agenesis (Vulsma and colleagues, 1989). The fetus with congenital hypothyroidism typically does not develop stigmata of cretinism until after birth. Because administration of thyroid hormone will prevent this, all newborns are tested for high serum levels of TSH (Chap. 28, p. 598).

Immediately after birth, there are major changes in thyroid function and metabolism. Cooling to room temperature evokes sudden and marked increase in TSH secretion, which in turn causes a progressive increase in serum T4 levels that are maximal 24 to 36 hours after birth. There are nearly simultaneous elevations of serum T3 levels.

**Adrenal Glands**

The fetal adrenal glands are much larger in relation to total body size than in adults. 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 detail in Chapter 3 (p. 69).

**DEVELOPMENT OF GENITALIA**

- **Embryology of Uterus and Oviducts**

The uterus and tubes arise from the müllerian ducts, which first appear near the upper pole of the urogenital ridge in the fifth week of embryonic development (Fig. 4-17). This ridge is composed of the mesonephros, gonad, and associated ducts. The first indication of müllerian duct development is a thickening of the coelomic epithelium at approximately the level of the fourth thoracic segment. This becomes the fimbriated extremity of the fallopian tube, which invaginates and grows caudally to form a slender tube at the lateral edge of the urogenital ridge. In the sixth week, the growing tips of the two müllerian ducts approach each other in the midline. One week later, they reach the urogenital sinus. At that time, the two müllerian ducts fuse to form a single canal at the level of the inguinal crest. This crest gives rise to the gubernaculum, which is the primordium of the round ligament. Thus, the upper ends of the müllerian ducts produce the oviducts, and the fused parts give rise to the uterus. The vaginal canal is not patent throughout its entire length until the sixth month (Koff, 1933). Because of the clinical importance of anomalies that arise from abnormal fusion and dysgenesis of these structures, their embryogenesis is discussed in detail in Chapter 40 (see also Fig. 40-1, p. 891).

- **Embryology of the Ovaries**

At approximately 4 weeks, gonads form on the ventral surface of the embryonic kidney at a site between the eighth thoracic and fourth lumbar segments. The coelomic epithelium thickens, and clumps of cells bud off into the underlying mesenchyme. This circumscribed area of is called the germinal epithelium. By the fourth to sixth week, however, there are many large ameboid cells in this region that have migrated into the body of the embryo from the yolk sac (see Fig. 4-17). These primordial germ cells are distinguishable by their large size and certain morphological and cytochemical features.
When the primordial germ cells reach the genital area, some enter the germinal epithelium and others mingle with groups of cells that proliferate from it or lie in the mesenchyme. By the end of the fifth week, rapid division of all these cell types results in development of a prominent genital ridge. The ridge projects into the body cavity medially to a fold in which there are the mesonephric—wolfian and paramesonephric—müllerian ducts (Fig. 4-18). By the seventh week, it is separated from the mesonephros except at the narrow central zone, the future hilum, where blood vessels enter. At this time, the sexes can be distinguished, because the testes can be recognized by well-defined radiating strands of cells termed sex cords. These cords are separated from the germinal epithelium by mesenchyme that is to become the tunica albuginea. The sex cords, which consist of large germ cells and smaller epithelioid cells derived from the germinal epithelium, develop into the seminiferous tubules and tubuli rectum. The latter establishes connection with the mesonephric tubules that develop into the epididymis. The mesonephric ducts become the vas deferens.

In the female embryo, the germinal epithelium proliferates for a longer time. The groups of cells thus formed lie at first in the region of the hilum. As connective tissue develops between them, these appear as sex cords. These cords give rise to the medulla cords and persist for variable times (Forbes, 1942). By the third month, medulla and cortex are defined (see Fig. 4-18). The bulk of the ovary is made up of cortex, a mass of crowded germ and epithelioid cells that show some signs of grouping, but there are no distinct cords as in the testis. Strands of cells extend from the germinal epithelium into the cortical mass, and mitoses are numerous. The rapid succession of mitoses soon reduces the size of the germ cells to the extent that these no longer are differentiated clearly from the neighboring cells. These germ cells are now called oogonia.

By the fourth month, some germ cells in the medullary region begin to enlarge. These are called primary oocytes at the beginning of the phase of growth that continues until maturity is reached. During this period of cell growth, many oocytes undergo degeneration, both before and after birth. A single layer of flattened follicular cells that were derived originally from the germinal epithelium soon surrounds the primary oocyte. These structures are now called primordial follicles and are seen first in the medulla and later in the cortex. Some follicles begin to grow even before birth, and some are believed to persist in the cortex almost unchanged until menopause.

By 8 months, the ovary has become a long, narrow, lobulated structure that is attached to the body wall along the line of the hilum by the mesovarium, in which lies the epoöphoron. The germinal epithelium has been separated for the most part from the cortex by a band of connective tissue—tunica albuginea. This band is absent in many small areas where strands of cells, usually referred to as cords of Pflüger, are in contact with the germinal epithelium. Among these cords are cells believed by many to be oogonia that resemble the other epithelial cells as a result of repeated mitosis. In the underlying cortex, there are two distinct zones. Superficially, there are nests of germ cells in meiotic synopsis, interspersed with Pflüger cords and strands of connective tissue. In the deeper zone, there are many groups of germ cells in

## Fetal Gender

Theoretically, there should be a primary gender ratio of 1:1 at the time of fertilization because there are equal numbers of X- and Y-bearing spermatozoa. This is not the case, however, and many factors have been shown to contribute to gender ratios at conception. These include differential susceptibility to environmental exposures as well as medical disorders. Also, couples with a large age discrepancy are more likely have a male offspring (Manning and associates, 1997). Whatever the cause, it is impossible to determine the primary gender ratio because this would require gender assignment to zygotes that fail to cleave, blastocysts that fail to implant, and other early pregnancy losses.

The secondary gender ratio is that of fetuses that reach viability and is usually held to be about 106 males to 100 females. The unbalanced secondary gender ratio is explicable by the loss of more female than male embryofetuses during early pregnancy. However, Davis and colleagues (1998) report a significant decline in male births since 1950 in Denmark, Sweden, the Netherlands, the United States, Germany, Norway, and Finland. Allan and coworkers (1997) reported that live births in Canada since 1970 dropped by 2.2 male births per 1000 live births.

## Gender Assignment at Birth

The first thing that parents in the delivery room want to know is the gender of their newborn. If the external genitalia of the newborn are ambiguous, the obstetrician faces a profound dilemma because it is not possible to assign proper functional gender by simple inspection in the delivery room. Assignment requires knowledge of the karyotypic sex, gonadal sex, hormonal milieu to which the fetus was exposed, exact anatomy, and all possibilities for surgical correction. In the past, most newborns with a small or likely insufficient phallus were often assigned to the female gender. Based on what is now known of the role of fetal exposure to hormones in establishing gender preference and behavior, it can be seen why such a policy may have caused gender identity disorder (Slijper and colleagues, 1998). Thus, it seems best to inform the parents that although their newborn appears healthy, the gender will need to be determined by a series of tests. To develop a plan that can assist in determining the cause of ambiguous genitalia, the mechanisms of normal and abnormal sexual differentiation must be considered.

## Sexual Differentiation

Phenotypic gender differentiation is determined by the chromosomal complement acting in conjunction with gonadal development.

### Chromosomal Gender

Genetic gender—XX or XY—is established at the time of fertilization, but for the first 6 weeks, development of male and female embryos is morphologically indistinguishable. The differentiation of the primordial gonad into testis or ovary heralds the establishment of gonadal sex (see Fig. 4-18).
FIGURE 4-18 Continuation of sexual differentiation of embryo. See text for explanation. (TDF = testis-determining factor.) (After Moore and colleagues, 2000.)
Gonadal Gender

As described earlier and shown in Figure 4-17, primordial germ cells that originate in the yolk sac endoderm migrate to the genital ridge to form the indifferent gonad. If a Y chromosome is present, at about 6 weeks after conception, the gonad begins developing into a testis (Simpson, 1997). Testis development is directed by a gene located on the short arm of Y—testis-determining factor (TDF), also called sex-determining region (SRY). This gene encodes a transcription factor that acts to modulate the rate of transcription of a number of genes involved in gonadal differentiation. The SRY gene is specific to the Y chromosome and is expressed in the human single-cell zygote immediately after ovum fertilization. It is not expressed in spermatozoa (Fiddler and co-workers, 1995; Gustafson and Donahoe, 1994). In addition, testis development requires a dose-dependent sex reversal (DDS) region on the X chromosome, as well as other autosomal genes (Brown and Warne, 2005).

The contribution of chromosomal gender to gonadal gender is illustrated by several paradoxical conditions. The incidence of 46,XX phenotypic human males is estimated to be about 1 in 20,000 male births (Page and colleagues, 1985). These infants apparently result from translocation of the Y chromosome fragment containing TDF to the X chromosome during meiosis of male germ cells (George and Wilson, 1988). Similarly, individuals with XY chromosomes can appear phenotypically female if they carry a mutation in the TDF/SRY gene. There is evidence that genes on the short arm of the X chromosome are capable of suppressing testicular development, despite the presence of the SRY gene. Indeed, this accounts for a form of X-linked recessive gonadal dysgenesis.

The existence of autosomal sex-determining genes is supported by several genetic syndromes in which disruption of an autosomal gene causes, among other things, gonadal dysgenesis. For example, campomelic dysplasia, localized to chromosome 17, is associated with XY phenotypic sex reversal. Similarly, male pseudohermaphroditism has been associated with a mutation in the Wilms tumor suppressor gene on chromosome 11.

Phenotypic Gender

After establishment of gonadal gender, phenotypic gender develops very rapidly. It is clear that male phenotypic sexual differentiation is directed by the function of the fetal testis. In the absence of a testis, female differentiation ensues irrespective of the genetic gender. The development of urogenital tracts in both sexes of human embryos is indistinguishable before 8 weeks. Thereafter, development and differentiation of the internal and external genitalia to the male phenotype is dependent on testicular function. The fundamental experiments to determine the role of the testis in male sexual differentiation were conducted by the French anatomist Alfred Jost. Ultimately, he established that the induced phenotype is male and that secretions from the gonads are not necessary for female differentiation. Specifically, the fetal ovary is not required for female sexual differentiation.

Jost and associates (1973) found that if castration of rabbit fetuses was conducted before differentiation of the genital anlagen, all newborns were phenotypic females with female external and internal genitalia. Thus, the müllerian ducts developed into uterus, fallopian tubes, and upper vagina.

If fetal castration was conducted before differentiation of the genital anlagen, and thereafter a testis was implanted on one side in place of the removed gonad, the phenotype of all fetuses was male. Thus, the external genitalia of such fetuses were masculinized. On the side of the testicular implant, the wolffian duct developed into the epididymis, vas deferens, and seminal vesicle. With castration, on the side without the implant, the müllerian duct developed but the wolffian duct did not.

Wilson and Gloyna (1970) and Wilson and Lasnitzki (1971) demonstrated that testosterone action was amplified by conversion to 5α-dihydrotestosterone (5α-DHT). They showed that in most androgen-responsive tissues, testosterone is converted by 5α-reductase to 5α-DHT. This hormone acts primarily and almost exclusively in the genital tubercle and labioscrotal folds.

Physiological and Biomolecular Basis of Gender Differentiation

Based on these observations, the physiological basis of gender differentiation can be summarized as follows. Genetic gender is established at fertilization. Gonadal gender is determined primarily by factors encoded by genes on the Y chromosome, such as the SRY gene. In a manner not yet understood, differentiation of the primitive gonad into a testis is accomplished.

Fetal Testicular Contributions to Male Sexual Differentiation

The fetal testis secretes a proteinaceous substance called müllerian-inhibiting substance, a dimeric glycoprotein with a molecular weight of about 140,000 Da. It acts locally as a paracrine factor to cause müllerian duct regression. Thus, it prevents the development of uterus, fallopian tube, and upper vagina. Müllerian-inhibiting substance is produced by the Sertoli cells of the seminiferous tubules. Importantly, these tubules appear in fetal gonads before differentiation of Leydig cells, which are the cellular site of testosterone synthesis. Thus, müllerian-inhibiting substance is produced by Sertoli cells even before differentiation of the seminiferous tubules and is secreted as early as 7 weeks. Müllerian duct regression is completed by 9 to 10 weeks, which is before testosterone secretion has commenced. Because it 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 uterus and fallopian tube would develop on that side.

Female external genital differentiation is complete by 11 weeks, whereas male external genital differentiation is complete by 14 weeks (Sobel and colleagues, 2004).

Fetal Testosterone Secretion

Apparently through stimulation initially by human chorionic gonadotropin (hCG), and later by fetal pituitary LH, the fetal testes secrete testosterone. This hormone acts directly on the wolffian duct to effect the development of the vas deferens, epididymis, and seminal vesicles. Testosterone also enters fetal blood and acts on the anlagen of the external genitalia. In these tissues, however, testosterone is converted to 5α-DHT to cause virilization of the external genitalia.
Genital Ambiguity of the Newborn

Ambiguity of the neonatal genitalia results from excessive androgen action in a fetus that was destined to be female or from inadequate androgen representation for one destined to be male. Rarely, genital ambiguity indicates true hermaphroditism. Abnormalities of gender differentiation causing genital ambiguity can be assigned to one of four clinically defined categories that include: (1) female pseudohermaphroditism; (2) male pseudohermaphroditism; (3) dysgenetic gonads, including true hermaphroditism; and rarely (4) true hermaphroditism (Low and Hutson, 2003).

Category 1. Female Pseudohermaphroditism

In this condition, müllerian-inhibiting substance is not produced. Androgen exposure is excessive, but variable, for a fetus genetically predestined to be female. The karyotype is 46,XX and ovaries are present.

Therefore, by genetic and gonadal gender, all are predestined to be female, and the basic abnormality is androgen excess. Because müllerian-inhibiting substance is not produced, the uterus, fallopian tubes, and upper vagina develop.

If affected fetuses were exposed to a small amount of excess androgen reasonably late in fetal development, the only genital abnormality will be slight to modest clitoral hypertrophy, with an otherwise normal female phenotype.

With somewhat greater androgen exposure, clitoral hypertrophy will be more pronounced, and the posterior labia will fuse. If androgen levels increase earlier in embryonic development, then more severe virilization can be seen. This includes formation of labioscrotal folds; development of a urogenital sinus, in which the vagina empties into the posterior urethra; and development of a penile urethra with scrotal formation—the empty scrotum syndrome (Fig. 4-19).

Figure 4-19 Female pseudohermaphroditism caused by congenital adrenal hyperplasia. Infant was 46,XX and has severe virilization with scrotal formation without a testis and has a penile urethra. (Used with permission from Dr. Lisa Halvorson.)

Category 2. Male Pseudohermaphroditism

This is characterized by incomplete and variable androgenic exposure of a fetus predestined to be male. The karyotype is 46,XY, and there are either testes or no gonads. In some cases, incomplete masculinization follows inadequate production of testosterone by the fetal testis. It also may arise from diminished responsiveness of the genital anlagen to normal quantities of androgen—including failure of the in situ formation of 5α-DHT in androgen-responsive tissue. Because testes were present for at least some time in embryonic life, müllerian-inhibiting substance is produced. Thus, the uterus, fallopian tubes, and upper vagina do not develop.

Fetal testicular testosterone production may fail if there is an enzymatic defect of steroidogenesis that involves any one of four enzymes in the biosynthetic pathway for testosterone synthesis. Impaired fetal testicular steroidogenesis can also be

Congenital Adrenal Hyperplasia. This is the most common cause of androgenic excess in fetuses with female pseudohermaphroditism. The hyperplastic glands synthesize defective enzymes that cause impaired cortisol synthesis. This leads to excessive pituitary ACTH stimulation of the fetal adrenal glands with secretion of large amounts of cortisol precursors, including androgenic prehormones. These prehormones, for example, androstenedione, are converted to testosterone in fetal extra-adrenal tissues.

Mutations may involve any of several enzymes, but the most common are steroid 21-hydroxylase, 11β-hydroxylase, and 3β-hydroxysteroid dehydrogenase. Deficiency of the last prevents synthesis of virtually all steroid hormones. Deficiency of either 17β- or 11β-hydroxylase results in increased deoxycorticosterone production to cause hypertension and hypokalemic acidosis. These forms of congenital adrenal hyperplasia thus constitute medical emergencies in the newborn (Speroff and colleagues, 1994). Currently, 21-hydroxylase deficiency can be diagnosed in utero through molecular fetal DNA analysis. Prenatal maternal dexamethasone administration has shown to safely reduce fetal genital virilization (Nimkarn and New, 2009).

Excessive Androgen from Maternal Sources. Another cause of androgen excess in the female embryo-fetus is the transfer of androgen from the maternal compartment. This may arise from the ovaries with hyperreaction luteinalis or theca-lutein cysts or from tumors such as Leydig cell tumors and Sertoli-Leydig cell tumors (see Chap. 3, p. 71, and Chap. 40, p. 905). In most of these conditions, the female fetus does not become virilized. This is because during most of pregnancy, the fetus is protected from excess maternal androgen by the extraordinary capacity of the syncytiotrophoblast to convert most C19-steroids, including testosterone, to estradiol-17β. The only exception to this generalization is fetal aromatase deficiency, which produces both maternal and fetal virilization (see Chap. 3, p. 71). Some drugs also can cause female fetal androgen excess. Most commonly, the drugs implicated are synthetic progestins or anabolic steroids (see Chap. 14, p. 321).

Importantly, except those with aromatase deficiency, all with female pseudohermaphroditism can be normal, fertile women if the proper diagnosis is made and appropriate and timely treatment initiated.
caused by an abnormality in the LH-hCG receptor and by Leydig cell hypoplasia.

With embryonic testicular regression, the testes regress during embryonic or fetal life, and there is no testosterone production thereafter (Edman and associates, 1977). This results in a spectrum of phenotypes that varies from a normal female with absent uterus, fallopian tubes, and upper vagina, to a normal male phenotype with anorchia.

Androgen resistance or deficiencies in androgen responsiveness are caused by an abnormal or absent androgen receptor protein or by enzymatic failure of conversion of testosterone to 5α-DHT in appropriate tissues (Wilson and MacDonald, 1978).

**Androgen Insensitivity Syndrome.** Formerly called testicular feminization, this is the most extreme form of the androgen resistance syndrome, and there is no tissue responsiveness to androgen. There is a female phenotype with a short, blind-ending vagina, no uterus or fallopian tubes, and no wolffian duct structures. At the expected time of puberty, testosterone levels in affected women increase to values for normal men. Nonetheless, virilization does not occur, and even pubic and axillary hair do not develop because of end-organ resistance. Presumably, because of androgen resistance at the level of the brain and pituitary, LH levels also are elevated. In response to high concentrations of LH, there is increased testicular secretion of estradiol-17β compared with that in normal men (MacDonald and colleagues, 1979). Increased estrogen secretion and absence of androgen responsiveness act in concert to cause feminization in the form of breast development.

Individuals with *incomplete androgen insensitivity* are slightly responsive to androgen. They usually have modest clitoral hypertrophy at birth (Fig. 4-20). And at the expected time of puberty, pubic and axillary hair develop but virilization does not occur. These women also develop feminine breasts, presumably through the same endocrine mechanisms as in women with the complete form of the disorder (Madden and co-workers, 1975).

Another group has been referred to as *familial male pseudohermaphroditism, type I* (Walsh and colleagues, 1974). Also commonly referred to as *Reifenstein syndrome*, it constitutes a spectrum of incomplete genital virilization. Phenotypes can vary from a phenotype similar to that of women with incomplete androgen insensitivity to that of a male phenotype with only a bifid scrotum, infertility, and gynecomastia.

The gene encoding the androgen-receptor protein is located on the X chromosome. More than 100 different mutations have been demonstrated. This accounts for the wide variability in androgen responsiveness among persons in whom the androgen-receptor protein is absent or abnormal, and for the many different mutations associated with one disorder (McPhaul and associates, 1991; Patterson and co-workers, 1994).

An alternate form of androgen resistance is caused by 5α-reductase deficiency in androgen-responsive tissues. Because androgen action in the external genitalia anlagen is mediated by 5α-DHT, persons with this enzyme deficiency have external genitalia that are female but with modest clitoral hypertrophy. But because androgen action in the wolffian duct is mediated directly by testosterone, there are well-developed epididymides, seminal vesicles, and vas deferens, and the male ejaculatory ducts empty into the vagina (Walsh and associates, 1974).

**Category 3: Dysgenetic Gonads**

In affected individuals, karyotype varies and is commonly abnormal. As the name describes, most have abnormally developed gonads, and streak gonads are typically found. As a result, müllerian-inhibiting substance is not produced and fetal androgen exposure is variable. The uterus, fallopian tubes, and upper vagina are present.

The most common form of gonadal dysgenesis is *Turner syndrome* (46X). The phenotype is female, but secondary gender characteristics do not develop at the time of expected puberty, and genital infantilism persists. In some persons with dysgenetic gonads, the genitalia are ambiguous, a finding indicating that an abnormal gonad produced androgen, albeit in small amounts, during embryonic-fetal life. Generally, there is mixed gonadal dysgenesis—one example is a dysgenetic gonad on one side and an abnormal testis or dysontogenetic tumor on the other.

**Category 4: True Hermaphroditism**

In most cases, the guidelines for category 3 are met. External genitalia of such a case are shown in Figure 4-21. In addition, true hermaphrodites have both ovarian and testicular tissues with germ cells for both ova and sperm in the abnormal gonads.

**Preliminary Diagnosis of the Cause of Genital Ambiguity**

A preliminary diagnosis of genital ambiguity can be made at the birth of an affected child. By history, during physical and sonographic examination of the newborn, an experienced examiner
can ascertain a number of important findings—whether gonads are palpable, and if so, where they are; phallus length and diameter; position of the urethral meatus; degree of labioscrotal fold fusion; and whether there is a vagina, vaginal pouch, or urogenital sinus (Speroff and associates, 1994). If the uterus is present, the diagnosis must be female pseudohermaphroditism. The clitoris and hood are apparent, and the probe is in the urogenital sinus. (Used with permission from Dr. Lisa Halvorson.)

**FIGURE 4-21** True hermaphroditism in infants with 46,XX/46,XY. A. The clitoris and hood are apparent, and the probe is in the urogenital sinus. B. A hemiscrotum is seen, and this infant shows different skin tones on each side. (Used with permission from Dr. Lisa Halvorson.)

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The anatomical, physiological, and biochemical adaptations to pregnancy are profound. Many of these remarkable changes begin soon after fertilization and continue throughout gestation, and most occur in response to physiological stimuli provided by the fetus and placenta. Equally astounding is that the woman who was pregnant is returned almost completely to her prepregnancy state after delivery and lactation.

Many of these physiological adaptations could be perceived as abnormal in the nonpregnant woman. For example, cardiovascular changes during pregnancy normally include substantial increases in blood volume and cardiac output, which may mimic thyrotoxicosis. On the other hand, these same adaptations may lead to ventricular failure if there is underlying heart disease. Thus, physiological adaptations of normal pregnancy can be misinterpreted as pathological but can also unmask or worsen preexisting disease.

During normal pregnancy, virtually every organ system undergoes anatomical and functional changes that can alter appreciably criteria for diagnosis and treatment of diseases. Thus, the understanding of these adaptations to pregnancy remains a major goal of obstetrics, and without such knowledge, it is almost impossible to understand the disease processes that can threaten women during pregnancy.

**Uterus**

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

During pregnancy, uterine enlargement involves stretching and marked hypertrophy of muscle cells, whereas the production of new myocytes is limited. Accompanying the increase in the muscle cell size is an accumulation of fibrous tissue, particularly in the external muscle layer, together with a considerable increase in elastic tissue. The network that is formed adds strength to the uterine wall.

Although the walls of the corpus become considerably thicker during the first few months of pregnancy, they actually thin gradually as gestation advances. By term, they are only 1 to 2 cm or even less in thickness. In these later months, the uterus is changed into a muscular sac with thin, soft, readily indentable walls through which the fetus usually can be palpated.

Uterine hypertrophy early in pregnancy probably is stimulated by the action of estrogen and perhaps that of progesterone. It is
apparent that hypertrophy of early pregnancy does not occur entirely in response to mechanical distention by the products of conception, because similar uterine changes are observed with ectopic pregnancy (see Chap. 10, p. 242). But after approximately 12 weeks, the increase in uterine size is related predominantly to pressure exerted by the expanding products of conception.

Uterine enlargement is most marked in the fundus. In the early months of pregnancy, the fallopian tubes and the ovarian and round ligaments attach only slightly below the apex of the fundus. In later months, they are located slightly above the middle of the uterus (see Fig. 2-11, p. 23). The position of the placenta also influences the extent of uterine hypertrophy, because the portion of the uterus surrounding the placental site enlarges more rapidly than does the rest.

**Arrangement of the Muscle Cells**

The uterine musculature during pregnancy is arranged in three strata:

1. An outer hoodlike layer, which arches over the fundus and extends into the various ligaments.
2. A middle layer, composed of a dense network of muscle fibers perforated in all directions by blood vessels.
3. An internal layer, with sphincter-like fibers around the fallopian tube orifices and internal os of the cervix.

The main portion of the uterine wall is formed by the middle layer. Each cell in this layer has a double curve so that the interlacing of any two gives approximately the form of a figure eight. This arrangement is crucial because when the cells contract after delivery, they constrict the penetrating blood vessels and thus act as ligatures (see Fig. 2-14, p. 25).

**Uterine Size, Shape, and Position**

For the first few weeks, the uterus maintains its original pear shape, but as pregnancy advances, the corpus and fundus assume a more globular form, becoming almost spherical by 12 weeks. Subsequently, the organ increases more rapidly in length than in width and assumes an ovoid shape. By the end of 12 weeks, the uterus has become too large to remain entirely within the pelvis. As the uterus continues to enlarge, it contacts the anterior abdominal wall, displaces the intestines laterally and superiorly, and continues to rise, ultimately reaching almost to the liver. With ascent of the uterus from the pelvis, it usually undergoes rotation to the right. This dextrorotation is likely 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 axis of the pelvic inlet. The abdominal wall supports the uterus and unless it is quite relaxed, maintains this relation between the long axis of the uterus and the axis of the pelvic inlet. When the pregnant woman is supine, the uterus falls back to rest on the vertebral column and the adjacent great vessels, especially the inferior vena cava and aorta.

**Contractility**

Beginning in early pregnancy, the uterus undergoes irregular contractions that are normally painless. During the second trimester, these contractions may be detected by bimanual examination. Because attention was first called to this phenomenon in 1872 by J. Braxton Hicks, the contractions have been known by his name. Such contractions appear unpredictably and sporadically and are usually nonrhythmic. Their intensity varies between approximately 5 and 25 mm Hg (Alvarez and Caldeyro-Barcia, 1950). Until the last several weeks of pregnancy, these Braxton Hicks contractions are infrequent, but they increase during the last week or two. At this time, the contractions may occur as often as every 10 to 20 minutes and also may assume some degree of rhythmicity. Correspondingly, studies of uterine electrical activity have shown low and uncoordinated patterns early in gestation, which become progressively more intense and synchronized by term (Garfield and associates, 2005). Late in pregnancy, these contractions may cause some discomfort and account for so-called false labor (see Chap. 17, p. 390). One clinical implication recently shown is that 75 percent of women with 12 or more of these contractions per hour were diagnosed with active labor within 24 hours (Pates and colleagues, 2007).

**Uteroplacental Blood Flow**

The delivery of most substances essential for growth and metabolism of the fetus and placenta, as well as removal of most metabolic wastes, is dependent on adequate perfusion of the placental intervillous space (see Chap. 3, p. 55). Placental perfusion is dependent on total uterine blood flow, which is principally from the uterine and ovarian arteries. Uteroplacental blood flow increases progressively during pregnancy, with estimates ranging from 450 to 650 mL/min near term (Edman and associates, 1981; Kauppila and co-workers, 1980).

The results of studies conducted in rats by Page and co-workers (2002) show that the uterine veins also undergo significant adaptations during pregnancy. Specifically, their remodeling includes reduced elastin content and adrenergic nerve density, which results in increased venous caliber and distensibility. Logically, such changes are necessary to accommodate massively increased uteroplacental blood flow.

Assali and co-workers (1968), using electromagnetic flow probes placed directly on a uterine artery, studied the effects of labor on uteroplacental blood flow in sheep and dogs at term. They found that uterine contractions, either spontaneous or induced, caused a decrease in uterine blood flow that was approximately proportional to the intensity of the contraction. They also showed that a tetanic contraction caused a precipitous fall in uterine blood flow. Harbert and associates (1969) made a similar observation in gravid monkeys. Uterine contractions appear to affect fetal circulation much less, and Brar and colleagues (1988) reported no adverse effects on umbilical artery flow.

**Regulation of Uteroplacental Blood Flow.** The progressive increase in maternal-placental blood flow during gestation occurs principally by means of vasodilation, whereas fetal-placental blood flow is increased by a continuing growth of placental vessels. Palmer and colleagues (1992) showed that uterine artery diameter doubled by 20 weeks and concomitant mean Doppler velocimetry was increased eightfold. It appears likely that
vasodilation at this stage of pregnancy is at least in part the consequence of estrogen stimulation. For example, Naden and Rosenfeld (1985) found that 17β-estradiol administration to nonpregnant sheep induced cardiovascular changes similar to those observed in pregnant animals. Using measurements of the uterine artery resistance index, Jauliaux and associates (1994) found that both estradiol and progesterone contributed to the downstream fall in vascular resistance in women with advancing gestational age (see Chap. 16, p. 364).

Other mediators, in addition to estradiol and progesterone, modify vascular resistance during pregnancy, including within the uteroplacental circulation. For example, significant decreases in uterine blood flow and placental perfusion have been demonstrated in sheep following nicotine and catecholamine infusions (Rosenfeld and co-workers, 1976; Rosenfeld and West, 1977; Xiao and associates, 2007). The latter is likely the consequence of greater sensitivity of the uteroplacental vascular bed to epinephrine and norepinephrine compared with that of the systemic vasculature. In contrast, normal pregnancy is characterized by vascular refractoriness to the pressor effects of infused angiotensin II (see p. 120). This insensitivity serves to increase uteroplacental blood flow (Rosenfeld and Gant, 1981; Rosenfeld, 2001). More recently, Rosenfeld and associates (2005) have discovered that large-conductance potassium channels expressed in uterine vascular smooth muscle also contribute to uteroplacental blood flow regulation through several mediators, including estrogen and nitric oxide.

### Cervix

As early as 1 month after conception, the cervix begins to undergo pronounced softening and cyanosis. These changes result from increased vascularity and edema of the entire cervix, together with hypertrophy and hyperplasia of the cervical glands (Straach and associates, 2005). Although the cervix contains a small amount of smooth muscle, its major component is connective tissue. Rearrangement of this collagen-rich connective tissue is necessary to permit functions as diverse as maintenance of a pregnancy to term, dilatation to aid delivery, and repair following parturition so that a successful pregnancy can be repeated (see Fig. 6-3, p. 139) (Timmons and Mahendroo, 2007; Word and associates, 2007).

As shown in Figure 5-1, the cervical glands undergo such marked proliferation that by the end of pregnancy they occupy approximately half of the entire cervical mass, rather than a small fraction as in the nonpregnant state. These normal pregnancy-induced changes represent an extension, or eversion, of the proliferating columnar endocervical glands. This tissue tends to be red and velvety and bleeds even with minor trauma, such as with Pap smear sampling.

The endocervical mucosal cells produce copious amounts of a tenacious mucus that obstruct the cervical canal soon after conception. As discussed on page 116, this mucus is rich in immunoglobulins and cytokines and may act as an immunological barrier to protect the uterine contents against infection from the vagina (Hein and colleagues, 2005). At the onset of labor, if not before, this mucus plug is expelled, resulting in a bloody show. Moreover, the consistency of the cervical mucus changes during pregnancy. In most pregnant women, when cervical mucus is spread and dried on a glass slide, it is characterized by crystallization, or beading, as a result of progesterone. In some women, arborization of the crystals, or ferning, is observed as a result of amniotic fluid leakage (see Figs. 8-3 and 8-4, p. 192).

During pregnancy, basal cells near the squamocolumnar junction are likely to be prominent in size, shape, and staining qualities. 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—which makes the identification of atypical glandular cells on Pap smear particularly difficult (Connolly and Evans, 2005).

### Ovaries

Ovulation ceases during pregnancy, and the maturation of new follicles is suspended. Ordinarily, only a single corpus luteum can be found in pregnant women. This functions maximally during the first 6 to 7 weeks of pregnancy—4 to 5 weeks postovulation—and thereafter contributes relatively little to progesterone production. These observations have been confirmed by surgical removal of the corpus luteum before 7 weeks—5 weeks postovulation—which results in a rapid fall in maternal serum progesterone and spontaneous abortion (Csapo and co-workers, 1973). After this time, however, corpus luteum removal ordinarily does not cause abortion. Indeed, even bilateral oophorectomy at 16 weeks has been reported to result in an otherwise uneventful pregnancy (Villaseca and associates, 2005). Interestingly in such cases, FSH levels do not reach perimenopausal levels until approximately 5 weeks postpartum.
A decidual reaction on and beneath the surface of the ovaries, similar to that found in the endometrial stroma, is common in pregnancy and is usually observed at cesarean delivery. These elevated patches of tissue 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. Although the development of such decidual reactions is incompletely understood, Tassig (1906) and others have deduced that these findings likely represent cellular detritus from the endometrium that has passed through the fallopian tubes.

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—recall that Poiseuille’s law is that flow in a tubular structure is dependent on the product of its radius to the fourth power!

**Relaxin**

As discussed in Chapter 3 (p. 65), this protein hormone is secreted by the corpus luteum, decidua, and placenta in a pattern similar to that of human chorionic gonadotropin (hCG). It is also expressed in a variety of nonreproductive tissues, including brain, heart, and kidney. It is mentioned here because one of its major biological actions appears to be remodeling of reproductive tract connective tissue to accommodate pregnancy parturition (Park and colleagues, 2005). Relaxin also appears to be an important factor in the initiation of augmented renal hemodynamics (p. 123) and decreased osmolality (p. 112) associated with pregnancy (Smith and associates, 2006). Despite its name, serum relaxin levels do not correlate with increasing peripheral joint laxity during pregnancy (Marnach and co-workers, 2003).

**Pregnancy Luteoma**

In 1963, Sternberg described a solid ovarian tumor that developed during pregnancy and was composed of large acidophilic luteinized cells, which represented an exaggerated luteinization reaction of the normal ovary. These so-called luteomas of pregnancy are variable in size, ranging from microscopic to over 20 cm in diameter (Fig. 5-2). Typical sonographic characteristics include a solid, complex-appearing unilateral or bilateral mass with cystic features that correspond to areas of hemorrhage. It is usually not possible to differentiate luteomas from other solid ovarian neoplasms, such as luteinized thecoma, granulosa cell tumor, or Leydig cell tumor, by sonographic characteristics alone (Choi and associates, 2000).

Pregnancy luteomas may result in maternal virilization, but usually the female fetus is not affected. This is presumably because of the protective role of the trophoblast with its high capacity to convert androgens and androgen-like steroids to estrogens (Edman and co-workers, 1979). Occasionally, however, a female fetus can become virilized (Spitzer and co-workers, 2007). Although luteomas regress after delivery, they may recur in subsequent pregnancies (Shortle and associates, 1987).

**Theca-Lutein Cysts**

These benign ovarian lesions result from exaggerated physiological follicle stimulation—termed hyperreactio luteinalis. Although the cellular pattern of hyperreactio luteinalis is similar to that of a luteoma, these usually bilateral cystic ovaries are moderately to massively enlarged. The reaction is associated with markedly elevated serum levels of hCG. And not surprisingly, theca-lutein cysts are found frequently with gestational trophoblastic disease (see Chap. 11, p. 259). They are also more likely to be found with a large placenta such as with diabetes, D–isoimmunization, and multiple fetuses (Tanaka and colleagues, 2001). Theca-lutein cysts have also been reported in chronic renal failure as a result of reduced hCG clearance, and in hyperthyroidism as a result of the structural homology between hCG and thyroid-stimulating hormone (Coccia and colleagues, 2003; Gherman and co-workers, 2003). But they also are encountered in women with otherwise uncomplicated pregnancies and are thought to result from an exaggerated response of the ovaries to normal levels of circulating hCG (Langer and Coleman, 2007).

Although usually asymptomatic, hemorrhage into the cysts may cause abdominal pain. Maternal virilization may be seen in up to 25 percent of women (Foulk and associates, 1997). Changes including 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 resolution follows delivery. In some women, increased ovarian responsiveness to gonadotropin can be confirmed by several weeks postpartum (Bradshaw and co-workers, 1986; Sherer and associates, 2006). Their management is discussed further in Chapter 40 (p. 904).

**Fallopian Tubes**

The musculature of the fallopian tubes undergoes little hypertrophy during pregnancy. The epithelium of the tubal mucosa, however, becomes somewhat flattened. Decidual cells may develop in the stroma of the endosalpinx, but a continuous decidual membrane is not formed. Very rarely, the increasing size of the gravid uterus, especially in the presence of parutubal or ovarian cysts, may result in fallopian tube torsion (Batukan and co-workers, 2007).
Blood Flow in Skin

Increased cutaneous blood flow in pregnancy serves to dissipate excess heat generated by increased metabolism (see Chap. 56, p. 1187).

Abdominal Wall

Beginning after midpregnancy, reddish, slightly depressed streaks commonly develop in the abdominal skin and sometimes in the skin over the breasts and thighs. These are called striae gravidarum or stretch marks. In multiparous women, in addition to the reddish striae of the present pregnancy, glistening, silvery lines that represent the cicatrices of previous striae frequently are seen. In a study of 110 primiparous patients, Osman and colleagues (2007) reported that 48 percent developed striae gravidarum on their abdomen; 25 percent, on their breasts; and 25 percent, on their thighs. The strongest associated risk factors were weight gain during pregnancy, younger maternal age, and family history.

Occasionally, the muscles of the abdominal walls do not withstand the tension to which they are subjected. As a result, rectus muscles separate in the midline, creating a 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. True fascial defects lead to ventral hernia, which uncommonly require antepartum surgical correction.

Hyperpigmentation

This develops in up to 90 percent of women. It is usually more accentuated in those with a darker complexion (Muallem and Rubeiz, 2006). The midline of the abdominal skin—linea alba—becomes especially pigmented, assuming a brownish-black color 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 so-called mask of pregnancy. Pigmentation of the areolae and genital skin may also be accentuated. These pigmentary changes usually disappear, or at least regress considerably, after delivery. Oral contraceptives may cause similar pigmentation.

Very little is known of the nature of these pigmentary changes, although melanocyte-stimulating hormone, a polypeptide similar to corticotropin, has been shown to be elevated remarkably from the end of the second month of pregnancy until term. Estrogen and progesterone also are reported to have melanocyte-stimulating effects. These conditions are considered in greater detail in Chapter 56 (p. 1185).

Vascular Changes

Angiomas, called vascular spiders, develop in about two thirds of white women and approximately 10 percent of black women. These are minute, red elevations on the skin, particularly common on the face, neck, upper chest, and arms, with radicles branching out from a central lesion. The condition is often designated as nevus, angioma, or telangiectasia. Palmar erythema is encountered during pregnancy in about two thirds of white women and one third of black women. The two conditions are of no clinical significance and disappear in most women shortly after pregnancy. They are most likely the consequence of hyperestrogenemia.

In the early weeks of pregnancy, women often experience breast tenderness and paresthesias. After the second month, the breasts increase in size, and delicate veins become 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 the areolae are a number of small elevations, the glands of Montgomery, which are hypertrophic sebaceous glands. If the increase in breast size is extensive, striations similar to those observed in the abdomen may develop. Rarely, breast enlargement may become so pathologically extensive—referred to as gigantomastia—that it requires surgical intervention (Pasrija and Sharma, 2006; Vidaeff and associates, 2003). Interestingly, prepregnancy breast size and volume of milk production do not correlate (Hytten, 1995). Histological and functional changes of the breasts induced by pregnancy and lactation are further discussed in Chapter 30 (p. 649).

Metabolic Changes

In response to the increased demands of the rapidly growing fetus and placenta, the pregnant woman undergoes metabolic changes that are numerous and intense. Certainly no other physiological event in postnatal life induces such profound
metabolic alterations. By the third trimester, maternal basal metabolic rate is increased by 10 to 20 percent compared with that of the nonpregnant state. This is increased by an additional 10 percent in women with twin gestations (Shinagawa and associates, 2005). Viewed another way, additional total pregnancy energy demands are estimated to be as high as 80,000 kcal or about 300 kcal/day (Hytten and Chamberlain, 1991).

**Weight Gain**
Most of the normal increase in weight during pregnancy is attributable to the uterus and its contents, the breasts, and increases in blood volume and extravascular extracellular fluid. A smaller fraction of the increased weight is the result of metabolic alterations that result in an increase in cellular water and deposition of new fat and protein—so-called maternal reserves. Hytten (1991) reported that the average weight gain during pregnancy is approximately 12.5 kg or 27.5 lb (Table 5-1). Maternal aspects of weight gain are considered in greater detail in Chapter 8 (p. 200).

**Water Metabolism**
Increased water retention is a normal physiological alteration of pregnancy. It is mediated, at least in part, by a fall in plasma osmolality of approximately 10 mOsm/kg induced by a resetting of osmotic thresholds for thirst and vasopressin secretion (Heenan and colleagues, 2003; Lindheimer and Davison, 1995). As shown in Figure 5-3, this phenomenon is functioning by early pregnancy.

At term, the water content of the fetus, placenta, and amniotic fluid approximates 3.5 L. Another 3.0 L accumulates as a result of increases in the maternal blood volume and in the size of the uterus and breasts. Thus, the minimum amount of extra water that the average woman accrues during normal pregnancy is approximately 6.5 L. Clearly demonstrable pitting edema of the ankles and legs is seen in most pregnant women, especially at the end of the day. This accumulation of fluid, which may amount to a liter or so, is caused by increased venous pressure below the level of the uterus as a consequence of partial vena cava occlusion. A decrease in interstitial colloid osmotic pressure induced by normal pregnancy also favors edema late in pregnancy (Olán and co-workers, 1985).

Longitudinal studies of body composition have shown a progressive increase in total body water and fat mass during pregnancy. Both initial maternal weight and weight gained during pregnancy are highly associated with birthweight. It is unclear, however, what role maternal fat or water have in fetal growth. Studies in well-nourished women suggest that maternal body water, rather than fat, contributes more significantly to infant birthweight (Lederman and co-workers, 1999; Mardones-Santander and associates, 1998).

### TABLE 5-1. Analysis of Weight Gain Based on Physiological Events During Pregnancy

<table>
<thead>
<tr>
<th>Tissues and Fluids</th>
<th>10 Weeks</th>
<th>20 Weeks</th>
<th>30 Weeks</th>
<th>40 Weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fetus</td>
<td>5</td>
<td>300</td>
<td>1500</td>
<td>3400</td>
</tr>
<tr>
<td>Placenta</td>
<td>20</td>
<td>170</td>
<td>430</td>
<td>650</td>
</tr>
<tr>
<td>Amniotic fluid</td>
<td>30</td>
<td>350</td>
<td>750</td>
<td>800</td>
</tr>
<tr>
<td>Uterus</td>
<td>140</td>
<td>320</td>
<td>600</td>
<td>970</td>
</tr>
<tr>
<td>Breasts</td>
<td>45</td>
<td>180</td>
<td>360</td>
<td>405</td>
</tr>
<tr>
<td>Blood</td>
<td>100</td>
<td>600</td>
<td>1300</td>
<td>1450</td>
</tr>
<tr>
<td>Extravascular fluid</td>
<td>0</td>
<td>30</td>
<td>80</td>
<td>1480</td>
</tr>
<tr>
<td>Maternal stores (fat)</td>
<td>310</td>
<td>2050</td>
<td>3480</td>
<td>3345</td>
</tr>
<tr>
<td>Total</td>
<td>650</td>
<td>4000</td>
<td>8500</td>
<td>12,500</td>
</tr>
</tbody>
</table>


**FIGURE 5-3** Mean values (black line) ± standard deviations (blue lines) for plasma osmolality ($P_{\text{osm}}$) measured at weekly intervals in nine women from preconception to 16 weeks. (LMP = last menstrual period; MP = menstrual period.) (From Davison and colleagues, 1981, with permission.)
Protein Metabolism

The products of conception, the uterus, and maternal blood are relatively rich in protein rather than fat or carbohydrate. At term, the fetus and placenta together weigh about 4 kg and contain approximately 500 g of protein, or about half of the total pregnancy increase (Hytten and Leitch, 1971). The remaining 500 g is added to the uterus as contractile protein, to the breasts primarily in the glands, and to the maternal blood as hemoglobin and plasma proteins.

Amino acid concentrations are higher in the fetal than in the maternal compartment (Cetin and co-workers, 2005; van den Akker and associates, 2009). This increased concentration is largely regulated by the placenta, which not only concentrates amino acids into the fetal circulation, but also is involved in protein synthesis, oxidation, and transamination of some nonessential amino acids (Galan and colleagues, 2009).

Mojtahedi and associates (2002) measured nitrogen balance across pregnancy in 12 healthy women. It increased with gestation and thus suggested a more efficient use of dietary protein. They also found that urinary excretion of 3-methylhistidinidine did not change, indicating that breakdown of maternal muscle is not required to meet metabolic demands. Further support that pregnancy is associated with nitrogen conservation comes from Kalhan and colleagues (2003), who found that the turnover rate of nonessential serine decreases across gestation. The daily requirements for dietary protein intake during pregnancy are discussed in Chapter 8 (p. 202).

Carbohydrate Metabolism

Normal pregnancy is characterized by mild fasting hypoglycemia, postprandial hyperglycemia, and hyperinsulinemia (Fig. 5-4). This increased basal level of plasma insulin in normal pregnancy is associated with several unique responses to glucose ingestion. For example, after an oral glucose meal, gravid women demonstrate both prolonged hyperglycemia and hyperinsulinemia as well as a greater suppression of glucagon (Phelps and associates, 1981). This cannot be explained by a decreased metabolism of insulin because its half-life during pregnancy is not changed (Lind and associates, 1977). Instead, this response is consistent with a pregnancy-induced state of peripheral insulin resistance, the purpose of which is likely to ensure a sustained postprandial supply of glucose to the fetus. Indeed, insulin sensitivity in late normal pregnancy is 45 to 70 percent lower than that of nonpregnant women (Butte, 2000; Freemark, 2006).

The mechanism(s) responsible for insulin resistance is not completely understood. Progesterone and estrogen may act, directly or indirectly, to mediate this resistance. Plasma levels of placental lactogen increase with gestation, and this protein hormone is characterized by growth hormone–like action that may result in increased lipolysis with liberation of free fatty acids (Freinkel, 1980). The increased concentration of circulating free fatty acids also may aid increased tissue resistance to insulin (Freemark, 2006).

The pregnant woman changes rapidly from a postprandial state characterized by elevated and sustained glucose levels to a fasting state characterized by decreased plasma glucose and some amino acids. Simultaneously, plasma concentrations of free fatty acids, triglycerides, and cholesterol are higher. Freinkel and colleagues (1985) have referred to this pregnancy-induced switch in fuels from glucose to lipids as 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 increase appreciably during pregnancy. The storage of fat occurs primarily during midpregnancy (Hytten and Thomson, 1968; Pipe and co-workers, 1979). This fat is deposited mostly in central rather than peripheral sites. It becomes available for placental transfer during the last trimester when fetal growth rate is maximal along with essential fatty acids requirements (Herrera and colleagues, 2006; Innis, 2005). It may be that progesterone acts to reset a lipostat in the hypothalamus, and at the end of pregnancy, the lipostat returns to its previous nonpregnant level, and the added fat is lost (Hytten and Thomson, 1968). Such a mechanism for energy storage, theoretically at least, might protect the mother and fetus during prolonged starvation or hard physical exertion.

Maternal hyperlipidemia is one of the most consistent and striking changes to take place in lipid metabolism during late pregnancy. Triacylglycerol and cholesterol levels in very-low-density lipoprotein (VLDL), low-density lipoproteins (LDLs), and high-density lipoproteins (HDLs) are increased during the third
trimester compared with those in nonpregnant women. The mechanisms responsible for these changes include increased lipolytic and decreased lipoprotein lipase activities in adipose tissue (Herrera and colleagues, 2006). The hepatic effects of estradiol and progesterone also play an important role (Desoye and associates, 1987).

During the third trimester, average total serum cholesterol, LDL-C, HDL-C, and triglyceride levels are approximately 267 \(\pm 30\) mg/dL, 136 \(\pm 33\) mg/dL, 81 \(\pm 17\) mg/dL, and 245 \(\pm 73\) mg/dL, respectively (Lippi and associates, 2007). After delivery, the concentrations of these lipids, as well as lipoproteins and apolipoproteins decrease. Lactation speeds the change in levels of many of these (Darmady and Postle, 1982).

Hyperlipidemia is of some concern because it is associated with endothelial dysfunction. From their studies, however, Saarelainen and associates (2006) found that endothelium-dependent vasodilation responses actually improved across pregnancy. This was partly because increased concentrations of HDL-cholesterol likely inhibit oxidation of low-density lipoprotein and thus protect the endothelium. Their findings suggest that the increased risk of cardiovascular disease in multiparous women may be related to factors other than maternal hypercholesterolemia.

**Leptin**

In nonpregnant humans, this peptide hormone is primarily secreted by adipose tissue. It has a key role in the regulation of body fat and energy expenditure. Maternal serum leptin levels increase and peak during the second trimester and plateau until term in concentrations two to four times higher than those in nonpregnant women. This increase is only partially due to pregnancy weight gain, because leptin also is produced in significant amounts by the placenta. Indeed, placental weight is significantly correlated with leptin levels measured in umbilical cord blood (Pighetti and co-workers, 2003). Hauguel-de Mouzon and associates (2006) have hypothesized that increased leptin production may be critical for the regulation of increased maternal energy demands. Leptin may also help to regulate fetal growth and play a role in fetal macrosomia as well as growth restriction (Gohike, 2006; Grisaru-Granovsky, 2008; Henson, 2006, Lepercq, 2003, and all their associates). This topic is discussed further in Chapter 38 (p. 842).

**Ghrelin**

This is another hormone secreted by adipose tissue that likely has a role in fetal growth and cell proliferation. It is also expressed in placental tissue, and this hormone regulates growth hormone secretion. Maternal serum levels of ghrelin increase and peak at midpregnancy and then decrease until term (Fuglsang, 2008). This is explicable in that ghrelin levels are known to be decreased in other insulin-resistant states such as metabolic syndrome (Riedl and associates, 2007).

**Electrolyte and Mineral Metabolism**

During normal pregnancy, nearly 1000 mEq of sodium and 300 mEq of potassium are retained (Lindheimer and colleagues, 1987). Although the glomerular filtration of sodium and potassium is increased, the excretion of these electrolytes is unchanged during pregnancy as a result of enhanced tubular resorption (Brown and colleagues, 1986, 1988). And although there are increased total accumulations of sodium and potassium, their serum concentrations are decreased slightly because of expanded plasma volume (see Appendix). Still, they remain very near the range of normal for nonpregnant women (Kametas and colleagues, 2003b).

Total serum calcium levels decline during pregnancy, the reduction reflecting lowered plasma albumin concentration and, in turn, the consequent decrease in the amount bound to protein. Levels of serum ionized calcium, however, remain unchanged (Power and associates, 1999). The developing fetus imposes a significant demand on maternal calcium homeostasis. For example, the fetal skeleton accretes 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, in part, by 1,25-dihydroxyvitamin D3 (Kovacs and Fuleihan, 2006). In addition, dietary intake of sufficient calcium is necessary to prevent excess depletion from the mother (see Table 8-7, p. 201). This is especially important in pregnant adolescents, in whom bones are still developing (Repke, 1994).

Serum magnesium levels also decline during pregnancy. Bardicef and colleagues (1995) concluded that pregnancy is actually a state of extracellular magnesium depletion. Compared with nonpregnant women, they found that both total and ionized magnesium were significantly lower during normal pregnancy. Serum phosphate levels are within the nonpregnant range (Kametas and colleagues, 2003b). The renal threshold for inorganic phosphate excretion is elevated in pregnancy due to increased calcitonin (Weiss and colleagues, 1998).

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 (see Chap. 4, p. 88, and Chap. 8, p. 202). An important exception is the considerably increased requirement for iron, which is discussed subsequently.

**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 (Pritchard, 1965; Whittaker and associates, 1996). In individual women, expansion varies considerably. In some there is only a modest increase, whereas in others the blood volume nearly doubles. A fetus is not essential for this because increased blood volume develops in some women with hydatidiform mole (Pritchard, 1965).

Pregnancy-induced hypervolemia has important functions:

1. To meet the metabolic demands of the enlarged uterus with its greatly hypertrophied vascular system.
2. To provide an abundance of nutrients and elements to support the rapidly growing placenta and fetus.
3. To protect the mother and in turn the fetus, against the deleterious effects of impaired venous return in the supine and erect positions.
4. To safeguard the mother against the adverse effects of blood loss associated with parturition.
Maternal blood volume begins to increase during the first trimester. By 12 menstrual weeks, plasma volume expands by approximately 15 percent compared with that of prepregnancy (Bernstein and co-workers, 2001). As shown in Figure 5-5, maternal blood volume expands most rapidly during the second trimester. It then rises at a much slower rate during the third trimester to plateau during the last several weeks of pregnancy.

Blood volume expansion results from an increase in both plasma and erythrocytes. Although more plasma than erythrocytes is usually added to the maternal circulation, the increase in erythrocyte volume is considerable, averaging about 450 mL (Pritchard and Adams, 1960). Moderate erythroid hyperplasia is present in the bone marrow, and the reticulocyte count is elevated slightly during normal pregnancy. As discussed in Chapter 51 (p. 1079), these changes are almost certainly related to the increase in maternal plasma erythropoietin levels, which peak early during the third trimester and correspond to maximal erythrocyte production (Clapp and colleagues, 2003; Harstad and co-workers, 1992).

**Hemoglobin Concentration and Hematocrit**

Because of great plasma augmentation, hemoglobin concentration and hematocrit decrease slightly during pregnancy (see Appendix). As a result, whole blood viscosity decreases (Huisman and colleagues, 1987). Hemoglobin concentration at term averages 12.5 g/dL, and in approximately 5 percent of women, it is below 11.0 g/dL (Table 51-1, p. 1080). Thus, a hemoglobin concentration below 11.0 g/dL, especially late in pregnancy, should be considered abnormal and usually due to iron deficiency rather than due to hypervolemia of pregnancy.

**Iron Metabolism**

**Storage Iron**

The total iron content of normal adult women ranges from 2.0 to 2.5 g or about half the amount found normally in men. Importantly, the iron stores of normal young women are only approximately 300 mg (Pritchard and Mason, 1964).

**Iron Requirements**

Of the approximate 1000 mg of iron required for normal pregnancy, about 300 mg are actively transferred to the fetus and placenta, and another 200 mg are lost through various normal routes of excretion, primarily the gastrointestinal tract. These are obligatory losses and occur even when the mother is iron deficient. The average increase in the total volume of circulating erythrocytes—about 450 mL—requires another 500 mg because 1 mL of erythrocytes contains 1.1 mg of iron. Because most iron is used during the latter half of pregnancy, the iron requirement becomes large after midpregnancy and averages 6 to 7 mg/day (Pritchard and Scott, 1970). This amount is usually not available from storage iron in most women, and the optimal increase in maternal erythrocyte volume will not develop without supplemental iron. Without supplementation, the hemoglobin concentration and hematocrit fall appreciably as the blood volume increases. At the same time, fetal red cell production is not impaired because the placenta transfers iron even when the mother has severe iron deficiency anemia. In severe cases, we have documented hemoglobin values of 3 g/dL and hematocrits of 10 percent. It follows that the amount of dietary iron, together with that mobilized from stores, will be insufficient to meet the average demands imposed by pregnancy. As shown in Figure 5-6, if the...
nonanemic pregnant woman is not given supplemental iron, which is discussed in Chapter 8, then serum iron and ferritin concentrations decline after midpregnancy. The early pregnancy increases in serum iron and ferritin are likely due to minimal iron demands early on combined with the positive iron balance from amenorrhea (see Fig. 5-6).

The Puerperium

Generally, not all the maternal iron added in the form of hemoglobin is lost with normal delivery. At the time of vaginal delivery, and through the next few days, only approximately half of the added erythrocytes are lost from most women. These normal losses are from the placental implantation site, episiotomy or lacerations, and lochia. On average, maternal erythrocytes corresponding to approximately 500 to 600 mL of predelivery whole blood are lost with vaginal delivery of a single fetus (Pritchard, 1965; Ueland, 1976). The average blood loss associated with cesarean delivery or with the vaginal delivery of twins is about 1000 mL (see Fig. 35-2, p. 760).

Immunological Functions

Pregnancy is thought to be associated with suppression of a variety of humoral and cell-mediated immunological functions to accommodate the "foreign" semiallogeneic fetal graft (Thellin and Heinen, 2003). This is discussed further in Chapter 3 (p. 58). One mechanism appears to involve suppression of T-helper (Th) 1 and T-cytotoxic (Tc) 1 cells, which decreases secretion of interleukin-2 (IL-2), interferon-γ, and tumor necrosis factor-β (TNF-β). There is also evidence that a suppressed Th1 response is requisite for pregnancy continuation. It also may explain pregnancy-related remission of some autoimmune disorders. Examples include rheumatoid arthritis, multiple sclerosis, and autoimmune thyroiditis—which are Th1-mediated diseases (Kumru and colleagues, 2005). As discussed in Chapter 34 (p. 711), failure of Th1 immune suppression may be related to development of preclampsia (Jonsson and co-workers, 2006).

Not all aspects of immunological function are depressed. For example, there is upregulation of Th2 cells to increase secretion of IL-4, IL-6, and IL-13 (Michimata and colleagues, 2003). In cervical mucus, peak levels of immunoglobulins A and G (IgA and IgG) are significantly higher during pregnancy. Similarly, the amount of interleukin-1β found in cervical mucus during pregnancy is approximately 10-fold greater than in nonpregnant women. Because oral contraceptives have been shown to induce similar changes, Kutteh and Franklin (2001) hypothesized that changes in the cervical mucus may be a result of estrogen and progesterone. Although these changes may be important for fetal protection, their actual clinical significance is unclear.

Leukocytes

Some polymorphonuclear leukocyte chemotaxis and adherence functions are depressed beginning in the second trimester and continuing throughout pregnancy (Krause and associates, 1987). Although incompletely understood, this may be partly related to the finding that relaxin (see p. 110) impairs neutrophil activation (Masini and co-workers, 2004). It is possible that these depressed leukocyte functions of pregnant women also account in part for the improvement of some autoimmune disorders and possible increased susceptibility to certain infections.

Although the leukocyte count varies considerably during pregnancy, usually it ranges from 5000 to 12,000/μL. During labor and the early puerperium, it may become markedly elevated, attaining levels of 25,000/μL or even more, however, it averages 14,000 to 16,000/μL (Taylor and co-workers, 1981). The cause for the marked increase is not known, but the same response occurs during and after strenuous exercise. It probably represents the reappearance of leukocytes previously shunted out of active circulation. Interestingly, increasing numbers of immune cells are also found in the uterine wall during normal pregnancy. Garfield and co-workers (2006) have found that these cells, especially mast cells, may play an important role in mediating uterine contractility.

In addition to normal variations in the leukocyte count, the distribution of cell types is altered significantly during pregnancy. Specifically, during the third trimester, the percentages of granulocytes and CD8 T lymphocytes are significantly increased along with a concomitant reduction in the percentages of CD4 T lymphocytes and monocytes. Moreover, circulating leukocytes undergo significant phenotypic changes including, for example, the upregulation of certain adhesion molecules (Luppi and associates, 2002).

Inflammatory Markers

Many tests performed to diagnose inflammation cannot be used reliably during pregnancy. For example, leukocyte alkaline phosphatase levels are used to evaluate myeloproliferative disorders and are increased beginning early in pregnancy. The concentration of C-reactive protein, an acute-phase serum reactant, rises rapidly to 1000-fold in response to tissue trauma or inflammation. Watts and colleagues (1991) measured C-reactive protein levels across pregnancy and found that median values were higher than for nonpregnant women. Levels were elevated further in labor. In women not in labor, 95 percent had levels of 1.5 mg/dL or less, 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 globulins and fibrinogen (Hyttén and Leitch, 1971). Lastly, complement factors C3 and C4 also are significantly elevated during the second and third trimesters (Gallery and colleagues, 1981; Richani and associates, 2005).

Coagulation and Fibrinolysis

During normal pregnancy, both coagulation and fibrinolysis are augmented but remain balanced to maintain hemostasis. They are even more enhanced in multifetal gestation (Morikawa and colleagues, 2006). Evidence of activation includes increased concentrations of all clotting factors, except factors XI and XIII, and increased levels of high-molecular-weight fibrinogen complexes (Table 5-2). The clotting time of whole blood, however, does not differ significantly in normal pregnant women. Considering the substantive physiological increase in plasma volume in normal pregnancy, such increased concentrations represent a markedly augmented production of these procoagulants. For example, plasma fibrinogen (factor I) in normal nonpregnant women averages about 300 mg/dL and ranges from 200 to 400 mg/dL.
During normal pregnancy, fibrinogen concentration increases approximately 50 percent. It averages 450 mg/dL late in pregnancy, with a range from 300 to 600 mg/dL. The percentage of high-molecular-weight fibrinogen is unchanged (Manten and colleagues, 2004). This contributes greatly to the striking increase in the erythrocyte sedimentation rate as discussed previously. Some of the pregnancy-induced changes in the levels of coagulation factors can be duplicated by the administration of estrogen plus progesterin contraceptive tablets to nonpregnant women.

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 causes fibrinolysis and produces fibrin degradation products such as D-dimers. Studies of the fibrinolytic system in pregnancy have produced conflicting results, although most evidence suggests that fibrinolytic activity is actually reduced (Holmes and Wallace, 2005). These changes—which may indicate that the fibrinolytic system is impaired—are countered by increased levels of plasminogen and decreased levels of another plasmin inhibitor type 1 (PAI-1) and type 2 (PAI-2), which inhibit tPA and regulate fibrin degradation by plasmin, increase during normal pregnancy (Baker and colleagues, 2004). This contributes greatly to the striking increase in the erythrocyte sedimentation rate as discussed previously. Some of the pregnancy-induced changes in the levels of coagulation factors can be duplicated by the administration of estrogen plus progesterone contraceptive tablets to nonpregnant women.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Nonpregnant</th>
<th>Pregnant (35–40 weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Activated PTT (sec)</td>
<td>31.6 ± 4.9</td>
<td>31.9 ± 2.9</td>
</tr>
<tr>
<td>Thrombin time (sec)</td>
<td>18.9 ± 2.0</td>
<td>22.4 ± 4.3</td>
</tr>
<tr>
<td>Fibrinogen (mg/dL)</td>
<td>256 ± 58</td>
<td>473 ± 72</td>
</tr>
<tr>
<td>Factor VII (%)</td>
<td>99.3 ± 19.4</td>
<td>181.4 ± 48.0</td>
</tr>
<tr>
<td>Factor X (%)</td>
<td>97.7 ± 15.4</td>
<td>144.5 ± 20.1</td>
</tr>
<tr>
<td>Plasminogen (%)</td>
<td>105.5 ± 14.1</td>
<td>136.2 ± 19.5</td>
</tr>
<tr>
<td>tPA (ng/mL)</td>
<td>5.7 ± 3.6</td>
<td>5.0 ± 1.5</td>
</tr>
<tr>
<td>Antithrombin III (%)</td>
<td>98.9 ± 13.2</td>
<td>97.5 ± 33.3</td>
</tr>
<tr>
<td>Protein C (%)</td>
<td>77.2 ± 12.0</td>
<td>62.9 ± 20.5</td>
</tr>
<tr>
<td>Total Protein S (%)</td>
<td>75.6 ± 14.0</td>
<td>49.9 ± 10.2</td>
</tr>
</tbody>
</table>

*Statistically significant difference.
Data shown as mean ± standard deviation.


### Platelets

Normal pregnancy also involves changes in platelets (Baker and Cunningham, 1999). In a study of almost 7000 healthy women at term, Boehlen and associates (2000) found that the average platelet count was decreased slightly during pregnancy to 213,000/μL compared with 250,000/μL in nonpregnant control women. They defined thrombocytopenia as below the 2.5th percentile, which corresponded to a platelet count of 116,000/μL. Decreased platelet concentrations are partially due to the effects of hemodilution. However, they also likely represent increased platelet consumption, leading to a greater proportion of younger, and therefore, larger platelets (Tygart and co-workers, 1986). Further supporting this concept, Hayashi and associates (2002) found that beginning in midpregnancy, production of thromboxane A2, which induces platelet aggregation, progressively increases.

### Regulatory Proteins

There are a number of natural inhibitors of coagulation, including proteins C, S, and Z 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 detail in Chapter 47.

**Activated protein C**, along with the co-factors protein S and factor V, functions as an anticoagulant by neutralizing the procoagulants factor Va and factor VIIIa (see Fig. 47-1, p. 1016). At the same time, resistance to activated protein C increases progressively and is related to a concomitant decrease in free protein S and increase in factor VIII. Between the first and third trimesters, levels of activated protein C decrease from about 2.4 to 1.9 U/mL, and free protein S decreases from 0.4 to 0.16 U/mL (Walker and colleagues, 1997). Oral contraceptives also decrease free protein S levels. **Protein Z** is a vitamin-K dependent glycoprotein that inhibits activation of factor X. Quack Loetscher and co-workers (2005) reported a 20-percent increase across pregnancy. Effraimidou and associates (2009) have speculated that low protein Z levels may prove to be a risk factor for otherwise unexplained recurrent early pregnancy loss. Levels of **antithrombin** remain relatively constant throughout gestation and the early puerperium (Delorme and associates, 1992).

### Spleen

By the end of normal pregnancy, the splenic area enlarges by up to 50 percent compared with the first trimester. The echogenic...
appearance of the spleen remains homogeneous throughout gestation (Maymon and co-workers, 2007).

**CARDIOVASCULAR SYSTEM**

During pregnancy and the puerperium, the heart and circulation undergo remarkable physiological adaptations. Changes in cardiac function become apparent during the first 8 weeks of pregnancy (McLaughlin and Roberts, 1999). Cardiac output is increased as early as the fifth week and reflects a reduced systemic vascular resistance and an increased heart rate. The resting pulse rate increases about 10 beats/min during pregnancy (Stein and co-workers, 1999). Between weeks 10 and 20, plasma volume expansion begins and preload is increased. Ventricular performance during pregnancy is influenced by both the decrease in systemic vascular resistance and changes in pulsatile arterial flow. As discussed subsequently, multiple factors contribute to these changes in overall hemodynamic function and allow the cardiovascular system to adjust to the physiological demands of the fetus while maintaining maternal cardiovascular integrity. These changes during the last half of pregnancy are graphically summarized in Figure 5-7, which also shows the important effects of maternal posture on hemodynamic events during pregnancy.

**Heart**

As the diaphragm becomes progressively elevated, the heart is displaced to the left and upward and rotated somewhat on its long axis. As a result, the apex is moved somewhat laterally from its usual position, causing a larger cardiac silhouette on chest radiograph (Fig. 5-8). Furthermore, pregnant women normally have some degree of benign pericardial effusion, which may increase the cardiac silhouette (Enein and colleagues, 1987). Variability of these factors makes it difficult to precisely identify moderate degrees of cardiomegaly by simple radiographic studies. Normal pregnancy induces no characteristic electrocardiographic changes other than slight left-axis deviation as a result of the altered heart position.

Many of the normal cardiac sounds are altered during pregnancy. Cutforth and MacDonald (1966) used phonocardiography and documented: (1) an exaggerated splitting of the first heart sound with 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 (Fig. 44-1, p. 960). They heard a systolic murmur in 90 percent of pregnant women that was intensified during inspiration in some or expiration in others, and disappeared shortly after delivery. A soft diastolic murmur was noted transiently in 20 percent, and continuous murmurs arising from the breast vasculature in 10 percent.

The increased plasma volume during normal pregnancy, which was discussed previously (p. 115), leads to several reversible morphological and functional adaptations. There is no doubt that the heart is capable of remodeling in response to stimuli such as hypertension and exercise. Cardiac plasticity likely is a continuum that encompasses physiological growth, such as that in exercise, as well as pathological hypertrophy—such as with hypertension (Hill and Olson, 2008). And although it is widely held that there is physiological hypertrophy of cardiac myocytes as a result of pregnancy, this has never been absolutely proven. For example, in one study, Schannwell and associates (2002) performed serial echocardiographic examinations across pregnancy and postpartum in 46 healthy women and found a 34-percent greater left ventricular muscle mass index during late versus early pregnancy. These and earlier studies with similar findings were derived with echocardiography but have not been verified with the more precise techniques of magnetic resonance.
imaging. Hibbard and colleagues (2009) concluded that any increased mass does not meet criteria for hypertrophy.

**Cardiac Output**

During normal pregnancy, mean arterial pressure and vascular resistance decrease, while blood volume and basal metabolic rate increase. As a result, cardiac output at rest, when measured in the lateral recumbent position, increases significantly beginning in early pregnancy (Duvekot and colleagues, 1993; Mabie and co-workers, 1994). It continues to increase and remains elevated during the remainder of pregnancy (Fig. 5-9).

During late pregnancy with the woman in the supine position, the large pregnant uterus rather consistently compresses venous return from the lower body. It also may compress the aorta (Bierniarz and associates, 1968). The results are that cardiac filling may be reduced with diminished cardiac output (see Fig. 5-7). Specifically, Bamber and Dresner (2003) found cardiac output at term to increase 1.2 L/min—almost 20 percent—when a woman was moved from her back onto her left side. Moreover, in the supine gravid patient, uterine blood flow estimated by Doppler velocimetry decreases by a third (Jeffreys and associates, 2006). Of note, Simpson and James (2005) found that fetal oxygen saturation is approximately 10 percent higher when a laboring woman is in a lateral recumbent position compared with supine. Upon standing, cardiac output falls to the same degree as in the nonpregnant woman (Easterling and associates, 1988).

In multifetal pregnancies, compared with singletons, maternal cardiac output is augmented further by another almost 20 percent because of a greater stroke volume (15 percent) and heart rate (3.5 percent). Left atrial diameter and left ventricular end-diastolic diameter are also increased due to augmented preload (Kametas and co-workers, 2003a). The increased heart rate and inotropic contractility imply that cardiovascular reserve is reduced in multifetal gestations.

During the first stage of labor, cardiac output increases moderately. During the second stage, with vigorous expulsive efforts, it is appreciably greater (see Fig. 5-9). The pregnancy-induced increase is lost after delivery, at times dependent on blood loss.

**Hemodynamic Function in Late Pregnancy**

To further elucidate the net changes of normal pregnancy-induced cardiovascular changes, Clark and colleagues (1989) conducted invasive studies to measure hemodynamic function late in pregnancy (Table 5-3). Right heart catheterization was performed in 10 healthy nulliparous women at 35 to 38 weeks, 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 decreased significantly, as did colloid osmotic pressure. Pulmonary capillary wedge pressure and central venous pressure did not change appreciably between late pregnancy and the puerperium. Thus, as shown in Figure 5-10, although cardiac output is increased, left ventricular function as measured by stroke work index remains similar to the nonpregnant normal range. Put another way, normal pregnancy is not a continuous “high-output” state.

**Circulation and Blood Pressure**

Changes in posture affect arterial blood pressure. Brachial artery pressure when sitting is lower than that when in the lateral recumbent supine position (Bamber and Dresner, 2003). Arterial pressure usually decreases to a nadir at 24 to 26 weeks and rises thereafter. Diastolic pressure decreases more than systolic (Fig. 5-11).

Antecubital venous pressure remains unchanged during pregnancy. However, in the supine position, femoral venous pressure rises steadily, from approximately 8 mm Hg early in pregnancy to 24 mm Hg at term. Wright and co-workers (1950) demonstrated that venous blood flow in the legs is retarded during pregnancy except when the lateral recumbent position is assumed. This tendency toward stagnation of blood in the lower extremities during the latter part of pregnancy is attributable to the 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 (McLennan, 1943). These alterations contribute to the dependent edema frequently experienced and to the development of varicose veins in the legs and vulva, as well as hemorrhoids. They also predispose to deep-venous thrombosis (see Chap. 47, p. 1019).
Renin, Angiotensin II, and Plasma Volume

The renin-angiotensin-aldosterone axis is intimately involved in renal control of blood pressure via sodium and water balance. All components of this system are increased in normal pregnancy (Bentley-Lewis and co-workers, 2005). Renin is produced by both the maternal kidney and the placenta, and increased renin substrate (angiotensinogen) is produced by both maternal and fetal liver. This increase in angiotensinogen results, in part, from high levels of estrogen production during normal pregnancy. August and colleagues (1995) observed that stimulation of the renin-angiotensin system is important in first-trimester blood pressure maintenance.

Gant and associates (1973) studied vascular reactivity to angiotensin II throughout pregnancy. Nulliparas who remained supine for extended periods experienced arterial hypotension, sometimes referred to as the supine hypotensive syndrome (Kinsella and Lohmann, 1994). Also when supine, uterine arterial pressure—and thus blood flow—is significantly lower than that in the brachial artery. As discussed in Chapter 18 (p. 432), this may directly affect fetal heart rate patterns (Tamás and colleagues, 2007). This also occurs with hemorrhage or with spinal analgesia (see Chap. 19, p. 452).

Supine Hypotension

In about 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 (Kinsella and Lohmann, 1994). Also when supine, uterine arterial pressure—and thus blood flow—is significantly lower than that in the brachial artery. As discussed in Chapter 18 (p. 432), this may directly affect fetal heart rate patterns (Tamás and colleagues, 2007). This also occurs with hemorrhage or with spinal analgesia (see Chap. 19, p. 452).

**TABLE 5-3. Central Hemodynamic Changes in 10 Normal Nulliparous Women Near Term and Postpartum**

<table>
<thead>
<tr>
<th></th>
<th>Pregnant (35–38 wks)</th>
<th>Postpartum (11–13 wks)</th>
<th>Changeb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>90 ± 6</td>
<td>86 ± 8</td>
<td>NSC</td>
</tr>
<tr>
<td>Pulmonary capillary wedge pressure (mm Hg)</td>
<td>8 ± 2</td>
<td>6 ± 2</td>
<td>NSC</td>
</tr>
<tr>
<td>Central venous pressure (mm Hg)</td>
<td>4 ± 3</td>
<td>4 ± 3</td>
<td>NSC</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>83 ± 10</td>
<td>71 ± 10</td>
<td>+17%</td>
</tr>
<tr>
<td>Cardiac output (L/min)</td>
<td>6.2 ± 1.0</td>
<td>4.3 ± 0.9</td>
<td>+43%</td>
</tr>
<tr>
<td>Systemic vascular resistance (dyne/sec/cm²)</td>
<td>1210 ± 266</td>
<td>1530 ± 520</td>
<td>−21%</td>
</tr>
<tr>
<td>Pulmonary vascular resistance (dyne/sec/cm²)</td>
<td>78 ± 22</td>
<td>119 ± 47</td>
<td>−34%</td>
</tr>
<tr>
<td>Serum colloid osmotic pressure (mm Hg)</td>
<td>18.0 ± 1.5</td>
<td>20.8 ± 1.0</td>
<td>−14%</td>
</tr>
<tr>
<td>COP-PCWP gradient (mm Hg)</td>
<td>10.5 ± 2.7</td>
<td>14.5 ± 2.5</td>
<td>−28%</td>
</tr>
<tr>
<td>Left ventricular stroke work index (g/m/m²)</td>
<td>48 ± 6</td>
<td>41 ± 8</td>
<td>NSC</td>
</tr>
</tbody>
</table>

aMeasured in lateral recumbent position.
bChanges significant unless NSC = no significant change.
COP = colloid osmotic pressure; PCWP = pulmonary capillary wedge pressure.
Adapted from Clark and colleagues (1989), with permission.

Renin, Angiotensin II, and Plasma Volume

The renin-angiotensin-aldosterone axis is intimately involved in renal control of blood pressure via sodium and water balance. All components of this system are increased in normal pregnancy (Bentley-Lewis and co-workers, 2005). Renin is produced by both the maternal kidney and the placenta, and increased renin substrate (angiotensinogen) is produced by both maternal and fetal liver. This increase in angiotensinogen results, in part, from high levels of estrogen production during normal pregnancy. August and colleagues (1995) observed that stimulation of the renin-angiotensin system is important in first-trimester blood pressure maintenance.

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**FIGURE 5-10** 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. (Figure from Hauth and Cunningham, 1999; data from Clark and colleagues, 1989.)

**FIGURE 5-11** Sequential changes (±SEM) in blood pressure throughout pregnancy in 69 women in supine (blue lines) and left lateral recumbent positions (red lines). PP = postpartum. (Adapted from Wilson and colleagues, 1980.)
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. Follow-up studies by Gant (1974) and Cunningham (1975) and their associates indicated that increased refractoriness to angiotensin II resulted from individual vessel refractoriness. Said another way, the abnormally increased sensitivity was an alteration in vessel wall refractoriness rather than the consequence of altered blood volume or renin-angiotensin secretion.

The vascular responsiveness to angiotensin II may be progesterone related. Normally, pregnant women lose their acquired vascular refractoriness to angiotensin II within 15 to 30 minutes after the placenta is delivered. Moreover, large amounts of intramuscular progesterone given during late labor delay this diminishing refractoriness. And although exogenous progesterone does not restore angiotensin II refractoriness to women with gestational hypertension, this can be done with infusion of its major metabolite—5α-dihydroprogesterone.

**Cardiac Natriuretic Peptides**

At least two species of these—atrial natriuretic peptide (ANP) and B-type 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 (Clerico and Emdin, 2004). In nonpregnant patients, levels of BNP as well as amino-terminal pro-brain natriuretic peptide—or Nt-pro-BNP—may be useful in screening for depressed left ventricular systolic function and determining prognosis in chronic heart failure (Heidenreich and associates, 2004; Jarolim, 2006).

During normal pregnancy, plasma ANP levels are maintained in the nonpregnant range despite increased plasma volume (Lowe and co-workers, 1992). In one study, Resnik and co-workers (2005) found that median BNP levels are less than 20 pg/mL and are stable across normal pregnancy. However, these levels are increased in severe preeclampsia. Tihtonen and colleagues (2007) concluded that this resulted from cardiac strain caused by high afterload. It would appear that ANP-induced physiological adaptations participate in the expansion of extracellular fluid volume and the increase in plasma aldosterone concentrations characteristic of normal pregnancy.

A third species, C-type natriuretic peptide (CNP), is predominantly secreted by noncardiac tissues. Among its diverse biological functions, this peptide appears to be a major regulator of fetal bone growth. Walther and Stepan (2004) have provided a detailed review of its role during pregnancy.

**Prostaglandins**

Increased production of prostaglandins during pregnancy is thought to have a central role in control of vascular tone, blood pressure, and sodium balance (Gallery and Lindheimer, 1999). Renal medullary prostaglandin E2 synthesis is increased markedly during late pregnancy and is presumed to be natriuretic. Prostacyclin (PGI2), the principal prostaglandin of endothelium, also is increased during late pregnancy and regulates blood pressure and platelet function. It also has been implicated in the angiotensin resistance characteristic of normal pregnancy (Friedman, 1988). The ratio of PGI2 to thromboxane in maternal urine and blood has been considered important in the pathogenesis of preeclampsia (see Chap. 34, p. 714).

**Endothelin**

There are a number of endothelins generated in pregnancy. Endothelin-1 is a potent vasoconstrictor produced in endothelial and vascular smooth muscle cells and regulates local vasomotor tone (Feletou and Vanhoucke, 2006). Its production is stimulated by angiotensin II, arginine vasopressin, and thrombin. Endothelins, in turn, stimulate secretion of ANP, aldosterone, and catecholamines. As discussed in Chapter 6 (p. 161), there are endothelin receptors in pregnant and nonpregnant myometrium. Endothelins also have been identified in the amnion, amniotic fluid, decidua, and placental tissue (Kubota and colleagues, 1992; Margarit and associates, 2005). Vascular sensitivity to endothelin-1 is not altered during normal pregnancy (Ajne and associates, 2005). These investigators postulated that vasodilating factors counterbalance the endothelin-1 vasoconstrictor effects and produce reduced peripheral vascular resistance.

**Nitric Oxide**

This potent vasodilator is released by endothelial cells and may have important implications for modifying vascular resistance during pregnancy (Seligman and colleagues, 1994). As discussed in Chapter 34 (p. 714), abnormal nitric oxide synthesis has been linked to the development of preeclampsia (Baksu, 2005; Savvidou, 2003; Teran, 2006, and all their colleagues).

**RESPIRATORY TRACT**

The diaphragm rises about 4 cm during pregnancy (see Fig. 5-8). The subcostal angle widens appreciably as the transverse diameter of the thoracic cage increases approximately 2 cm. The thoracic circumference increases about 6 cm, but not sufficiently to prevent a reduction in the residual lung volume created by the elevated diaphragm. Diaphragmatic excursion is actually greater in pregnant than in nonpregnant women.

**Pulmonary Function**

The respiratory rate is essentially unchanged, but tidal volume and resting minute ventilation increase significantly as pregnancy advances. In a study of 51 healthy pregnant women, Kolarzyk and co-workers, (2005) reported significantly increased mean tidal volume—0.66 to 0.8 L/min—and minute ventilation—10.7 to 14.1 L/min—compared with nonpregnant women. The increase in minute ventilation is caused by several factors including enhanced respiratory drive primarily due to the stimulatory effects of progesterone, low expiratory reserve volume, and compensated respiratory alkalosis (Wise and associates, 2006). These are discussed in more detail subsequently.

The functional residual capacity and the residual volume are decreased as a consequence of the elevated diaphragm (Fig. 5-12). Peak expiratory flow rates decline progressively as gestation advances (Harirah and associates, 2005). Lung compliance is unaffected by pregnancy, but 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 changed. It has been held that this is higher in
pregnancy, but this is disputed (DeSwiet, 1991). The increased
oxygen requirements and perhaps the increased critical closing
volume imposed by pregnancy tend to make respiratory diseases
more serious during gestation (see Chap. 46).

McAuliffe and associates (2002) compared pulmonary func-
tion in 140 women with a singleton pregnancy with that in 68
women with twins. They found no significant differences be-
tween the two groups.

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, increases appreciably during
normal pregnancy, as does cardiac output. As a consequence,
the maternal arteriovenous oxygen difference is decreased.

Acid–Base Equilibrium
An increased awareness of a desire to breathe is common even
evry early in pregnancy (Milne and colleagues, 1978). This may be
interpreted as dyspnea, which may suggest pulmonary or car-
diac abnormalities when none exist. This physiological dyspnea
is thought to result from increased tidal volume that lowers the
blood P CO₂ slightly, which paradoxically causes dyspnea. The
increased respiratory effort, and in turn the reduction in P CO₂,
during pregnancy is most likely induced in large part by proges-
terone and to a lesser degree by estrogen. Progesterone appears
to act centrally, where it lowers the threshold and increases the
sensitivity of the chemoreflex response to CO₂ (Jensen and as-
sociates, 2005).

To compensate for the resulting respiratory alkalosis, plasma
bicarbonate levels decrease from 26 to approximately 22
mmol/L. Although blood pH is increased only minimally, it
does shift the oxygen dissociation curve to the left. This shift in-
creases the affinity of maternal hemoglobin for oxygen—the
Bohr effect—thereby decreasing the oxygen-releasing capacity of
maternal blood. This is offset because the slight pH increase also
stimulates an increase in 2,3-diphosphoglycerate in maternal erythrocytes. This shifts the curve back to the right (Tsai and de Leeuw, 1982). Thus, reduced PCO₂ from maternal hyperventilation aids carbon dioxide (waste) transfer from the fetus to the mother while also facilitating oxygen release to the fetus.

**URINARY SYSTEM**

**Kidney**

A remarkable number of changes are observed in the urinary system as a result of pregnancy (Table 5-4). Kidney size increases slightly. Using radiographs, Bailey and Rolleston (1971) reported that the kidney was 1.5 cm longer during the early puerperium compared with 6 months later. The glomerular filtration rate (GFR) and renal plasma flow increase early in pregnancy. The GFR increases as much as 25 percent by the second week after conception and 50 percent by the beginning of the second trimester. Renal plasma flow increases are even greater (Davison and Noble, 1981; Lindheimer and co-workers, 2001). Animal studies suggest that both relaxin and neuronal nitric oxide synthase may be important for mediating both increased glomerular filtration and plasma flow during pregnancy (Abram and colleagues, 2001; Conrad and associates, 2005). As shown in Figure 5-13, elevated glomerular filtration persists until term, even though renal plasma flow decreases during late pregnancy. Primarily as a consequence of this elevated GFR, approximately 60 percent of women report urinary frequency during pregnancy (Sanhu and associates, 2009).

<table>
<thead>
<tr>
<th>Alteration</th>
<th>Clinical Relevance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kidney size</td>
<td>Approximately 1 cm longer on radiograph</td>
</tr>
<tr>
<td>Dilatation</td>
<td>Resembles hydronephrosis on sonogram or IVP (more marked on right)</td>
</tr>
<tr>
<td>Renal function</td>
<td>Glomerular filtration rate and renal plasma flow increase ~50%</td>
</tr>
<tr>
<td>Maintenance of acid-base</td>
<td>Decreased bicarbonate threshold; progesterone stimulates respiratory center</td>
</tr>
<tr>
<td>Plasma osmolality</td>
<td>Osmoregulation altered: osmotic thresholds for AVP release and thirst decrease; hormonal disposal rates increase</td>
</tr>
</tbody>
</table>

**TABLE 5-4. Renal Changes in Normal Pregnancy**

<table>
<thead>
<tr>
<th>Alteration</th>
<th>Clinical Relevance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kidney size</td>
<td>Size returns to normal postpartum</td>
</tr>
<tr>
<td>Dilatation</td>
<td>Can be confused with obstructive uropathy; retained urine leads to collection errors; renal infections are more virulent; may be responsible for “distension syndrome”; elective pyelography should be deferred to at least 12 weeks postpartum</td>
</tr>
<tr>
<td>Renal function</td>
<td>Serum creatinine decreases during normal gestation; &gt;0.8 mg/dL (&gt;72 μmol/L) creatinine already borderline; protein, amino acid, and glucose excretion all increase</td>
</tr>
<tr>
<td>Maintenance of acid-base</td>
<td>Serum bicarbonate decreased by 4–5 mEq/L; PCO₂ decreased 10 mm Hg; a PCO₂ of 40 mm Hg already represents CO₂ retention</td>
</tr>
<tr>
<td>Plasma osmolality</td>
<td>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</td>
</tr>
</tbody>
</table>

AVP = vasopressin; CO₂ = carbon dioxide; IVP = intravenous pyelography; PCO₂ = partial pressure carbon dioxide. Modified from Lindheimer and colleagues (2000).
Kallikrein, a tissue protease synthesized in cells of the distal renal tubule, is increased in several conditions associated with increased glomerular perfusion in nonpregnant individuals. Platts and colleagues (2000) found increased urinary kallikrein excretion rates in women at 18 and 34 weeks, but excretion returned to nonpregnant levels by term. The significance of these fluctuations remains unknown.

As with blood pressure, maternal posture may have a considerable influence on several aspects of renal function. Late in pregnancy, for instance, urinary flow and sodium excretion average less than half the excretion rate in the supine position compared with that in the lateral recumbent position. The impact of posture on glomerular filtration and renal plasma flow is much more variable.

Loss of Nutrients

One unusual feature of the pregnancy-induced changes in renal excretion is the remarkably increased amounts of various nutrients lost in the urine. Amino acids and water-soluble vitamins are lost in the urine in much greater amounts in pregnancy (Hytten, 1973; Powers and associates, 2004).

Tests of Renal Function

The physiological changes in renal hemodynamics induced during normal pregnancy have several implications for the interpretation of tests of renal function (see Appendix). Serum creatinine levels decrease during normal pregnancy from a mean of 0.7 to 0.5 mg/dL. Values of 0.9 mg/dL suggest underlying renal disease and should prompt further evaluation (Lindheimer and associates, 2000). Creatinine clearance in pregnancy averages about 30 percent higher than the 100 to 115 mL/min in nonpregnant women (Lindheimer and associates, 2000).

Creatinine clearance is a useful test to estimate renal function provided that complete urine collection is made during an accurately timed period. If either is done incorrectly, results are misleading (Davison and colleagues, 1981). During the day, pregnant women tend to accumulate water as dependent edema, and at night, while recumbent, they mobilize this fluid with diuresis. This reversal of the usual nonpregnant diurnal pattern of urinary flow causes nocturia, and the 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 kidney in these circumstances functions perfectly normally by excreting mobilized extracellular fluid of relatively low osmolality.

Urinalysis

Glucosuria during pregnancy may not be abnormal. The appreciable increase in glomerular filtration, together with impaired tubular reabsorptive capacity for filtered glucose, accounts in most cases for glucosuria (Davison and Hytten, 1974). For these reasons alone, Chesley (1963) calculated that about a sixth of pregnant women should spill glucose in the urine. That said, although common during pregnancy, the possibility of diabetes mellitus should not be ignored when glucosuria is identified.

Proteinuria normally is not evident during pregnancy except occasionally in slight amounts during or soon after vigorous labor. Higby and associates (1994) measured protein excretion in 270 normal women throughout pregnancy. Their mean 24-hour excretion was 115 mg, and the upper 95-percent confidence limit was 260 mg/day without significant differences by trimester (Fig. 5-14). These investigators also showed that albumin excretion is minimal and ranges from 5 to 30 mg/day. Nomograms for urinary microalbumin and creatinine ratios during uncomplicated pregnancies have been developed by Waugh and co-workers (2003).

Hematuria is often the result of contamination during collection. If not, it most often suggests urinary tract disease as discussed in Chapter 48 (p. 1033). Hematuria is common after difficult labor and delivery because of trauma to the bladder and urethra.

Ureters

After the uterus rises completely out of the pelvis, it rests upon the ureters, laterally displacing and compressing them at the pelvic brim. This results in increased intrarenal tonus above this level (Rubi and Sala, 1968). Ureteral dilatation is impressive, and Schulman and Herlinger (1975) found it to be greater on the right side in 86 percent of women (Fig. 5-15). Unequal dilatation may result from a cushioning provided the left ureter by the sigmoid colon and perhaps from greater compression of the right ureter as the consequence of dextrorotation of the uterus. The right ovarian vein complex, which is remarkably dilated during pregnancy, lies obliquely over the right ureter and may contribute significantly to right ureteral dilatation.

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

Ureteral elongation accompanies distention, and the ureter is frequently thrown into curves of varying size, the smaller of which may be sharply angulated. These so-called kinks are poorly named, because the term connotes obstruction. They are usually single or double curves, which when viewed in the 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 more gentle curves. Despite these anatomical changes, Semins and associates (2009) concluded, based upon their review of the literature, that complication
rates associated with ureteroscopy in pregnant and nonpregnant patients do not differ significantly.

**Bladder**

There are few significant anatomical changes in the bladder before 12 weeks. From that time onward, however, increased uterine size, the hyperemia that affects all pelvic organs, and the hyperplasia of the bladder’s muscle and connective tissues elevates the bladder trigone and causes thickening of its posterior, or intraperitoneal, margin. Continuation of this process to the end of pregnancy produces marked deepening and widening of the trigone. There are no mucosal changes other than an increase in the size and tortuosity of its blood vessels.

Using urethrocytometry, Iosif and colleagues (1980) reported that bladder pressure in primigravidas increased from 8 cm H₂O early in pregnancy to 20 cm H₂O at term. To compensate for reduced bladder capacity, absolute and functional urethral lengths increased by 6.7 and 4.8 mm, respectively. At the same time, maximal intravesical pressure increased from 70 to 93 cm H₂O, and thus continence is maintained. Still, at least half of women experience some degree of urinary incontinence by the third trimester (van Brummen and colleagues, 2006; Wesnes and co-workers, 2009). Indeed, this is always considered in the differential diagnosis of ruptured membranes.

Toward the end of pregnancy, particularly in nulliparas in whom the presenting part often engages before labor, the entire base of the bladder is pushed forward and upward, converting the normal convex surface into a concavity. As a result, difficulties in diagnostic and therapeutic procedures are greatly increased. In addition, the pressure of the presenting part impairs the drainage of blood and lymph from the bladder base, often rendering the area edematous, easily traumatized, and probably more susceptible to infection.

**GASTROINTESTINAL TRACT**

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

*Gastric emptying time*, studied using acetaminophen absorption techniques, appears to be unchanged during each trimester and during comparison with nonpregnant women (Macfie and colleagues, 1991; Wong and associates, 2002, 2007). During labor, however, and especially after administration of analgesic agents, gastric emptying time may be prolonged appreciably. As a result, a major danger of general anesthesia for delivery is regurgitation and aspiration of either food-laden or highly acidic gastric contents (see Chap. 19, p. 459).

*Pyrosis* (heartburn) is common during pregnancy and is most likely caused by reflux of acidic secretions into the lower esophagus (see Chap. 49, p. 1052). Although the altered position of the stomach probably contributes to its frequent occurrence, lower esophageal sphincter tone also is decreased. In addition, intraesophageal pressures are lower and intragastric pressures higher in pregnant women. At the same time, esophageal peristalsis has lower wave speed and lower amplitude (Ulmsten and Sundström, 1978).

The gums may become hyperemic and softened during pregnancy and may bleed when mildly traumatized, as with a toothbrush. A focal, highly vascular swelling of the gums, the so-called *epulis* of pregnancy, develops occasionally but typically regresses spontaneously after delivery. Most evidence indicates that pregnancy does not incite tooth decay.

*Hemorrhoids* are fairly common during pregnancy. They are caused in large measure by constipation and elevated pressure in veins below the level of the enlarged uterus (see Fig. 2-7, p. 21).
Liver
Unlike in some animals, there is no increase in liver size during human pregnancy (Combes and Adams, 1971). Hepatic blood flow, however, increases substantively as does the diameter of the portal vein (Clapp and colleagues, 2000). Histological evaluation of liver biopsies, including examination with the electron microscope, has shown no distinct morphological changes in normal pregnant women (Ingerslev and Telium, 1946).

Some laboratory test results of hepatic function are altered during normal pregnancy, and some would be considered abnormal for nonpregnant patients. Total alkaline phosphatase activity almost doubles, but much of the increase is attributable to heat-stable placental alkaline phosphatase isozymes. Serum aspartate transaminase (AST), alanine transaminase (ALT), γ-glutamyl transferase (GGT), and bilirubin levels are slightly lower compared with nonpregnant values (Girling and colleagues, 1997; Ruiz-Extremera and associates, 2005).

The concentration of serum albumin decreases during pregnancy. By late pregnancy, albumin concentrations may be near 3.0 g/dL compared with approximately 4.3 g/dL in nonpregnant women (Mendenhall, 1970). Total albumin is increased, however, because of a greater volume of distribution from plasma volume increase. There is also a slight increase in serum globulin levels.

Leucine aminopeptidase is a proteolytic liver enzyme whose serum levels may be increased with liver disease. Its activity is markedly elevated in pregnant women. The increase, however, results from the appearance of a pregnancy-specific enzyme(s) with distinct substrate specificities (Song and Kappas, 1968). Pregnancy-induced aminopeptidase has oxytocinase and vasopressinase activity which occasionally causes transient diabetes insipidus (see Chap. 53, p. 1139).

Gallbladder
During normal pregnancy, the contractility of the gallbladder is reduced, leading to an increased residual volume (Braverman and co-workers, 1980). This may be because progesterone impairs gallbladder contraction by inhibiting cholecystokinin-mediated smooth muscle stimulation, which is the primary regulator of gallbladder contraction. Impaired emptying leads to stasis, which associated with increased bile cholesterol saturation of pregnancy, contributes to the increased prevalence of cholesterol gallstones in multiparous women.

The effects of pregnancy on maternal bile acid serum concentrations have been incompletely characterized despite the long-acknowledged propensity for pregnancy to cause intrahepatic cholestasis and pruritus gravidarum from retained bile salts. Intrahepatic cholestasis has been linked to high circulating levels of estrogen, which inhibit intraductal transport of bile acids (Simon and colleagues, 1996). In addition, increased progesterone and genetic factors have been implicated in the pathogenesis (Lammert and associates, 2000). Cholestasis of pregnancy is described in greater detail in Chapter 50 (p. 1073).

ENDOCRINE SYSTEM
Some of the most important endocrine changes of pregnancy are discussed elsewhere, especially in Chapter 3.

Pituitary Gland
During normal pregnancy, the pituitary gland enlarges by approximately 135 percent (Gonzalez and colleagues, 1988). Although it has been suggested that the increase may be sufficient to compress the optic chiasma and reduce visual fields, impaired vision due to physiological pituitary enlargement during normal pregnancy is rare (Inoue and associates, 2007). Scheithauer and colleagues (1990) have provided evidence that the incidence of pituitary prolactinomas is not increased during pregnancy. When these tumors are large before pregnancy—a macroadenoma is 10 mm or greater—then enlargement during pregnancy is more likely (see Chap. 53, p. 1139).

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

Growth Hormone
During the first trimester, growth hormone is secreted predominantly from the maternal pituitary gland, and concentrations in serum and amnionic fluid are within nonpregnant values of 0.5 to 7.5 ng/mL (Kletzky and associates, 1985). As early as 8 weeks, growth hormone secreted from the placenta becomes detectable (Lønberg and co-workers, 2003). By approximately 17 weeks, the placenta is the principal source of growth hormone secretion (Obuobie and co-workers, 2001). Maternal serum values increase slowly from approximately 3.5 ng/mL at 10 weeks to plateau after 28 weeks at approximately 14 ng/mL. Growth hormone in amnionic fluid peaks at 14 to 15 weeks 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 syncytiotrophoblasts in a nonpulsatile fashion (Fuglsang and co-workers, 2006). The regulation and physiological effects of placental growth hormone are incompletely understood, but it appears to have some influence on fetal growth as well as the development of preeclampsia (Mittal and co-workers, 2007). For example, placental growth hormone is a major determinant of maternal insulin resistance after midpregnancy. And maternal serum levels correlate positively with birthweight, and negatively with fetal-growth restriction and uterine artery resistance (Chellakooty and colleagues, 2004; Schiessl and associates, 2007). That said, fetal growth still progresses in the complete absence of placental growth hormone. Freemark (2006) concluded that the hormone, although not absolutely essential, may act in concert with human placental lactogen and other somatolactogens to regulate fetal growth.

Prolactin
Maternal plasma levels of prolactin increase markedly during normal pregnancy and concentrations are usually 10-fold greater at
term—about 150 ng/mL—compared with nonpregnant women. Paradoxically, plasma concentrations decrease after delivery even in women who are breast feeding. During early lactation, there are pulsatile bursts of prolactin secretion in response to suckling.

The physiological basis of the marked increase in prolactin prior to parturition is still unclear. What is known is that estrogen stimulation increases the number of anterior pituitary lactotrophs and may stimulate their release of prolactin (Andersen, 1982). Thyroid-releasing hormone also acts to cause an increased prolactin level in pregnant compared with nonpregnant women, but the response decreases as pregnancy advances (Miyamoto, 1984). Serotonin also is believed to increase prolactin, and dopamine—previously known as prolactin-inhibiting factor—inhibits its secretion.

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 increases the number of estrogen and prolactin receptors in these cells. Finally, prolactin promotes mammary alveolar cell RNA synthesis, galactopoiesis, and production of casein, lactalbumin, lactose, and lipids (Andersen, 1982). A woman with isolated prolactin deficiency described by Kauppila and co-workers (1987) failed to lactate after two pregnancies, thus establishing prolactin as a requisite for lactation but not for pregnancy.

Prolactin is present in amniotic fluid in high concentrations. Levels of up to 10,000 ng/mL are found at 20 to 26 weeks. Thereafter, levels decrease and reach a nadir after 34 weeks. There is convincing evidence that the uterine decidua is the site of prolactin synthesis found in amniotic fluid (see Chap. 3, p. 46). Although the exact function of amniotic fluid prolactin is not known, it has been suggested that this prolactin impairs water transfer from the fetus into the maternal compartment, thus preventing fetal dehydration.

### Thyroid Gland

Physiological changes of pregnancy cause the thyroid gland to increase production of thyroid hormones by 40 to 100 percent to meet maternal and fetal needs (Smallridge and associates, 2005). To accomplish this, there are a number of pregnancy-induced changes that are documented.

Anatomically, the thyroid gland undergoes moderate enlargement during pregnancy caused by glandular hyperplasia and increased vascularity. Glinoer and colleagues (1990) reported that mean thyroid volume increased from 12 mL in the first trimester to 15 mL at delivery. Total volume was inversely proportional to serum thyrotropin concentrations. Such enlargement is not pathological, but normal pregnancy does not typically cause significant thyromegaly. Thus, any goiter should be investigated.

A number of alterations in thyroid physiology and function during pregnancy are detailed in Figure 5-16. Beginning early in the first trimester, levels of the principal carrier protein—thyroxine-binding globulin—increases, reaches its zenith at about 20 weeks, and stabilizes at approximately double baseline values for the remainder of pregnancy. Total serum thyroid hormone ($T_4$) increases sharply beginning between 6 and 9 weeks and reaches a plateau at 18 weeks. Free serum $T_4$ levels rise slightly and peak along with hCG levels, and then they return to normal. The rise in total triiodothyronine ($T_3$) is more pronounced up to 18 weeks, and thereafter, it plateaus. Thyroid-releasing hormone (TRH) levels are not increased during normal pregnancy, but this neurotransmitter does cross the placenta and may serve to stimulate the fetal pituitary to secrete thyrotropin (Thorpe-Beeston and associates, 1991).

Interestingly, the secretion of $T_4$ and $T_3$ is not similar for all pregnant women (Glinnoer and associates, 1990). Approximately a third of women experience relative hypothyroxinemia, preferential $T_3$ secretion, and higher, albeit normal, serum thyrotropin levels. Thus, there may be considerable variability in thyroidal adjustments during normal pregnancy.

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**Figure 5-16** Relative changes in maternal thyroid function during pregnancy. Maternal changes include a marked and early increase in hepatic production of thyroxine-binding globulin (TBG) and placental production of chorionic gonadotropin (hCG). Increased thyroxine-binding globulin increases serum thyroxine ($T_4$) concentrations, and chorionic gonadotropin has thyrotropin-like activity and stimulates maternal $T_4$ secretion. The 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. ($T_3 = \text{triiodothyronine}$.) (Modified from Burrow and colleagues, 1994.)
The modifications in serum thyroid-stimulating hormone (TSH)—known also as thyroid-stimulating hormone (TSH)—and chorionic gonadotrophin (hCG) as a function of gestational age also are shown in Figure 3-16. As discussed in Chapter 3 (p. 63), 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 levels cause thyroid stimulation. Indeed, thyrotropin levels decrease in more than 80 percent of pregnant women, whereas they remain in the normal range for nonpregnant women (see p. 1126).

As shown in Figure 5-17, 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 co-workers (2005) conducted a population-based study at Parkland Hospital to develop gestational-age-specific TSH nomograms for both singleton and twin pregnancies.

These complex alterations of thyroid regulation do not appear to alter maternal thyroid status as measured by metabolic studies. Although basal metabolic rate increases progressively during normal pregnancy by as much as 25 percent, most of this increase in 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. Fetal thyroid physiology is discussed in Chapter 4 (p. 97).

Parathyroid Glands

The regulation of calcium concentration is closely interrelated to magnesium, phosphate, parathyroid hormone, vitamin D, and calcitonin physiology. Any alteration of one of these factors is likely to change the others. In a longitudinal investigation of 20 women, More and associates (2003) found that all markers of bone turnover increased during normal pregnancy and failed to reach baseline level by 12 months postpartum. They concluded that the calcium needed for fetal growth and lactation may be drawn at least in part from the maternal skeleton.

Parathyroid Hormone and Calcium

Acute or chronic decreases in plasma calcium or acute decreases in magnesium stimulate the release of parathyroid hormone, whereas increases in calcium and magnesium suppress parathyroid hormone levels. The action of this hormone on bone resorption, intestinal absorption, and kidney reabsorption is to increase extracellular fluid calcium and decrease phosphate.

Parathyroid hormone plasma concentrations decrease during the first trimester and then increase progressively throughout the remainder of pregnancy (Pitkin and associates, 1979). Increased levels likely result from the lower calcium concentration in the pregnant woman. As discussed earlier, this is the result of increased plasma volume, increased glomerular filtration rate, and maternal-fetal transfer of calcium. Ionized calcium is decreased only slightly, and Reitz and co-workers (1977) suggest that during pregnancy a new “set point” is established for ionized calcium and parathyroid hormone. Estrogens also appear to block the action of parathyroid hormone on bone resorption, resulting in another mechanism to increase parathyroid hormone during pregnancy. The net result of these actions is a physiological hyperparathyroidism of pregnancy, likely to supply the fetus with adequate calcium.

Calcitonin and Calcium

The calcitonin-secreting C cells are derived embryologically from the neural crest and are located predominantly in the perilobular areas of the thyroid gland. Calcium and magnesium increase the biosynthesis and secretion of calcitonin. Various gastric hormones—gastrin, pentagastrin, glucagon, and pancreozymin—and food ingestion also increase calcitonin plasma levels.

The known actions of calcitonin generally are considered to oppose those of parathyroid hormone and vitamin D to protect skeletal calcification during times of calcium stress. Pregnancy and lactation cause profound calcium stress, and during these times, calcitonin levels are appreciably higher than those in nonpregnant women (Weiss and co-workers, 1998).

Vitamin D and Calcium

After its ingestion or synthesis in the skin, vitamin D is converted by the liver into 25-hydroxyvitamin D₃. This form then is converted in the kidney, decidua, and placenta to 1,25-dihydroxyvitamin D₃, serum levels of which are increased during normal pregnancy (Weisman and co-workers, 1979; Whitehead and associates, 1981). Most likely this form is the biologically active compound, and it stimulates resorption of calcium from bone and absorption from the intestines. Although its control is unclear, the conversion of 25-hydroxyvitamin D₃ to 1,25-dihydroxyvitamin D₃ is...
facilitated by parathyroid hormone and by low calcium and phosphate plasma levels and is opposed by calcitonin.

- **Adrenal Glands**

  In normal pregnancy, the maternal adrenal glands undergo little, if any, morphological change.

- **Cortisol**

  The serum concentration of circulating cortisol is increased, but much of it is bound by transcortin, the cortisol-binding globulin. The rate of adrenal cortisol secretion is not increased, and probably it is decreased compared with that of the nonpregnant state. The metabolic clearance rate of cortisol, however, is lower during pregnancy because its half-life is nearly doubled over that for nonpregnant women (Migeon and associates, 1957). Administration of estrogen, including most oral contraceptives, causes changes in serum cortisol levels and transcortin similar to those of pregnancy.

  During early pregnancy, the levels of circulating corticotropin (ACTH) are reduced strikingly. As pregnancy progresses, the levels of ACTH and free cortisol rise (Fig. 5-18). This apparent paradox is not understood completely. Nolten and Rueckert (1981) have presented evidence that the higher free cortisol levels observed in pregnancy are the result of a “resetting” of the maternal feedback mechanism to higher levels. They further propose that this might result from tissue refractoriness to cortisol. Keller-Wood and Wood (2001) later suggested that these incongruities may result from an antagonistic action of progesterone on mineralocorticoids. Thus, in response to elevated progesterone levels during pregnancy, an elevated free cortisol is needed to maintain homeostasis. Indeed, experiments in pregnant ewes demonstrate that elevated maternal cortisol and aldosterone secretion are necessary to maintain the normal increase in plasma volume during late pregnancy (Jensen and associates, 2002).

- **Aldosterone**

  As early as 15 weeks, the maternal adrenal glands secrete considerably increased amounts of aldosterone. By the third trimester, about 1 mg/day is secreted. If sodium intake is restricted, aldosterone secretion is elevated even further (Watanabe and co-workers, 1963). At the same time, levels of renin and angiotensin II substrate normally are increased, especially during the latter half of pregnancy. This scenario gives rise to increased plasma levels of angiotensin II, which by acting on the zona glomerulosa of the maternal adrenal glands, accounts for the markedly elevated aldosterone secretion. It has been suggested that the increased aldosterone secretion during normal pregnancy affords protection against the natriuretic effect of progesterone and atrial natriuretic peptide.

- **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 and associates, 1980). This marked elevation is not derived from adrenal secretion but instead represents increased 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.

- **Dehydroepiandrosterone Sulfate**

  Maternal serum and urine levels of dehydroepiandrosterone sulfate are decreased during normal pregnancy. As discussed in Chapter 3 (p. 68), this is a consequence of increased metabolic clearance through extensive maternal hepatic 16α-hydroxylation and placental conversion to estrogen.

- **Androstenedione and Testosterone**

  Maternal plasma levels of both of these androgens are increased during pregnancy. This finding is not totally explained by alterations in their metabolic clearance. Maternal plasma androstenedione and testosterone are converted to estradiol in the placenta, which increases their clearance rates. Conversely, increased plasma sex hormone-binding globulin in pregnant women retards testosterone clearance. Thus, the production rates of maternal testosterone and androstenedione during human pregnancy are increased. The source of this increased C19-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 levels in umbilical cord blood are likely to be undetectable and are the result of the near complete trophoblastic conversion of testosterone to 17β-estradiol (Edman and associates, 1979).

**OTHER SYSTEMS**

- **Musculoskeletal System**

  Progressive lordosis is a characteristic feature of normal pregnancy. Compensating for the anterior position of the enlarging
uterus, the lordosis shifts the center of gravity back over the lower extremities. In a recent and interesting anthropological study, Whitcome and colleagues (2007) demonstrated that this curvature and reinforcement of the lumbar vertebrae have evolved in humans to permit bipedal posture and locomotion despite up to a 31-percent increase in the maternal abdominal mass by term.

The sacroiliac, sacrococcygeal, and pubic joints have increased mobility during pregnancy. As discussed earlier (p. 110), the increase in joint laxity during pregnancy does not correlate with increased maternal serum levels of estradiol, progesterone, or relaxin (Marnach and co-workers, 2003). Joint mobility may contribute to the alteration of maternal posture and in turn may cause discomfort in the lower back. This is especially bothersome late in pregnancy, during which time aching, numbness, and weakness also occasionally are experienced in the upper extremities. This may result from the marked lordosis with anterior neck flexion and slumping of the shoulder girdle, which in turn produce traction on the ulnar and median nerves (Crisp and DeFrancesco, 1964).

The bones and ligaments of the pelvis undergo remarkable adaptation during pregnancy. In 1934, Abramson and colleagues described the normal relaxation of the pelvic joints, and particularly the symphysis pubis, that occurs during pregnancy (Fig. 5-19). They reported that most relaxation takes place in the first half of pregnancy. However, pelvic dimensions measured by magnetic resonance imaging are not significantly different before compared with up to 3 months after delivery (Huerta-Enochian and associates, 2006).

Although some symphyseal separation likely accompanies many deliveries, those greater than 1 cm may cause significant pain (Jain and Sternberg, 2005). Regression begins immediately following delivery, and it is usually complete within 3 to 5 months.

**Eyes**

Intraocular pressure decreases during pregnancy, attributed in part to increased vitreous outflow (Sunness, 1988). 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—have also been observed with a higher than expected frequency during pregnancy. Hormonal effects similar to those observed for skin lesions are postulated to cause this increased pigmentation. Other than transient loss of accommodation reported with both pregnancy and lactation, visual function is unaffected by pregnancy. These changes during pregnancy, as well as pathological eye aberrations, were reviewed by Dinn and colleagues (2003).

**Central Nervous System**

Women often report problems with attention, concentration, and memory throughout pregnancy and the early postpartum period. Systematic studies of memory in pregnancy, however, are limited and often anecdotal. Keenan and colleagues (1998) longitudinally investigated memory in pregnant women as well as a matched control group. They found pregnancy-related memory decline, which was limited to 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. Interestingly, Rana and associates (2006) found that attention and memory were improved in women with preeclampsia receiving magnesium sulfate compared with normal pregnant women.

Zeeman and co-workers (2003) used magnetic resonance imaging to measure cerebral blood flow across pregnancy in 10 healthy women. They found that mean blood flow in the middle and posterior cerebral arteries decreased progressively from 147 and 56 mL/min when nonpregnant to 118 and 44 mL/min late in the third trimester, respectively. The mechanism and clinical significance of this decrease is unknown. Pregnancy does not appear to impact cerebrovascular autoregulation (Bergersen and co-workers, 2006).
Sleep
Beginning as early as about 12 weeks and extending through the first 2 months postpartum, women have difficulty going to sleep, frequent awakenings, fewer hours of night sleep, and reduced sleep efficiency (Lee and colleagues, 2000; Swain and colleagues, 1997). The frequency and duration of sleep apnea episodes were reported to be decreased significantly in pregnant women compared with those postpartum (Trakada and coworkers, 2003). In the supine position, however, average PaO2 levels were lower. The greatest disruption of sleep is encountered postpartum and may contribute to postpartum blues or to frank depression (see Chap. 55, p. 1176).

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S E C T I O N 2

Maternal and Fetal Anatomy and Physiology
The last few hours of human pregnancy are characterized by uterine contractions that effect cervical dilatation and cause the fetus to descend through the birth canal. Long before these forceful, painful contractions, there are extensive preparations in both the uterus and cervix, and these progress throughout gestation. 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 termed softening, yet maintains structural integrity. Following this prolonged uterine quiescence, there is a transitional phase during which myometrial unresponsiveness is suspended, and the cervix undergoes ripening, effacement, and loss of structural integrity.

The physiological processes that regulate parturition and the onset of labor continue to be defined. It is clear, however, that parturition should not be confused with the clinical stages of labor, that is, the first, second, and third stages—which comprise the third phase of parturition (Fig. 6-2).

**Phase 1 of Parturition: Uterine Quiescence and Cervical Softening**

**Uterine Quiescence**

Beginning even before implantation, a remarkably effective period of myometrial quiescence is imposed. This phase normally comprises 95 percent of pregnancy and is characterized by uterine smooth muscle tranquility with maintenance of cervical structural integrity. The inherent propensity of the myometrium to contract is held in abeyance, and uterine muscle is rendered unresponsive to natural stimuli. Concurrently, the uterus must initiate extensive changes in its size and vascularity to accommodate the pregnancy and prepare for uterine contractions in phase 3 of parturition. The myometrial unresponsiveness of phase 1 continues until near the end of pregnancy.

Although some myometrial contractions are noted during the quiescent phase, they do not normally cause cervical dilatation. They are characterized by their unpredictability, low intensity, and brief duration. Any discomfort that they produce usually is...
FIGURE 6-1 The phases of parturition.

FIGURE 6-2 Composite of the average dilatation curve for labor in nulliparous women. The curve is based on analysis of data derived from a large, nearly consecutive series of women. The first stage is divided into a relatively flat latent phase and a rapidly progressive active phase. In the active phase, there are three identifiable component parts: an acceleration phase, a linear phase of maximum slope, and a deceleration phase. (Redrawn from Friedman, 1978.)
Cervical Softening

The cervix has multiple functions during pregnancy that include: (1) maintenance of barrier function to protect the reproductive tract from infection, (2) maintenance of cervical competence despite the increasing gravitational forces imposed by the expanding uterus, and (3) orchestrating extracellular matrix changes that allow progressive increases in tissue compliance in preparation for birth.

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. Thus, the first stage of this remodeling—termed softening—is characterized by an increase in 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 continuation of pregnancy to term. Preterm cervical dilatation, structural incompetence, or both may forecast an unfavorable pregnancy outcome that ends most often in preterm delivery (see Chap. 36, p. 814). Indeed, cervical softening between 16 and 24 weeks has been associated with an increased risk of preterm delivery (Hibbard and associates, 2000; Lams and colleagues, 1996).

Structural Changes with Softening. Cervical softening results from increased vascularity, stromal hypertrophy, glandular hypertrophy and hyperplasia, and compositional or structural changes of the extracellular matrix (Danforth and colleagues, 1974; Leppert, 1995; Liggins, 1978; Word and associates, 2007). Specifically, during phase 1 of parturition, the cervix begins a slow, progressive increase in turnover of matrix components. For example, in mouse models with deficiency of the extracellular matrix protein, thrombospondin 2, collagen fibril morphology is altered and there is premature cervical softening (Kokenyesi and co-workers, 2004).

Another change found in animal models is that physiological softening is preceded by an increase in collagen solubility (Read and associates, 2007). This reflects a change in collagen processing or a change in the number or type of covalent cross-links between collagen triple helices which are normally required for stable collagen fibril formation (Fig. 6-3) (Canty and Kadler, 2005). A reduction in cross-linking of newly synthesized collagen may aid cervical softening because decreased transcripts and activity of the cross-linking enzyme, lysyl oxidase, have been reported in the mouse cervix during pregnancy (Drewes and associates, 2007; Ozasa and colleagues, 1981).

In humans, the clinical importance of these matrix changes is shown by the greater prevalence of cervical incompetence in women with inherited defects in collagen and elastin synthesis or assembly—for example, Ehlers-Danlos and Marfan syndromes (Anum, 2009; Hermanns-Lé, 2005; Paternoster, 1998; Rahman, 2003; Wang, 2006, and all their colleagues).

Cervical Ripening During Phase 2

Prior to the initiation of contractions, the cervix must undergo more extensive remodeling. This eventually results in cervical yielding and dilatation upon initiation of forceful uterine contractions in the third phase of parturition. Cervical modifications during this second phase principally involve connective tissue changes—so-called cervical ripening. The transition from the softening to the ripening phase begins weeks or days before onset of contractions. During this transformation, the total amount and composition of proteoglycans and glycosaminoglycans within the matrix are altered. Many of the processes that aid cervical remodeling are controlled by the same hormones regulating uterine function. That said, the molecular events of each are varied because of differences in cellular composition and physiological requirements. The uterine corpus is predominantly smooth muscle, whereas the cervix is primarily connective tissue. Cellular components of the cervix include smooth muscle, fibroblasts, and epithelia.

Phase 2 of Parturition: Preparation for Labor

To prepare for labor, the myometrial tranquility of phase 1 of parturition must be suspended through what has been called uterine awakening or activation. This process constitutes phase 2 and represents a progression of uterine changes during the last 6 to 8 weeks of pregnancy. Importantly, shifting events associated with phase 2 can cause either preterm or delayed labor. Thus, understanding myometrial and cervical modifications during phase 2 provides a better understanding of events leading to normal and abnormal labor.

Myometrial Changes During Phase 2

Most myometrial changes during phase 2 prepare it for labor contractions. This shift probably results from alterations in the expression of key proteins that control contractility. These contraction-associated proteins (CAPs) include the oxytocin receptor, prostaglandin F receptor, and connexin 43 (Smith, 2007). Thus, myometrial oxytocin receptors markedly increase along with increased numbers and surface areas of gap junction proteins such as connexin 43. Together these lead to increased uterine irritability and responsiveness to uterotonin—agents that stimulate contractions.

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—so-called lightening. The abdomen commonly undergoes a change in shape, sometimes described as “the baby dropped.” It is also likely that the lower segment myometrium is unique from that in the upper uterus segment, resulting in distinct roles for each during labor. This is supported by baboon studies that demonstrate differential expression of prostaglandin receptors within myometrial regions. There are also human studies that report an expression gradient of oxytocin receptors, with higher expression in fundal myometrial cells (Fuchs, 1984; Havelock, 2005; Smith, 2001, and all their colleagues).

Section 2
FIGURE 6-3  Fibrillar collagen synthesis and organization. Three α chains (A) are synthesized to form procollagen. B. Amino terminal and carboxy terminal propeptide (indicated in green) are cleaved from procollagen by specific proteases outside the cell. C. Tropocollagen results from this cleavage. D. Removal of these propeptides results in a decline in solubility of collagen and self-assembly of collagen α chains into fibrils. The enzyme lysyl oxidase catalyzes the formation of nonreducible cross-links between two triple helical regions to make stable collagen fibrils (E). F. Fibrils, in turn, are assembled into collagen fibers. G. Fibril size and packing are regulated in part by small proteoglycans that bind collagen such as decorin. Before cervical ripening, fibril size is uniform, and fibrils are well-packed and organized. H. During cervical ripening, fibril size is less uniform, and spacing between collagen fibrils and fibers is increased and disorganized.
Endocervical Epithelia. During pregnancy, endocervical epithelial cells proliferate such that endocervical glands occupy a significant percentage of cervical mass by the end of pregnancy. The endocervical canal is lined with mucus-secreting columnar and stratified squamous epithelia, which protect against microbial invasion. Mucosal epithelium function as sentinels that recognize antigens, respond in ways that lead to bacterial and viral killing, and signal to underlying immune cells when pathogenic challenge exceeds their protective capacity (Wira and co-workers, 2005). Recent studies in mice suggest that cervical epithelia may also aid cervical remodeling by regulating tissue hydration and maintenance of barrier function. Hydration may be regulated by expression of aquaporins—water channel proteins, whereas paracellular transport of ion and solutes and maintenance of barrier function is regulated by tight junction proteins, such as claudins 1 and 2 (Anderson and colleagues, 2006; Timmons and Mahendra, 2007).

Cervical Connective Tissue. The cervix is made up of only 10 to 15 percent smooth muscle with the remaining tissue comprised primarily of extracellular connective tissue. Constituents of the latter include type I, III, and IV collagen, glycosaminoglycans, proteoglycans, and elastin.

Collagen. This material is the major component of the cervix and it is largely responsible for its structural disposition. Collagen is the most abundant mammalian protein, and it has a complex biosynthesis pathway including at least six enzymes and chaperones to accomplish maturation (see Fig. 6-3). Each collagen molecule is composed of three alpha chains, which wind around each other to form procollagen. Multiple collagen triple-helical molecules are cross-linked to one another by the actions of lysyl oxidase to form long fibrils. Collagen fibrils interact with small proteoglycans such as decorin or biglycan, as well as matricellular proteins such as thrombospondin 2. These interactions determine fibril size, packing, and organization so collagen fibrils are of uniform diameter and are packed together in a regular and highly organized pattern (Canty and associates, 2005). During cervical ripening, collagen fibrils are disorganized, and there is increased spacing between fibrils.

Matrix metalloproteases (MMPs) are proteases capable of degrading extracellular matrix proteins. Of these, collagenase members of the MMP family degrade collagen. Some studies support a role of MMPs in cervical ripening, whereas others suggest that the biomechanical changes are not consistent solely with collagenase activation and loss of collagen. For example, Buhimschi and colleagues (2004) performed tissue biomechanical studies in the rat and suggest that ripening correlates with changes in collagen’s three-dimensional structure rather than its degradation by collagenases. Moreover, mouse and human studies document no changes in collagen content between nonpregnancy and term pregnancy (Myers and associates, 2008; Read and co-workers, 2007).

Collagen solubility—a marker of less mature collagen—is increased early in the cervical softening phase in mice and continues for the remainder of pregnancy (Read and colleagues, 2007). Increased solubility may result in part from a decline in expression of the cross-linking enzyme, lysyl oxidase, during pregnancy (Drewes and associates, 2007; Ozasa and co-workers, 1981). Although collagen solubility has not been determined during cervical softening in early human pregnancy, increased solubility of collagen during cervical ripening has been noted (Granström and colleagues, 1989; Myers and associates, 2008).

Thus, it is possible that dynamic changes in collagen structure rather than collagen content may regulate remodeling. Specifically, ultrastructure analysis by electron microscopy in the rat cervix suggests that collagen dispersion predominates rather than degradation during ripening (Yu and colleagues, 1995). Dispersion of collagen fibrils leads to a loss of tissue integrity and increased tissue compliance. In further support, polymorphisms or mutations in genes required for collagen assembly are associated with an increased incidence of cervical insufficiency (Anum, 2009; Paternoster, 1998; Rahman, 2003; Warren, 2007; and all their colleagues).

Glycosaminoglycans (GAGs). These are high-molecular-weight polysaccharides that contain amino sugars and can form complexes with proteins to form proteoglycans. One glycosaminoglycan is hyaluronan (HA), a carbohydrate polymer whose synthesis is carried out by hyaluronan synthase isoenzymes. In both women and mice, hyaluronan content and hyaluronan synthase 2 expression is increased in the cervix during ripening (Osmers and associates, 1993; Straach and co-workers, 2005).

Hyaluronans’ functions are dependent on size, and the breakdown of large-molecular-weight HA to small-molecular-weight products is carried out by a family of enzymes termed hyaluronidases. Large-molecular-weight HA, which in the mouse cervix predominates during cervical ripening, has a dynamic role in creating and filling space to increase viscoelasticity and matrix disorganization. Low-molecular-weight HA has proinflammatory properties, and studies in mice reveal increases in low-molecular-weight HA during labor and the puerperium (Ruscheinsky and colleagues, 2008). The importance of regulated changes in HA size during cervical ripening and dilatation is supported by a study reporting administration of hyaluronidase to the cervix of term pregnant women. Administration resulted in a reduction in labor duration and a reduced incidence of cesarean delivery due to cervical malfunction (Spallacci and co-workers, 2007). Activation of intracellular signaling cascades and other biological functions requires interactions with cell-associated HA-binding proteins. There are several in the cervix and include the proteoglycan, versican, and the cell surface receptor, CD44 (Ruscheinsky and colleagues, 2008).

Proteoglycans. These glycoproteins are found in abundance in the cervix, and changes in proteoglycan composition within the cervical matrix also accompany cervical ripening. At least two small leucine-rich proteoglycans are expressed in the cervix—decorin and biglycan. Although mRNA content of these two does not change during cervical ripening, changes in proteoglycan content are reported during ripening in support of posttranslational regulation (Westergren-Thorsson and colleagues, 1998). Decorin and other family members interact with collagen and influence the packing and order of collagen fibrils (Ameye and co-workers, 2002). The net result of their decreased expression is a rearrangement of collagen such that collagen fibers are weakened, shortened, and disorganized. Mice
deficient in decorin have loose, fragile skin due to the inability of collagen fibrils to form uniform, packed structures. (Danielson and associates, 1997).

**Inflammatory Changes.** The marked changes within the extracellular matrix during cervical ripening in Phase 2 are accompanied by stromal invasion with inflammatory cells. This has led to a model in which cervical ripening is considered an inflammatory process such that cervical chemoattractants attract inflammatory cells, which in turn release proteases that may aid degradation of collagen and other matrix components. In phase 3 or 4 of parturition, there is increased cervical expression of chemokines and collagenase/protease activity. It was assumed that processes regulating phases 3 and 4 of dilation and postpartum recovery of the cervix were similar to those in phase 2 of cervical ripening (Osman, 2003; Bokström, 1997; Sennström, 2000; Young, 2002, and all their colleagues). This, however, may not be the case. Recent observations from both human and animal studies have challenged the importance of inflammation in initiation of cervical ripening. For example, Sakamoto and associates (2004, 2005) found no correlation between the degree of clinical cervical ripening with cervical interleukin 8 tissue (IL-8) concentrations. Interleukin 8, a cytokine that chemoattracts neutrophils, however, is present in increased levels in cervical tissue collected after vaginal delivery—phases 3 and 4.

Word and colleagues (2005) described an animal model in which parturition fails due to a small rigid cervix despite uterine contractions. Although this model has a robust recruitment of inflammatory cells to the stromal matrix, cervical ripening does not develop. In mouse models, monocyte migration, but not activation, takes place prior to labor (Timmons and Mahendroo, 2006, 2007; Timmons and associates, 2009). Furthermore, tissue depletion of neutrophils before birth has no effect on the timing or success of parturition. Finally, activation of neutrophils, proinflammatory M1 macrophages, and alternatively, activated M2 macrophages is increased within 2 hours after birth, suggesting a role for inflammatory cells in postpartum cervical remodeling.

**Induction and Prevention of Cervical Ripening.** The exact mechanisms that lead to cervical ripening are still being defined, and therapies to prevent premature cervical ripening remain to be identified. Therapies to promote cervical ripening for labor induction include direct application of prostaglandins E2 (PGE2) and F20 (PGF20). These modify collagen and alter relative glycosaminoglycan concentrations. This property is useful clinically to aid labor induction (see Chap. 22, p. 502).

In some nonhuman species, the cascades of events that allow cervical ripening are induced by decreasing serum progesterone concentrations. And in humans, administration of progesterone antagonists causes cervical ripening. As discussed later, humans may have developed unique mechanisms to localize decreases in progesterone action in the cervix and myometrium.

**Phase 3 of Parturition: Labor**

Phase 3 is synonymous with active labor, that is, uterine contractions that bring about progressive cervical dilatation and delivery. Clinically, phase 3 is customarily divided into the three stages of labor. These stages compose the commonly used labor graph shown in Figure 6-2. The clinical stages of labor may be summarized as follows:

1. The first stage begins when widely spaced uterine contractions of sufficient frequency, intensity, and duration are attained to bring about cervical thinning, termed effacement. This labor stage ends when the cervix is fully dilated—about 10 cm—to allow passage of the fetal head. The first stage of labor, therefore, is the stage of cervical effacement and dilatation.
2. The second stage begins when cervical dilatation is complete, and ends with delivery. Thus, the second stage of labor is the stage of fetal expulsion.
3. The third stage begins immediately after delivery of the fetus and ends with the delivery of the placenta. Thus, the third stage of labor is the stage of placental separation and expulsion.

**First Stage of Labor: Clinical Onset of Labor**

In some women, forceful uterine contractions that effect delivery begin suddenly. In others, the initiation of labor 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 “show” or “bloody show.” There is very little blood with the mucous plug, and its passage indicates that labor is already in progress or likely will ensue in hours to days.

**Uterine Labor Contractions.** Unique among physiological muscular contractions, those of uterine smooth muscle during labor are painful. The pain’s cause is not known definitely, but several possibilities have been suggested:

- Hypoxia of the contracted myometrium—such as that with angina pectoris
- Compression of nerve ganglia in the cervix and lower uterus by contracted interlocking muscle bundles
- Stretching of the cervix during dilatation
- Stretching of the peritoneum overlying the fundus.

Compression of nerve ganglia in the cervix and lower uterine segment by the contracting myometrium is an especially attractive hypothesis. Paracervical infiltration with a local anesthetic usually produces appreciable pain relief with contractions (see Chap. 19, p. 450). 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 has been referred to as the Ferguson reflex (Ferguson, 1941). Its exact mechanism is not clear, and release of oxytocin has been suggested but not proven. Manipulation of the cervix and “stripping” the fetal membranes is associated with an increase in blood levels of prostaglandin F20 metabolite (PGFM). As shown in Figure 6-4, this could also increase contractions (see also Chap. 22, p. 504).

The interval between contractions diminishes gradually from about 10 minutes at the onset of the first stage of 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, averaging about 1 minute. There is appreciable variability in contraction intensity during normal labor. Specifically, amnionic fluid pressures generated by contractions during spontaneous labor average approximately 40 mm Hg, but with variations from 20 to 60 mm Hg (see Chap. 18, p. 437).

Distinct Lower and Upper Uterine Segments. During active labor, the uterine divisions that were initiated in phase 2 of parturition become increasingly evident (Figs. 6-5 and 6-6). By abdominal palpation, even before rupture of the membranes, the two segments can sometimes be 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 be decreased markedly. 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 the 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. 6-5). 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 upon 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 dilatation, the musculature of the lower segment must stretch. This permits increasingly more 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. Recall that after each contraction of the upper segment, the muscles do not return to the

**FIGURE 6-4** Clinically, membrane stripping may aid cervical ripening and in some cases, labor induction.

**FIGURE 6-5** Sequence of development of the segments and rings in the uterus at term and in labor. Note comparison between the uterus of a nonpregnant woman, 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.)
there is considerably less myometrial tone. The active upper segment retracts around the presenting part as the fetus descends through the birth canal. In the passive lower segment, upper segment thinning and concomitant upper segment thickening, a few millimeters in the thinnest part. As a result of the lower fibers with labor is accompanied by thinning, normally to only comparison, in the lower segment, successive lengthening of the previous length, but tension remains essentially the same. By comparison, 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. As a result of the 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 (see Fig. 6-5). This abnormal condition is also known as the Bandl ring, which is discussed further in Chapter 20 (p. 486).

**Uterine Shape Changes During Labor.** Each contraction produces an elongation of the ovoid uterine shape with a concomitant decrease in horizontal diameter. This change in shape has important effects on the process of labor. First, there is increased fetal axis pressure. The decreased horizontal diameter serves to straighten the fetal vertebral column. This presses the upper pole of the fetus firmly against the fundus, whereas the lower pole is thrust farther downward. The lengthening of the ovoid shape has been estimated at 5 and 10 cm. Second, with lengthening of the uterus, the longitudinal 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 in Labor.** After the cervix is dilated fully, the most important force in fetal expulsion is that produced by maternal intra-abdominal pressure. Contraction of the abdominal muscles simultaneously with forced respiratory efforts with the glottis closed is referred to as pushing. The nature of the force is similar to that with defecation, but the intensity usually is much greater. The importance of intra-abdominal pressure is attested to by prolonged descent during labor in paraplegic women. And although increased intra-abdominal pressure is necessary to complete second-stage labor, pushing accomplishes little in the first stage. It exhausts the mother, and its associated increased intrauterine pressures may be harmful to the fetus.

**Cervical Changes During First-Stage Labor**

As the result of contraction forces, two fundamental changes—effacement and dilatation—take place in the already-ripened cervix. For an average-sized fetal head to pass through the cervix, its canal must dilate to a diameter of approximately 10 cm. At this time, the cervix is said to be completely or fully dilated. Although there may be no fetal descent during cervical effacement, most commonly, the presenting fetal part descends somewhat as the cervix dilates. During second-stage labor in nulliparas, the presenting part typically descends slowly and steadily. In multiparas, however, particularly those of high parity, descent may be rapid.

Cervical effacement is “obliteration” or “taking up” of the cervix. It is manifest clinically by shortening of the cervical canal from a length of about 2 cm to a mere circular orifice with almost paper-thin edges. The muscular fibers at about 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. 6-7).

Effacement may be compared with a funneling process in which the whole length of a narrow cylinder is converted into a very obtuse, flaring funnel with a small circular opening. Because of increased 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 mucus plug as the cervical canal is shortened.

Because the lower segment and cervix have lesser resistance during a contraction, a centrifugal pull is exerted on the cervix leading to distension, or cervical dilatation (Figs. 6-8). As uterine contractions cause pressure on the membranes, the hydrostatic action of the amnionic sac in turn dilates the cervical canal like a wedge. In the absence of intact membranes, the pressure of the presenting part against the cervix and lower uterine segment is similarly effective. Early rupture of the membranes does not retard cervical dilatation so long as the presenting fetal part is positioned to exert pressure against the cervix and lower segment. The process of cervical effacement and dilatation causes the formation of the forebag of amnionic fluid, which is the leading portion of the amnionic sac and fluid located in front of the presenting part.

Referring back to Figure 6-2, recall that cervical dilatation is divided into latent and active phases. The active phase is subdivided further into the acceleration phase, the phase of maximum slope, and the deceleration phase (Friedman, 1978). The duration of the latent phase is more variable and sensitive to changes by 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 accelerated phase are usually predictive of a particular labor outcome. Completion of cervical dilatation during the active phase is accomplished by cervical retraction about the presenting part. The first stage ends when cervical dilatation is complete. Once the second stage commences, only progressive descent of the presenting part will foretell further progress.

**Second Stage of Labor: 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. Station describes descent of the fetal biparietal diameter in relation to a line drawn between maternal ischial spines (Chap. 17, p. 392). Active descent usually takes place after dilatation has progressed for some time (Fig. 6-9). In nulliparas, increased rates of descent are observed ordinarily during cervical dilatation phase of maximum slope. At this time, the speed of descent is also maximal and is maintained until the presenting part reaches the perineal floor (Friedman, 1978).

**Pelvic Floor Changes During Labor**

The birth canal is supported and is functionally closed by several layers of tissues that together form the pelvic floor. The
The levator ani muscle varies in thickness from 3 to 5 mm, although its margins encircling the rectum and vagina are somewhat thicker. During pregnancy, the levator ani usually undergoes hypertrophy, forming a thick band that extends backward from the pubis and encircles the vagina about 2 cm above the plane of the hymen. On contraction, the levator ani draws both the rectum and the vagina forward and upward in the direction of the symphysis pubis and thereby acts to close the vagina. The more superficial muscles of the perineum are too delicate to serve more than an accessory function.

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 the stretching of levator ani
muscle fibers. This is accompanied by thinning of the central portion of the perineum, which becomes transformed from a wedge-shaped, 5-cm-thick mass of tissue 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. The extraordinary number and size of the blood vessels that supply the vagina and pelvic floor result in substantive blood loss if these tissues are torn.

**Third Stage of Labor: Delivery of Placenta and Membranes**

This stage begins immediately after delivery of the fetus and involves the separation and expulsion of the placenta and membranes. As the neonate is born, the uterus spontaneously contracts around its diminishing contents. Normally, by the time the infant is completely delivered, the uterine cavity is nearly obliterated. The organ consists of 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. 6-10). For the placenta to accommodate itself to this reduced area, it increases in thickness, but because of limited placental elasticity, it is forced to buckle. The resulting tension pulls the weakest layer of the decidua—the decidua spongiosa—from that site. Thus, placental separation follows disproportion created between the unchanged placental size and the reduced size of the implantation site. During cesarean delivery, this phenomenon may be directly observed when the placenta is implanted posteriorly.

Cleavage of the placenta is aided greatly by the loose structure of the spongy decidua, which may be likened to the row of perforations between postage stamps. As separation proceeds, a hematoma forms between the separating placenta and the decidua. The hematoma is usually the result, rather than the cause of the separation, because in some cases bleeding is negligible. The hematoma may, however, accelerate cleavage. Because placental separation is through its spongy layer, part of the decidua is cast off with the placenta, whereas the rest remains attached to the myometrium. The amount of decidual tissue retained at the placental site varies.

The placenta ordinarily separates within minutes after delivery. Occasionally, some degree of separation begins even before the third stage of labor. This probably accounts for certain cases of fetal heart rate decelerations that occur just before fetal expulsion.

**Separation of Fetal Membranes**

The great decrease in uterine cavity surface area simultaneously throws the fetal membranes—the amniochorion and the
parietal decidua—into innumerable folds (Fig. 6-11). 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, which lies in the lower segment or upper vagina. Following separation, the body of the uterus normally forms an almost solid mass of muscle, the anterior and posterior walls of which, each measuring 4 to 5 cm in thickness, lie in close apposition such that the uterine cavity is almost obliterated.

Placental Extrusion

After the placenta has separated and occupies the lower uterine segment or upper vagina, it may be expelled by increased abdominal pressure. Women in the recumbent position, however, frequently cannot expel the placenta spontaneously. Thus, completion of the third stage is accomplished usually by alternately compressing and elevating the fundus, while exerting minimal traction on the umbilical cord (Fig. 17-31, p. 398).

Most commonly during placental delivery, a retroplacental hematoma forms and pushes the center forward and causes it to separate toward the uterine cavity. Weighted by this hematoma, the placenta descends, drags the membranes, and peels them from their uterine attachment. Consequently, the glistening amnion, covering the placental surface, presents at the vulva. The retroplacental hematoma either follows the placenta or is found within the inverted sac. 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 method of placental extrusion, known as the Duncan mechanism, the placenta separates first at the periphery. As a result, blood collects between the membranes and the uterine wall and escapes from the vagina. In this circumstance, the placenta descends sideways, and the maternal surface appears first.

Phase 4 of Parturition: The Puerperium

Immediately and for about an hour or so after delivery, the myometrium remains in a state of rigid and persistent contraction and retraction. This directly compresses large uterine vessels and allows thrombosis of their lumens (Fig. 2-14, p. 25). For this reason, severe postpartum hemorrhage is prevented.

 Concurrently during the early puerperium, a maternal-type behavior pattern develops and maternal-neonatal bonding begins. The onset of lactogenesis and milk let-down in mammary glands also is, in an evolutionary sense, crucial to the bringing forth of young. Both compression of uterine vessels and maternal-type behavior patterns are mediated by oxytocin (p. 159).

Uterine involution and cervical repair, both remodeling processes that restore these organs to the nonpregnant state, follow in a timely fashion. These protect the reproductive tract from invasion by commensal microorganisms and restore endometrial responsiveness to normal hormonal cyclicity. Reinstitution of ovulation signals preparation for the next pregnancy. This generally occurs within 4 to 6 weeks after birth, but it is dependent on the duration of breast feeding. Infertility usually persists as long as breast feeding is continued because of lactation-induced, prolactin-mediated anovulation and amenorrhea (Chap. 32, p. 694).

PHYSIOLOGICAL AND BIOCHEMICAL PROCESSES REGULATING PARTURITION

The physiological processes that result in the initiation of parturition and the onset of labor remain poorly defined. There are two general contemporaneous theorems concerning labor initiation. Viewed simplistically, these are the loss of function of pregnancy maintenance factors and the synthesis of factors that induce parturition. Selected tenets of these two postulates are incorporated into most theorems.

Some investigators also speculate that the mature fetus is the source of the initial signal for parturition commencement. Others suggest that one or more uterotonins, produced in increased amounts, or an increase in the population of its myometrial receptors is the proximate cause. Indeed, an obligatory role for one or more uterotonins is included in most parturition theories, as either a primary or a secondary phenomenon in the final events of childbirth. Both rely on careful regulation of smooth muscle contraction.

Anatomical and Physiological Considerations of the Myometrium

There are unique characteristics of smooth muscle, including myometrium, compared with those of skeletal muscle that may confer advantages for the myometrium in the efficiency of uterine contractions and delivery of the fetus. 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, whereas the contraction force generated by skeletal muscle is always aligned with the axis of the muscle fibers. Third, smooth muscle is not organized in the same...
manner as skeletal muscle. In myometrium, the thick and thin filaments are found in long, random bundles throughout the cells. This plexiform arrangement aids greater shortening and force-generating capacity. Lastly, greater multidirectional force generation in the uterine fundus compared with that of the lower uterine segment permits versatility in expulsive force directionality. These forces thus can be brought to bear irrespective of the fetal lie or presentation.

**Regulation of Myometrial Contraction and Relaxation**

Myometrial contraction is controlled by the transcription of key genes, which produce proteins that repress or enhance cellular contractility. These proteins function to: (1) enhance the interactions between the actin and myosin proteins that cause muscle contraction; (2) increase excitability of individual myometrial cells; and (3) promote intracellular cross talk that allow development of synchronous contractions.

**Actin-Myosin Interactions**

The interaction of myosin and actin is essential to muscle contraction. This interaction requires that actin be converted from a globular to filamentous form. Moreover, actin must be attached to the cytoskeleton at focal points in the cell membrane to allow development of tension (Fig. 6-12). Actin must partner with myosin, which is comprised of multiple light and heavy chains. The interaction of myosin and actin causes activation of adenosine triphosphatase, adenosine triphosphate hydrolysis, and force generation. This interaction is effected by enzymatic phosphorylation of the 20-kDa light chain of myosin (Stull and colleagues, 1988, 1998). This phosphorylation reaction is catalyzed by the enzyme *myosin light-chain kinase*, which...
is activated by calcium. Calcium binds to calmodulin, a calcium-binding regulatory protein, which in turn binds to and activates myosin light-chain kinase.

**Intracellular Calcium**

Agents that promote contraction act on myometrial cells to increase intracellular cytosolic calcium concentration—\[Ca^{2+}\]—or allow an influx of extracellular calcium through ligand- or voltage-regulated calcium channels (see Fig. 6-12). For example, prostaglandin F\textsubscript{2\alpha} and oxytocin bind their receptors during labor, which opens ligand-activated calcium channels. Activation of these receptors also releases calcium from internal stores in the sarcoplasmic reticulum. This leads to a drop in electronegativity within the cell. Voltage-gated ion channels open, additional calcium ions move into the cell, and cellular depolarization follows. The increase in \([Ca^{2+}]\) is often transient, but contractions can be prolonged through the inhibition of myosin phosphatase activity (Woodcock and associates, 2004).

Conditions that decrease \([Ca^{2+}]\), and increase intracellular concentrations of cyclic adenosine monophosphate (cAMP) or cyclic guanosine monophosphate (cGMP) ordinarily promote uterine relaxation. Animal studies reveal the importance of small conductance calcium-activated K\textsubscript{+} (SK3) channel in maintenance of uterine relaxation. Expression of the SK3 channel declines at the end of pregnancy as contractility is increased (Pierce and colleagues, 2008). Agents such as corticotropin-releasing hormone (CRH) and prostaglandin E\textsubscript{2} increase intracellular cAMP. Another potential mechanism for maintenance of relaxation is the promotion of actin in a globular form rather than in fibrils, which is required for contraction (Macphee and Lye, 2000; Yu and Lopéz Bernal, 1998).

In addition to myocyte contractility, myocyte excitability is also regulated by changes in the electrochemical potential gradient across the plasma membrane. Prior to labor, myocytes maintain a relatively high interior electronegativity. This state is maintained by the combined actions of the ATPase-driven sodium-potassium pump and the large conductance, voltage- and Ca\textsuperscript{2+}-sensitive K channel—\textit{maxi-K} channels (Parkington and Coleman, 2001). During uterine quiescence, the maxi-K channel is open and allows potassium to leave the cell to maintain interior electronegativity. At the time of labor, changes in electronegativity lead to depolarization and contraction (Brainard and colleagues, 2005; Chanrachakul and co-workers, 2003).

Another important facet of uterine contractility is the need for myocytes to work in synchrony to allow powerful waves of myometrial contraction. These contractions must be coordinated, be of sufficient amplitude, and be interspersed with periods of uterine relaxation to allow appropriate placental blood flow. As parturition progresses, there is increased synchronization of electrical uterine activity.

**Myometrial Gap Junctions**

As in other muscle cells, the cellular signals that control myometrial contraction and relaxation can be effectively transferred between cells through intercellular junctional channels. Communication is established between myometrial cells by gap junctions, which aid the passage of electrical or ionic coupling currents as well as metabolitic coupling. The transmembrane channels that make up the gap junctions consist of two protein “hemichannels” (Sáez and associates, 2005). These are termed connexons, and each is composed of six \textit{connexin} subunit proteins (Fig. 6-13). These pairs of connexons establish a conduit between coupled cells for the exchange of small molecules that can be nutrients, waste products, metabolites, second messengers, or ions.

Optimal numbers of functional permeable gap junctions between myometrial cells are believed to be important for electrical myometrial synchrony. At least 21 human connexin genes have been identified. Four described in the uterus are connexins 26, 40, 43, and 45. Because connexin 43 junctions are scarce in the nonpregnant uterus, they are thought to be most important in gap junction formation during parturition. Most certainly, these increase in size and abundance during human parturition (Chow and Lye, 1994). Finally, mouse models deficient in connexin 43-enriched gap junctions exhibit delayed parturition, further supporting their role (Döring and colleagues, 2006; Tong, 2009).
There are various cell surface receptors that can directly regulate myocyte contractile state. Three major classes are G-protein-linked, ion channel-linked, and enzyme-linked. Multiple examples of each have been identified in human myometrium. These further appear to be modified during the phases of parturition. Most G-protein-coupled receptors are associated with adenylyl cyclase activation—for example, CRHR1 and the LH receptors (Fig. 6-14). Other G-protein-coupled myometrial receptors, however, are associated with G-protein-mediated activation of phospholipase C.

Ligands for the G-protein-coupled receptors include neuropeptides, hormones, and autacoids. Many of these are available to the myometrium during pregnancy in high concentration by several routes. Modes include endocrine, via maternal blood; paracrine, via contiguous tissues or adjacent cells; or autocrine, by direct synthesis in the myocyte (Fig. 6-15). Importantly, myometrial response to a hormone can change during pregnancy. It therefore is conceivable that hormonal myometrial action is regulated by expression of the G-protein-coupled receptor, its associated G-proteins, and the effector plasma membrane proteins.

**Cervical Dilatation During Labor**
Cervical dilatation is characterized by a large influx of leukocytes into the cervical stroma (Sakamoto and co-workers, 2004, 2005). Cervical tissue levels of leukocyte chemoattractants such as IL-8 are increased just after delivery, as are IL-8 receptors. Identification of genes upregulated just after vaginal delivery further suggests that dilatation and early stages of postpartum repair are aided by inflammatory responses, apoptosis, and activation of proteases that degrade extracellular matrix components (Hasan and associates, 2006; Havelock and co-workers, 2005). The composition of glycosaminoglycans, proteoglycans, and poorly formed collagen fibrils that were necessary during ripening and dilatation must be rapidly removed to allow reorganization and recovery of cervical structure. In the days that follow completion of parturition, rapid recovery of cervical structure involves processes that resolve inflammation, promote tissue repair, and recreate dense cervical connective tissue and structural integrity.

**Phase 1: Uterine Quiescence and Cervical Competence**
The myometrial quiescence of parturition phase 1 is so remarkable and successful that it probably is induced by multiple
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Independent and cooperative biomolecular processes. Individually, some of these processes may be redundant so that pregnancy may continue in the absence of one or more that normally contribute to pregnancy maintenance. It is likely that all manners of molecular systems—neural, endocrine, paracrine, and autocrine—are called on to implement and coordinate a state of relative uterine unresponsiveness. Moreover, a complementary system that protects the uterus against agents that could perturb the tranquil state of phase 1 also must be in place (Fig. 6-16).

Phase 1 of human parturition and its quiescent state are likely the result of many factors that include:

- Actions of estrogen and progesterone via intracellular receptors
- Myometrial cell plasma membrane receptor-mediated increases in cAMP
- The generation of cGMP
- Other systems, including modifications in myometrial cell ion channels.

### Progesterone and Estrogen Contributions to Phase 1

In many species, the role of the sex steroid hormones is clear—progesterone inhibits and estrogen promotes the events leading to parturition. In humans, however, it seems most likely that both estrogen and progesterone are components of a broader-based molecular system that implements and maintains phase 1 of parturition. In many species, the removal of progesterone—or progesterone withdrawal—directly precedes the progression of phase 1 into phase 2 of parturition. In addition, providing progesterone to some species will delay parturition via a decrease in myometrial activity and continued maintenance of cervical competency (Challis and Lye, 1994). Studies in these species have led to a better understanding of why the progesterone-replete myometrium of phase 1 is relatively noncontractile.

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 teleological evidence, however, for an increased progesterone-to-estrogen ratio in the maintenance of pregnancy and a decline in the progesterone-to-estrogen ratio for parturition is overwhelming. In all species studied to date, including humans, administration of the progesterone-receptor antagonist mifepristone (RU486) or onapristone will promote some or all key features of parturition. These include cervical ripening, increased cervical distensibility, and increased uterine sensitivity to uterotonins (Bygdeman and co-workers, 1994; Chwalisz, 1994; Wolf and colleagues, 1993).

The exact role of estrogen in regulating human uterine activity and cervical competency is even less well understood. That said, it appears that estrogen can act to promote progesterone responsiveness, and in doing so, promote uterine quiescence. The estrogen receptor, acting via the estrogen-response element of the progesterone-receptor gene, induces progesterone-receptor synthesis, which allows increased progesterone-mediated function.

### Steroid Hormone Regulation of Myometrial Cell-to-Cell Communication

Progesterone likely increases uterine quiescence by direct or indirect effects that cause decreased expression...
of the contraction-associated proteins (CAPs). Progesterone has been shown to inhibit expression of the gap junctional protein connexin 43 in several rodent models of labor, and progesterone administration prevents or delays labor (Fig. 6-17). Conversely, inhibition of progesterone activity at midgestation using the progesterone-receptor antagonist RU486 leads to a premature induction of myometrial connexin 43 protein production, and thus stimulates labor.

Estrogen treatment also promotes myometrial gap junction formation in some animals by increasing connexin 43 synthesis. The simultaneous administration of anti-estrogens prevents this (Burghardt and colleagues, 1984). Progesterone treatment, however, negates the stimulatory effect of estrogen on the development of gap junctions in some animals.

**G-Protein-Coupled Receptors That Promote Myometrial Relaxation**

A number of G-protein-coupled receptors that normally are associated with $G_{o}$-mediated activation of adenylyl cyclase and increased levels of cAMP are present in myometrium. These receptors together with appropriate ligands may act—in concert with sex steroid hormones—as part of a fail-safe system to maintain uterine quiescence (Price and associates, 2000; Sanborn and colleagues, 1998).

**Beta-Adrenoreceptors.** The $\beta$-adrenergic receptors have served as prototypes of cAMP signaling in causing myometrium relaxation. Most commonly, $\beta$-adrenergic receptors mediate $G_{o}$-stimulated increases in adenylyl cyclase, increased levels of cAMP, and myometrial cell relaxation. The rate-limiting factor in the $\beta$-receptor system is likely the number of receptors expressed and the level of adenylyl cyclase expression. The number of G-proteins in most systems far exceeds the number of receptors and effector molecules. These properties have led to development of $\beta$-mimetic agents that are used clinically to promote uterine quiescence and thereby forestall labor. Examples are ritodrine and terbutaline, which are discussed in Chapter 36 (p. 823).

**Luteinizing Hormone (LH) and Human Chorionic Gonadotropin (hCG) Receptors.** The G-protein-coupled receptor for LH-hCG has been demonstrated in myometrial smooth muscle and blood vessels (Lei and co-workers, 1992; Ziecik and colleagues, 1992). Levels of myometrial LH-hCG receptors during pregnancy are greater before than during labor (Zuo and colleagues, 1994). Chorionic gonadotropin acts to activate adenylyl cyclase by way of a plasma membrane receptor-$G_{o}$-linked system. This decreases contraction frequency and force and decreases the number of tissue-specific myometrial cell gap junctions (Ambrus...
and Rao, 1994; Eta and co-workers, 1994). Thus, high circulating levels of hCG may be one mechanism causing uterine quiescence.

**Relaxin.** This peptide hormone consists of an A and B chain and is structurally similar to the insulin family of proteins (Bogic and associates, 1995; Weiss, 1995). Relaxin mediates lengthening of the pubic ligament, cervical softening, vaginal relaxation, and inhibition of myometrial contractions. There are two separate human relaxin genes, designated H1 and H2. The H1 gene is primarily expressed in the decidua, trophoblast, and prostate, whereas the H2 gene is primarily expressed in the corpus luteum.

Relaxin in plasma of pregnant women is believed to originate exclusively by secretion from the corpus luteum. Plasma levels peak at about 1 ng/mL between 8 and 12 weeks and thereafter decline to lower levels that persist until term. The plasma membrane receptor for relaxin—*relaxin family peptide receptor 1 (RXFP1)—mediates activation of adenyl cyclase. Relaxin may promote myometrial relaxation. Although it inhibits contractions of nonpregnant myometrial strips, it does not inhibit those of uterine tissue taken from pregnant women.

Relaxin also affects cervical remodeling through cell proliferation and modulation of extracellular matrix components such as collagen and hyaluronan (Park and associates, 2005). Consistent with a role in cervical remodeling, mice deficient in relaxin or its RXFP1 receptor have difficult parturition and in some cases, are unable to deliver their young (Feng and co-workers, 2005).

**Corticotropin-Releasing Hormone (CRH).** This hormone is synthesized in the placenta and hypothalamus. As discussed later, CRH plasma levels increase dramatically during the final 6 to 8 weeks of normal pregnancy and have been implicated in the mechanisms controlling the timing of human parturition (Smith, 2007; Wadhwa and colleagues, 1998). Recent studies reveal a dual role of CRH during pregnancy and labor that is mediated by specific CRH-receptor variants and the signalling pathways they initiate (Zhang and co-workers, 2008). During phase 2, CRH binds the receptor CRH-R1, which acting through Gαq protein and adenylyl cyclase, leads to production of cAMP and subsequent inhibition of myometrial activity. In contrast, at term, CRH can activate the Gqα protein pathway, which favors myometrial contraction. Another aspect of CRH regulation is union of CRH to its binding protein, which can limit bioavailability. CRH-binding protein levels are high during pregnancy and are reported to decline at the time of labor.

**Prostaglandins.** The prostanoids interact with a family of eight different G-protein-coupled receptors, several of which are expressed in myometrium (Myatt and Lye, 2004). Prostaglandins most commonly have been considered as uterotonic. However, they have diverse effects, and some act as smooth muscle relaxants.

The major synthetic pathways involved in prostaglandin biosynthesis are shown in Figure 6-18. Prostaglandins are produced using plasma membrane–derived arachidonic acid, which usually is released by the action of the phospholipases A2 or C on membrane phospholipids. Arachidonic acid can then act as substrate for both type 1 and type 2 prostaglandin H synthase—PGHS-1 and -2, also called cyclooxygenase-1 and -2—COX-1 and 2. Both PGHS isoforms convert arachidonic acid to the unstable endoperoxide prostaglandin G2 and then to prostaglandin H2. These enzymes are the target of many nonsteroidal anti-inflammatory drugs (NSAIDs). Indeed, ability of specific NSAIDs to work as tocolytics was considered promising until they were shown to have adverse effects on fetal physiology and development (see Chap. 14, p. 319) (Loudon and co-workers, 2003; Olson and colleagues, 2003, 2007). Through prostaglandin isomerases, prostaglandin H2 is converted to active prostaglandins, including PGE2, PGF2α, and PGI2.

Prostaglandin isomerase expression is tissue-specific, thus controlling 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 can be regulated in the uterus, which is important because of its ability to rapidly inactivate prostaglandins to their 15-keto metabolites.

The effect of prostaglandins on tissue targets is complicated in that there are a number of G-protein-coupled prostaglandin

![Figure 6-17](image-url)
receptors (Coleman and associates, 1994). This family of receptors is classified according to the binding specificity of a given receptor to a particular prostaglandin. The receptors are TP—thromboxane A2; DP—PGD2; IP—prostacyclin or PGI2; FP—PGF2α receptor; and EP1,2,3, and 4-PGE2 receptors. Both PGE2 and PGI2 could potentially act to maintain uterine quiescence by increasing cAMP signaling, yet PGE2 can promote uterine contractility through binding to EP1 and EP3 receptors. And also, PGE2, PGD2, and PGI2 have been shown to cause vascular smooth muscle relaxation and vasodilatation in many circumstances. Thus, either the generation of specific prostaglandins or the relative expression of the various prostaglandin receptors may determine myometrial responses to prostaglandins (Lyall, 2002; Olson, 2003, 2007; Smith, 2001; Smith, 1998, and all their colleagues).

In addition to gestational changes, other studies show that there may be regional changes in the upper and lower uterine segments. Expression of COX-2 was shown to be spatiallyregulated in myometrium and cervix in pregnancy and labor, and an increasing concentration gradient from the fundus to the cervix was noted (Havelock and associates, 2005). Thus, it is entirely possible that prostanoids contribute to myometrial relaxation at one stage of pregnancy and to regional—fundal—myometrial contractions—after initiation of parturition (Myatt and Lye, 2004). Animal studies suggest changes in relative levels of PGE2 receptors in the term cervix (Schmitz and co-workers, 2006).

**Atrial and Brain Natriuretic Peptides and Cyclic Guanosine Monophosphate (cGMP)**

Activation of guanylyl cyclase increases intracellular cGMP levels, which also promotes smooth muscle relaxation (Word and colleagues, 1993). Guanylate cyclase activity and cGMP content is increased in pregnant myometrium before labor starts compared with after labor has begun (Telfer and colleagues, 2001). Intracellular cGMP levels can be stimulated by either atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) receptors, which are both present in myometrium during pregnancy (Itoh and co-workers, 1994). BNP is secreted by amnion in large amounts, and ANP is expressed in placenta (Itoh and associates, 1993; Lim and Gude, 1995).

Soluble guanylyl cyclase is also activated by nitric oxide, which because of its hydrophobic nature, readily penetrates the plasma membrane to enter cells. Nitric oxide reacts with iron and stimulates it to produce cGMP and myometrial relaxation (Izumi and colleagues, 1993). Nitric oxide is synthesized in decidua, myometrial blood vessels, and nerves (Yallampalli and colleagues, 1994a, 1994b). Its role in possible uterine quiescence is not understood.

**Accelerated Uterotonin Degradation and Phase 1 of Parturition**

In addition to pregnancy-induced compounds that stimulate myometrial cell refractoriness, there are striking increases in the activities of enzymes that degrade or inactivate endogenously produced urotensins. Some of these and their degradative enzymes include PGDH, which degrades 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) acetylhydrolase and PAF. Activities of several of these enzymes are increased by progesterone action and many decrease late in gestation (Bates, 1979; Casey, 1980; Germain, 1994, and all their colleagues).

**Phase 2: Uterine Activation and Cervical Ripening**

**Classical Progesterone Withdrawal and Parturition**

In species that exhibit progesterone withdrawal, progression of parturition to labor can be blocked by administering progesterone to the mother. In pregnant women, however, there are conflicting reports as to whether or not progesterone administration can delay the timely onset of parturition or prevent preterm labor. Some studies suggest that progesterone neither prevents preterm labor nor appears to extend labor, but others suggest the opposite (Mackenzie and associates, 2006). Clinically, any advantages to the use of progesterone or its metabolite, 17-hydroxyprogesterone, to decrease the incidence of preterm labor in high-risk populations seem minimal (Fonseca, 2007; Meis, 2003; Rouse, 2007, and all their colleagues). The 17-hydroxyprogesterone molecule binds and activates the

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**FIGURE 6-18** Overview of the prostaglandin biosynthetic pathway.
progesterone receptor less so than progesterone. Further research may help explain its differential action and how it could be better used to prevent preterm labor.

**Progesterone Receptor Antagonists and Human Parturition**

When the steroidal antiprogestin, mifepristone or RU486, is administered during the latter phase of the ovarian cycle, it induces menstruation prematurely. It is also an effective abortifacient during early pregnancy (see Chap. 9, p. 232). Mifepristone is a classical steroid antagonist, acting at the level of the progesterone receptor. Although less effective in inducing abortion or labor in women later in pregnancy, mifepristone appears to have some effect on cervical ripening and increasing myometrial sensitivity to uterotonins (Chwalisz and Garfield, 1994; Chwalisz, 1994; Berkane and associates, 2005). These data suggest that humans have a mechanism for progesterone inactivation, whereby the myometrium and cervix becomes refractory to the blocking actions of progesterone.

**Functional Progesterone Withdrawal in Human Parturition**

As an alternative to classical progesterone withdrawal resulting from decreased secretion, research has focused on unique human mechanisms that have evolved to inhibit progesterone action. In theory, functional progesterone withdrawal or antagonism could be mediated through several mechanisms:

- Changes in the relative expression of the nuclear progesterone receptor (PR) protein isoforms, PR-A, PR-B, and PR-C
- Changes in the relative expression of membrane-bound progesterone receptors
- Posttranslational modifications of the progesterone receptor
- Alterations in progesterone receptor activity through changes in the expression of co-activators or co-repressors that directly influence receptor function
- Local inactivation of progesterone by steroid-metabolizing enzymes or synthesis of a natural antagonist.

Indeed, there is experimental evidence that lends support to each of these possibilities. Evidence now suggests that progesterone receptor activity is decreased late in gestation. As discussed in Chapter 3 (p. 41), there are numerous isoforms of the receptor—these include PR-A, PR-B, and PR-C. In vitro studies have led to the concept that PR-B is the principal mediator of progesterone actions, whereas PR-A and PR-C decrease progesterone responsiveness by repressing the transcriptional activation of the PR-B isoform. With respect to functional progesterone withdrawal, in a series of studies, it has been shown that there is a shift in the relative ratio of PR-A to PR-B within the myometrium late in gestation (Madsen, 2004; Mesiano, 2002; Pieber, 2001, and all their colleagues). Analysis of placental tissues for PR-A and PR-B suggests that the ratio is similarly modified in decidua and chorion, but that there is decreased overall progesterone receptor expression in the amnion (Haluska and co-workers, 2002). Similarly, studies of cervical stroma suggest changes in receptor isoforms (Stjernholm-Vladic and associates, 2004). And Condon and associates (2006) reported that myometrial PR-C to PR-B ratio increased, but only in fundal—and not lower-segment—myometrium. PR coactivators have also been shown to decline in term myometrium, which may contribute to reduced progesterone action (Condon and associates, 2003).

In addition to the nuclear progesterone receptors described above, a number of membrane-associated progesterone receptors have been identified that include mPRα, mPRβ, and mPRγ. The first two couple to inhibitory G-proteins. Ligand binding to these receptors decreases cAMP levels and increases myosin phosphorylation, both of which promote uterine contractility. Although still not entirely clear, current evidence suggests that changes in expression of membrane PR isoforms may also promote the transition from myometrial quiescence to activation (Karteris and co-workers, 2006).

There is evidence in human and rodent models that local action of enzymes catabolize progesterone to metabolites that have a weak affinity for the progesterone receptor. One of these enzymes is steroid 5α-reductase type 1. In mice that cannot express this enzyme, the cervix does not ripen and parturition does not ensue (Mahendroo and colleagues, 1999). Similarly, mice deficient in the enzyme 20α-hydroxy-steroid dehydrogenase have delayed parturition (Piekorz and associates, 2005). A decline in 17β-hydroxysteroid dehydrogenase type 2 in the human cervix at term results in a net increase in estrogen and decline in progesterone (Andersson and co-workers, 2008).

And lastly, there is some support for antiprogestin-like activities of glucocorticoids on progesterone receptor activity (Karalis and co-workers, 1996). Because glucocorticoids play an important role in parturition initiation in several species, examining their potential role as an antiprogestin in humans warrants further study.

Taken together, all of these observations support the concept that multiple pathways exist for a functional progesterone withdrawal that includes changes in PR isoform and receptor coactivator levels and in local hormone metabolism to less active products.

**Oxytocin Receptors**

It is still controversial 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 the rat and mouse. 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. There is little doubt, however, that there is an increase in myometrial oxytocin receptors during phase 2 of parturition. Moreover, their activation results in increased phospholipase C activity and subsequent increases in cytosolic calcium and uterine contractility.

Progestrone and estradiol appear to be the primary regulators of oxytocin receptor expression. Estradiol treatment in vivo or in myometrial explants increases myometrial oxytocin receptors. This action, however, is prevented by simultaneous treatment with progesterone (Fuchs and colleagues, 1983). Progesterone also may act within the myometrial cell to increase
oxygen receptor degradation and inhibit oxytocin activation of its receptor at the cell surface (Bogacki and associates, 2002; Soloff and colleagues, 1983). These data indicate that one of the mechanisms whereby progesterone maintains uterine quiescence is through the inhibition of myometrial oxytocin response.

The increase in oxytocin receptors in nonhuman species appears to be mainly regulated either directly or indirectly by estradiol. Treatment of several species with estrogen leads to a uterine oxytocin receptors increase (Blanks and co-workers, 2003; Challis and Lyce, 1994). The level of oxytocin receptor mRNA in human myometrium at term is greater than that found in preterm myometrium (Wathes and co-workers, 1999). Thus, increased receptors at term may be attributable to increased gene transcription. An estrogen response element, however, is not present in the oxytocin receptor gene, suggesting that the stimulatory effects of estrogen may be indirect.

Human studies suggest that inflammatory-related rapid-response genes may regulate oxytocin receptors (Bethin, 2003; Kimura, 1999; Massrieh, 2006, and all their colleagues). These receptors also are present in human endometrium and in decidua at term and stimulate prostaglandin production (Fuchs and associates, 1981). In addition, these receptors are found in the myometrium and at lower levels, in amniochorion–decidual tissues (Benedetto and associates, 1990; Wathes and co-workers, 1999).

Relaxin

Although relaxin may play a role in maintenance of uterine quiescence, it also has roles in phase 2 of parturition. These include remodeling of the extracellular matrix of the uterus, cervix, vagina, breast, and pubic symphysis as well as promoting cell proliferation and inhibiting apoptosis. Relaxin’s actions on cell proliferation and apoptosis are mediated through the G-protein-coupled receptor, RXFP1, whereas some but not all actions of relaxin on matrix remodeling are mediated through RXFP1 (Samuel and co-workers, 2009; Yao and associates, 2008). Although the precise mechanisms for modulation of matrix turnover have not been fully elucidated, relaxin appears to mediate synthesis of glycosaminoglycans and proteoglycans and to degrade matrix macromolecules such as collagen by induction of matrix metalloproteases. Relaxin promotes growth of the cervix, vagina, and pubic symphysis and is necessary for breast remodeling for lactation. Consistent with its proposed roles, mice deficient in relaxin or the RXFP1 receptor have protracted labor, reduced growth of the cervix, vagina, and symphysis, and are unable to nurse because of incomplete nipple development (Feng, 2005; Park, 2005; Yao, 2008, and all their associates).

Fetal Contributions to Initiation of Parturition

It is intellectually intriguing to envision that the mature human fetus provides the signal to initiate parturition. Teleologically, this seems most logical because such a signal could be transmitted in several ways to suspend uterine quiescence. The fetus may provide a signal through a blood-borne agent that acts on the placenta. Research is ongoing to better understand the fetal signals that contribute to the initiation of parturition (Mendelson, 2009). Although signals may arise from the fetus, it is likely that the uterus and cervix first must be prepared for labor before a uterotonin produced by the fetus or elsewhere can be optimally effective (Casey and MacDonald, 1994).

Uterine Stretch and Parturition

There is now considerable evidence that fetal growth is an important component in uterine activation in phase 1 of parturition. In association with fetal growth, significant increases in myometrial tensile stress and amniotic fluid pressure follow (Fisk and co-workers, 1992). With uterine activation, stretch is required for induction of specific contraction-associated proteins (CAPs). Stretch increases expression of the gap junction protein—connexin 43, as well as oxytocin receptors. Others have hypothesized that stretch plays an integrated role with fetal–maternal endocrine cascades of uterine activation (Lyall and co-workers, 2002; Ou and colleagues, 1997, 1998).

Clinical support for a role of stretch comes from the observation that multifetal pregnancies are at a much greater risk for preterm labor than singletons (Gardner and co-workers, 1995). Preterm labor is also significantly more common in pregnancies complicated by hydramnios (Many and associates, 1996). Although the mechanisms causing preterm birth in these two examples are debated, a role for uterine stretch must be considered.

Cell signaling systems used by stretch to regulate the myometrial cell continue to be defined. This process—mechanotransduction—may include activation of cell-surface receptors or ion channels, transmission of signals through extracellular matrix, or release of autocrine molecules that act directly on myometrium (Shynlova and co-workers, 2009). For example, the extracellular matrix protein, fibronectin, and its cell surface receptor, alpha 5 integrin receptor, are induced in the rodent in response to stretch (Shynlova and colleagues, 2007). This interaction may aid force transduction during labor contraction by anchoring hypertrophied myocytes to the uterine extracellular matrix.

Fetal Endocrine Cascades Leading to Parturition

The ability of the fetus to provide endocrine signals that initiate parturition has been demonstrated in several species. More than 30 years ago, Liggins and associates (1967, 1973) demonstrated that the fetus provides the signal for the timely onset of parturition in sheep. This signal was shown to come from the fetal hypothalamic-pituitary-adrenal axis (Whittle and co-workers, 2001). Defining the exact mechanisms regulating human parturition has proven more difficult, and all evidence suggests that it is not regulated in the exact manner seen in the sheep. Even so, activation of 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 and co-workers, 2000, 2001). As in the sheep, steroid products of the human fetal adrenal gland are believed to have effects on the placenta and membranes that eventually transform myometrium from a quiescent to contractile state. A key component in the human
may be the unique ability of the placenta to produce large amounts of corticotropin-releasing hormone (CRH).

**Actions of Corticotropin-Releasing Hormone on the Fetal Adrenal Gland**

The human fetal adrenal glands are morphologically, functionally, and physiologically remarkable organs. At term, the fetal adrenal glands weigh the same as those in the adult and are similar in size to the adjacent fetal kidney (Chap. 3, p. 69). The daily steroid production by the fetal adrenal glands near term is estimated to be 100 to 200 mg/day. This is higher than the 30 to 40 mg/day seen in adult glands at rest. Within the fetal adrenal gland, steroidogenic function and zonation differ from the adult. For example, significant amounts of cortisol are not produced in the fetal gland until the last trimester. As a result, fetal cortisol levels increase during the last weeks of gestation (Murphy, 1982). During this same period, levels of dehydroepiandrosterone sulfate (DHEA-S) production also are increasing significantly, leading to increases in maternal estrogens, particularly estriol.

These increases in fetal adrenal gland activity contrast with fetal pituitary adrenocorticotropic hormone (ACTH) levels, which do not increase until actual labor onset. Thus, substantial growth and increased steroid synthesis during latter gestation is at a time when fetal plasma ACTH levels are low (Winters and co-workers, 1974). It is presumed that alternate stimuli for growth and steroidogenesis are likely placenta-derived. In support of this, the fetal zone of the adrenal gland undergoes rapid involution immediately after birth, when placenta-derived factors are no longer available.

Many favor CRH of placental origin to be a critical agent for fetal adrenal hypertrophy and increased steroidogenesis in late pregnancy. Some in vitro studies have shown that CRH stimulates fetal adrenal DHEA-S and cortisol biosynthesis (Parker and associates, 1999; Smith and co-workers, 1998). The ability of CRH to regulate the adrenal glands and of the adrenals to regulate placental CRH production supports the idea of a feed-forward endocrine cascade that initiates late in gestation (Fig. 6-19).

**Placental Corticotropin-Releasing Hormone Production.**

A CRH hormone identical to maternal and fetal hypothalamic CRH is synthesized by the placenta in relatively large amounts (Grino and associates, 1987; Saijonmaa and colleagues, 1988). One important difference is that, unlike hypothalamic CRH, which is under glucocorticoid negative feedback, cortisol has been shown to stimulate placental CRH production (Jones and co-workers, 1989; Marinoni and associates, 1998). This makes it possible to create a feed-forward endocrine cascade that does not end until separation of the fetus from the placenta at 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, peaking during labor and then falling precipitously after delivery (Frim and associates, 1988; Sasaki and colleagues, 1987). Amnionic fluid CRH levels similarly increase in late gestation. And although umbilical cord blood CRH levels are lower than those in maternal circulation, they are within the range of concentrations that are found to stimulate fetal adrenal steroidogenesis (Goland and co-workers, 1986, 1993; Perkins and associates, 1995).

Corticotropin-releasing hormone is the only trophic hormone-releasing factor to have a specific serum binding protein. During most of pregnancy, it appears that CRH-binding protein (CRH-BP) binds most maternal circulating CRH. Binding likely inactivates ACTH-stimulating activity of placental CRH (Lowry, 1993). During later pregnancy, however, CRH-BP levels in both maternal plasma and amnionic fluid decline at the same time CRH levels are strikingly increasing. This leads to markedly increased levels of bioavailable CRH (Perkins and co-workers, 1995; Petragni and associates, 1997).

In pregnancies in which the fetus can be considered to be “stressed” from various complications, concentrations of CRH in fetal plasma, amnionic fluid, and maternal plasma are increased compared with those seen in normal gestation (Berkowitz, 1996; Goland, 1993; McGrath, 2002; Perkins, 1995, and all their co-workers). The placenta is likely the source for this increased CRH. For example, placental CRH content was fourfold higher in placentas from women with preeclampsia than in those from normal pregnancies (Perkins and co-workers, 1995). Moreover, the biological impact of increased CRH levels is likely to be amplified in such instances as a result of gestational age.
of subnormal levels of CRH-BP (Petraglia and co-workers, 1996). Such increases in placental CRH production during normal gestation and the excessive secretion of placental CRH in complicated pregnancies may play a role in the normal gestational increases in fetal adrenal cortisol synthesis (Murphy, 1982). It also may result in the supranormal levels of umbilical cord blood cortisol noted in stressed neonates (Falkenberg and colleagues, 1999; Goland and co-workers, 1994).

Corticotropin-Releasing Hormones and Parturition Timing

Placental CRH has been proposed to play several roles in parturition regulation. Placental CRH may enhance fetal cortisol production to provide positive feedback so that the placenta produces more CRH. Resulting high levels of CRH may modulate myometrial contractility via interaction with the CRH receptor isoform, CRH-R1d. This isoform is known to enhance myometrial contractile response (Grammatopoulos, 1994, 1995, 1999; Hillhouse, 1993; Markovic, 2007, and all their colleagues). It has also been proposed that cortisol affects the myometrium indirectly by stimulating the fetal membranes to increase prostaglandin synthesis.

And finally, CRH has been shown to stimulate fetal adrenal C19-steroid synthesis, thereby increasing substrate for placental aromatization. Increased production of estrogens would shift the estrogen-to-progesterone ratio and promote the expression of a series of contractile proteins in the myometrium, leading to a loss of myometrial quiescence.

Some have proposed that the rising level of CRH at the end of gestation reflects a fetal-placental clock (McLean and colleagues, 1995). CRH levels vary greatly among women, and it appears that the rate of increase in maternal CRH levels is a more accurate predictor of pregnancy outcome than is a single measurement (Leung and associates, 2001; McGrath and Smith, 2002). In this regard, the placenta and fetus, through endocrinological events, influence the timing of parturition at the end of normal gestation.

Fetal Lung Surfactant and Parturition

Surfactant protein A (SP-A) produced by the fetal lung is required for lung maturation. Its levels are increased in amniotic fluid at term in women and mice. Recent studies in the mouse suggest that the increasing SP-A concentrations in amniotic fluid activate fluid macrophages to migrate into the myometrium and induce a transcription factor—nuclear factor-κB (Condon and co-workers, 2004). This factor activates inflammatory response genes in the myometrium, which in turn promote uterine contractility. This model supports the supposition that fetal signals play a role in parturition initiation. The exact mechanisms by which SP-A activates myometrial contractility in women, however, remains to be clarified as studies in women suggest that fetal macrophages in the amniotic cavity do not enter the myometrium during labor (Kim and colleagues, 2006; Leong and associates, 2008). Pulmonary surfactant and components of surfactant such as platelet activating factor, when secreted into human amniotic fluid, have been reported to stimulate prostaglandin synthesis (PGE2) and uterine contractility. This supports a function of SP-A in human parturition (Lopez and co-workers, 1988; Toyoshima and associates, 1995).

Fetal Anomalies and Delayed Parturition

There is fragmentary evidence that pregnancies with markedly diminished estrogen production may be associated with prolonged gestation. Some of these “natural experiments” include fetal anencephaly with adrenal hypoplasia and placental sulfatase deficiency. The broad range of gestational length seen with these disorders questions the exact role of estrogen in human parturition initiation.

Other fetal abnormalities that prevent or severely reduce the entry of fetal urine into amniotic fluid—renal agenesis, or into lung secretions—pulmonary hypoplasia, do not prolong human pregnancy. Thus, a fetal signal through the paracrine arm of the fetal—maternal communication system does not appear to be mandated for parturition initiation.

Some brain anomalies of the fetal calf, fetal lamb, and sometimes the human fetus delay the normal timing of parturition. More than a century ago, Rea (1898) observed an association between fetal anencephaly and prolonged human gestation. Malpas (1933) extended these observations and described a pregnancy with an anencephalic fetus that was prolonged to 374 days—53 weeks. He concluded that the association between anencephaly and prolonged gestation was attributable to anomalous fetal brain–pituitary–adrenal function. 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 C19-steroid hormones (see Chap. 3, p. 70). Such pregnancies are also associated with delayed labor (Anderson and Turnbull, 1973). These findings are suggestive that in humans, as in sheep, the fetal adrenal glands are important for the timely onset of parturition.

Systems to Ensure Success of Phase 3 of Parturition

Phase 3 of parturition is synonymous with uterine contractions that bring about progressive cervical dilatation and delivery. Current data favor the uterotonins theory of labor initiation. Increased uterotonin production would follow once phase 1 is suspended and uterine phase 2 processes are implemented. A number of uterotonins may be important to the success of phase 3, that is, active labor (see Fig. 6-17). Just as multiple processes likely contribute to myometrial unresponsiveness of phase 1 of parturition, other processes may contribute jointly to a system that ensures labor success.

Uterotonins that are candidates for labor induction include oxytocin, prostaglandins, serotonin, histamine, PAF, angiotensin II, and many others. All have been shown to stimulate smooth muscle contraction through G-protein coupling.

Oxytocin and Phase 3 of Parturition

Late in pregnancy, during phase 2 of parturition, there is a 50-fold or more increase in the number of myometrial oxytocin receptors (Fuchs and associates, 1982; Kimura and co-workers, 1996). This increase coincides with an increase in uterine contractile responsiveness to oxytocin (Soloff and co-workers, 1979). Moreover, prolonged gestation is associated with a delay in the increase of these receptors (Fuchs and colleagues, 1984).
Oxytocin—literally, *quick birth*—was the first uterotonin to be implicated in parturition initiation. This nanopeptide is synthesized in the magnocellular neurons of the supraoptic and paraventricular neurons (Fig. 6-20). 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 and colleagues, 1988; Leake, 1990). Although oxytocin does not appear to cause the initiation of parturition, it may be one of several participants to ensure labor effectiveness.

**Role of Oxytocin in Phases 3 and 4 of Parturition.** Because of successful labor induction with oxytocin, it was logically suspected in parturition initiation. First, in addition to its effectiveness in inducing labor at term, oxytocin is a potent uterotonin and occurs naturally in humans. Subsequent observations provide additional support for this theory:

- The number of oxytocin receptors strikingly increases in myometrial and decidual tissues near the end of gestation
- Oxytocin acts on decidual tissue to promote prostaglandin release
- Oxytocin is synthesized directly in decidual and extraembryonic fetal tissues and in the placenta (Chibbar and associates, 1993; Zingg and colleagues, 1995).

Although little evidence suggests a role for oxytocin in phase 2 of parturition, abundant data support its important role during second-stage labor and the puerperium—phase 4 of parturition. Specifically, there are increased maternal serum oxytocin levels: (1) during second-stage labor—the end of phase 3 of parturition, (2) in the early postpartum period, and (3) during breast feeding—phase 4 of parturition (Nissen and co-workers, 1995). Immediately after delivery of the fetus, placenta, and membranes—completion of parturition phase 3—firm and persistent uterine contraction and retraction are essential to prevent postpartum hemorrhage. Oxytocin likely causes persistent contractions.

Oxytocin infusion in women promotes increased levels of mRNAs in myometrial genes that encode proteins essential for uterine involution. These include interstitial collagenase, monocyte chemoattractant protein-1, interleukin-8, and urokinase plasminogen activator receptor. Therefore, oxytocin action at the end of labor and during phase 3 of parturition may be involved in uterine involution.

**Prostaglandins and Phase 3 of Parturition**

Although their role in phase 2—activation phase—of uncomplicated pregnancies is less well defined, a critical role for prostaglandins in phase 3 of parturition is clear (MacDonald and Casey, 1993). Evidence supportive of this theory includes:

- Levels of prostaglandins—or their metabolites, in amniotic fluid, maternal plasma, and maternal urine are increased during labor (Keirse, 1979)
- Treatment of pregnant women with prostaglandins, by any of several routes of administration, causes abortion or labor at all stages of gestation (Novy and Liggins, 1980)
- Administration of prostaglandin H synthase type 2 (PGHS-2) inhibitors to pregnant women will delay spontaneous labor onset and sometimes arrest preterm labor (Loudon and co-workers, 2003)

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**FIGURE 6-20** Hypothalamic-pituitary-adrenal (HPA) axis. Many reproductive functions are regulated by the HPA axis. During parturition, the magnocellular neurons in the maternal hypothalamus synthesize oxytocin, a uterotonin. Oxytocin in its prohormone form is transported to the posterior pituitary for storage and subsequent release. The fetal HPA axis begins to secrete hormones as early as 6-8 weeks of fetal life. During pregnancy and parturition, this axis plays important roles in regulating fetal DHEA-S production, which is the precursor for estrogen synthesis in the placenta, and in CRH production by the fetus and placenta. (AHA = anterior hypothalamic area; AN = arcuate nucleus; DMN = Dorsomedial nucleus; PHN = posterior hypothalamic nucleus; POA = preoptic area; PVN = paraventricular nucleus; SO = supraoptic nucleus; VMN = ventromedial nucleus.)
Prostaglandin treatment of myometrial tissue in vitro sometimes causes contraction, dependent on the prostanoid tested and the physiological status of the tissue treated.

**Uterine Events Regulating Prostaglandin Production.**

During labor, the production of prostaglandins within the myometrium and decidua is an efficient mechanism of activating contractions. For example, PG synthesis is high and unchanging in the decidua during phase 2 and 3 of parturition, in support of a role of prostaglandins in activation and stimulation. The receptor for PGF$_{2\alpha}$ is increased in the decidua at term, and this increase most likely is the regulatory step in PG action in the uterus. The myometrium synthesizes PGHS-2 with the onset of labor, but most PG likely comes from the decidua.

The fetal membranes and placenta also produce prostaglandins. Prostaglandins, primarily PGE$_2$, but also PGF$_{2\alpha}$, are detected in amnionic fluid at all stages of gestation. As the fetus grows, prostaglandins levels in the amnionic fluid increase gradually. The major increases in amnionic fluid, however, are demonstrable after labor begins (Fig. 6-21). There are higher levels, which likely result as the cervix dilates and exposes decidual tissue (Fig. 6-22). These increased levels in the forebag as compared with the upper compartment are believed to be the result of an inflammatory response that signals the events leading to active labor. Together, the increases in cytokines and

**Figure 6-21** Mean (±SD) concentrations of prostaglandin F$_{2\alpha}$ (PGF$_{2\alpha}$) and prostaglandin E$_2$ (PGE$_2$) in amnionic fluid at term before labor and in the upper and forebag compartments during labor at all stages of cervical dilatation. (Data from MacDonald and Casey, 1993.)
prostaglandins further degrade the extracellular matrix, thus weakening fetal membranes.

Findings of Kemp and co-workers (2002) and Kelly (2002) support a possibility that inflammatory mediators aid cervical dilatation and alterations to the lower uterine segment. It can be envisioned that, along with the increased prostaglandins measured in vaginal fluid during labor, add to the relatively rapid cervical changes that are characteristic of parturition.

Platelet-Activating Factor (PAF)

There are a number of allergic and inflammatory responses in which PAF is involved. This mediator is produced in basophils, neutrophils, eosinophils, monocytes, and endothelial cells. The PAF receptor is a member of the G-protein–coupled receptor family of transmembrane receptors. Its stimulation by PAF increases myometrial cell calcium levels and promotes uterine contractions. Levels of PAF in amnionic fluid are increased during labor, and PAF treatment of myometrial tissue promotes contraction (Nishihara and associates, 1984; Zhu and colleagues, 1992). This factor is inactivated enzymatically by PAF-acetylhydrolase (PAF-AH), which is present in macrophages, which are found in large numbers in decidua (Prescott and associates, 1990). Thus, the myometrium may be protected from PAF action by PAF-AH during pregnancy.

Endothelin-1

The endothelins are a family of 21-amino acid peptides that powerfully induce myometrial contraction (Word and colleagues, 1990). The endothelin A receptor is preferentially expressed in smooth muscle and effects an increase in intracellular calcium. Endothelin-1 is produced in myometrium, and its potential contribution to phase 3 of parturition is not defined. Although endothelin-1 is also synthesized in amnion, it is unlikely that it is transported from the amnion or amnionic fluid to the myometrium without degradation (Eis and colleagues, 1992). Enkephalinase, which catalyzes the degradation of endothelin-1, is highly active in chorion laeve (Germain and associates, 1994).

Angiotensin II

There are two G-protein-linked angiotensin II receptors—expressed in the uterus—AT1 and AT2. In nonpregnant women, the AT2 receptor is predominant, but the AT1 receptor is preferentially expressed in pregnant women (Cox and associates, 1993). Angiotensin II binding to the plasma-membrane receptor evokes contraction. During pregnancy, the vascular smooth muscle that expresses the AT2 receptor is refractory to the pressor effects of infused angiotensin II (see Chap. 5, p. 120). In myometrium near term, however, angiotensin II may be another component of the uterotonin system of phase 3 of parturition. A potential mechanism for increased angiotensin II responsiveness in preeclampsia via increased levels of heterodimers between the vasopressor receptor AT1 and the vasodepressor receptor B2 also emphasizes a role of angiotensin II in the normal physiology of parturition (Quitterer and associates, 2004).

Corticotropin-Releasing Hormone (CRH)

Late in pregnancy—phase 2 or 3 of parturition—modification in the CRH receptor favors a switch from cAMP forma-
It is likely that progesterone maintains chorion PGDH expression, whereas cortisol decreases its expression. Thus, PGDH levels would decrease late in gestation as fetal cortisol production increases and as part of progesterone withdrawal.

Decidua Parietalis. A metabolic contribution of decidua pari-etalis to parturition initiation is an appealing possibility for both anatomical and functional reasons. The generation of decidual uterotonins that act in a paracrine manner on contiguous myometrium is intuitive. In addition, decidua expresses steroid metabolizing enzymes such as 20α-HSD and steroid 5αR1 that may regulate local progesterone withdrawal. There is also evidence that decidual activation is an accompaniment of human parturition (Casey and MacDonald, 1988a, 1988b, 1990; MacDonald and colleagues, 1991). The central question is whether decidual activation precedes or follows labor onset.

Decidual activation appears to be localized to the exposed decidual fragments lining the forebag. Trauma, hypoxia, and exposure of forebag decidua to endotoxin lipopolysaccharide, microorganisms, and interleukin-1β (IL-1β) in the vaginal fluids provoke an inflammatory reaction—an inevitable and consistent sequela of labor. With this inflammation, cytokines are produced that can either increase uterotonin production—principally prostaglandins, or act directly on myometrium to cause contraction—for example, tumor necrosis factor-α (TNF-α) and interleukins 1, 6, 8, and 12. These molecules also can act as chemokines that recruit to the myometrium neutrophils and eosinophils, which further increase contractions and labor (Keelan and co-workers, 2003).

There is uncertainty whether PG concentration or output from the decidua increases with term labor onset. Olson and Ammann (2007) suggest that the major regulation of decidual PG action is not PG synthesis, but rather increased expression of the PGF2α, receptor.

Regulation of Phase 3 and 4 of Parturition: Summary

It is likely that multiple and possibly redundant processes contribute to the success of the three active labor phases once phase 1 of parturition is suspended and phase 2 is implemented. Phase 3 is highlighted by increased activation of G-protein-coupled receptors that inhibit cAMP formation, increase intracellular calcium stores, and promote interaction of actin and myosin and subsequent force generation. Simultaneously, cervical proteoglycan composition and collagen structure are altered to a form that promotes tissue distensibility and increased compliance. The net result is initiation of coordinated myometrial contractions of sufficient amplitude and frequency to dilate the prepared cervix and push the fetus through the birth canal. The source of regulatory ligands for these receptors varies from endocrine cervix such as oxytocin to locally produced prostaglandins.

In phase 4 of parturition, a complicated series of repair processes are initiated to resolve inflammatory responses and remove glycosaminoglycans, proteoglycans, and structurally compromised collagen. Simultaneously, matrix and cellular components required for complete uterine involution are synthesized, and the dense connective tissue and structural integrity of the cervix is reformed.

Physiology and Biochemistry of Preterm Labor

Preterm birth has major human consequences—after congenital anomalies, it is the greatest cause of neonatal morbidity and mortality (Chap. 36, p. 804). Spontaneous preterm labor with intact fetal membranes is the most common cause of preterm delivery and accounts for about half of preterm births. In another quarter, preterm premature rupture of the membranes is almost always followed by preterm delivery. Many factors increase the likelihood of preterm delivery. Some of these are genetics, infection, nutrition, behavior, and the environment (Fig. 6-24).

Genetic Influence on Preterm Birth

Analogous to other complex disease processes, multiple coexistent genetic alterations and environment may lead to preterm birth (Esplin and Varner, 2005; Ward, 2008). There are polymorphisms
Births are idiopathic. This term defines spontaneous rupture of the fetal membranes before 37 completed weeks and before labor onset (American College of Obstetricians and Gynecologists, 2007). Such rupture likely has a variety of causes, but many believe intrauterine infection to be a major predisposing event (Gomez and colleagues, 1997; Mercer, 2003). Some studies suggest that the pathogenesis of preterm rupture relates to increased apoptosis of membranes’ cellular components and to increased levels of specific proteases in membranes and amniotic fluid. Much of the membranes’ tensile strength is provided by the extracellular matrix within the amnion. Interstitial amnionic collagens, primarily types I and III, are produced in mesenchymal cells and are the structural component most important for its strength (Casey and MacDonald, 1996). For that reason, collagen degradation has been a focus of research.

The matrix metalloproteinase (MMP) family is involved with normal tissue remodeling and particularly with collagen degradation. The MMP-2, MMP-3, and MMP-9 members of this family are found in higher concentrations in amniotic fluid from pregnancies with PPROM (Park and colleagues, 2003; Romero and associates, 2002). The activity of MMPs is in part regulated by tissue inhibitors of matrix metalloproteinases (TIMPs). Several of these inhibitors are found in lower concentrations in amniotic fluid from women with PPROM. Elevated MMP levels found at a time when protease inhibitor expression decreases supports further that their expression alters amnionic tensile strength. Studies of amniochorion explants have demonstrated that the expression of MMPs can be increased by treatment with IL-1, TNF-α, and IL-6 (Fortunato and colleagues, 1999a,b, 2002). Thus, MMP induction may be part of an inflammatory process. Proteins involved in the synthesis of mature cross-linked collagen or matrix proteins that bind collagen and promote tensile strength have also been found to be altered in PPROM (Wang and associates, 2006).

In pregnancies with PPROM, the amnion exhibits a higher degree of cell death than that in the term amnion (Arechavaleta-Velasco and colleagues, 2002; Fortunato and Menon, 2003). Markers of apoptosis with PPROM also show increased levels compared with those of term membranes. In vitro studies indicate that apoptosis is likely regulated by bacterial endotoxins IL-1β and TNF-α. Taken together, these observations suggest that many cases of PPROM result from activation of collagen degradation, alterations in collagen assembly, and cell death all leading to a weakened amnion.

A number of studies have been done to ascertain the incidence of infection-induced PPROM. Bacterial cultures of amniotic fluid support a role for infection in a significant proportion. A review of 18 studies comprised of almost 1500 women with PPROM found that in a third, bacteria were isolated from amniotic fluid (Goncalves and co-workers, 2002). Because of these findings, some have given prophylactic antimicrobial treatment to prevent PPROM. Although results are conflicting, there is evidence that early treatment of selected asymptomatic lower genital tract infections and active periodontal inflammation will reduce the incidence of PPROM and preterm birth (Chap. 36, p. 812).

Thus, there is compelling evidence that infection causes a significant proportion of PPROM cases. The inflammatory response that leads to membrane weakening is currently being defined. Research is focused on mediators of this process with a goal of identification of early markers for women at risk for PPROM.

Spontaneous Preterm Labor

Pregnancies with intact fetal membranes and spontaneous preterm labor—for clinical as well as research purposes—must be distinguished from those complicated by PPROM. Even so, pregnancies complicated by spontaneous preterm labor do not constitute a homogeneous group characterized singularly by early initiation of parturition. Among the more common associated findings are multifetal pregnancy, intrauterine infection, bleeding, placental infarction, premature cervical dilatation, cervical incompetence, uterine fundal abnormalities, and fetal anomalies. Severe maternal illness as a result of nonobstetrical infections, autoimmune diseases, and gestational hypertension also increases the risks for preterm labor. Taken together, these disorders cause about half of spontaneous preterm deliveries, and their relative contribution varies between populations.

Although there are unique aspects to each cause of preterm labor, recent studies have suggested that they share certain common denominators. Thus, fetal or maternal conditions provide important clues. It seems important to reemphasize that the actual process of preterm labor should be considered a final step—one that results from premature uterine activation that was initiated weeks before the onset of labor. Indeed, many forms of spontaneous preterm labor that result from premature initiation

![FIGURE 6-24 Risks for preterm birth. Approximately 50 percent of preterm births are idiopathic.](image-url)
of phase 2 of parturition may be viewed in this light. Although the end result in preterm birth is the same as at term, namely cervical ripening and myometrial activation, recent studies question the idea that preterm birth is simply acceleration of the normal process. Identification of both common and uncommon factors has begun to explain the physiological processes of human parturition at term and preterm. Three major causes of spontaneous preterm labor include uterine distension, maternal–fetal stress, and infection.

**Uterine Distension**

There is no doubt that multifetal pregnancy and hydramnios lead to an increased risk of preterm birth (Chap. 39, p. 869). It is likely that early uterine distension acts to initiate expression of contraction-associated proteins (CAPs) in the myometrium. The CAP genes influenced by stretch include those coding for gap junction proteins such as connexin 43, for oxytocin receptors, and for prostaglandin synthase (Korita, 2002; Lyall, 2002; Sooranna, 2004, all their colleagues). Thus, excessive uterine stretch causes premature loss of myometrial quiescence.

Uterine stretch also leads to early activation of the placental–fetal endocrine cascade shown in Figure 6-17. The resulting early rise in maternal CRH and estrogen levels can further enhance the expression of myometrial CAP genes (Warren and co-workers, 1990; Wolfe and colleagues, 1988).

Finally, the influence of uterine stretch should be considered with regard to the cervix. For example, cervical length is an important risk factor for preterm birth in multifetal pregnancies (Gravett and colleagues, 2000; Warren and co-workers, 1996). Prematurely increased stretch and endocrine activity may initiate events that shift the timing of uterine activation, including premature cervical ripening.

**Maternal-Fetal Stress**

The complexities of measuring “stress” lead to difficulty in defining its exact role (Lobel, 1994). That said, considerable evidence shows a correlation between maternal psychological stress and preterm birth (Hedegaard, 1993; Hobel, 2003; Ruiz, 2003; Zambrana, 1999, and all their co-workers). Moreover, there is a correlation between maternal psychological stress and the placental–adrenal endocrine axis that provides a potential mechanism for stress-induced preterm birth (Lockwood, 1999; Wadhwa and associates, 2001).

As discussed earlier, the last trimester is marked by rising maternal serum levels of placental-CRH. This hormone works with ACTH to increase adult and fetal adrenal steroid hormone production, including the initiation of fetal cortisol biosynthesis. Rising levels of maternal and fetal cortisol further increase placental CRH secretion, which develops a feed-forward endocrine cascade that does not end until delivery (see Fig. 6-19). Rising levels of CRH further stimulate fetal adrenal DHEA-S biosynthesis, which acts as substrate to increase maternal plasma estrogens, particularly estriol.

It has been hypothesized that a premature rise in cortisol and estrogens results in an early loss of uterine quiescence. Supporting this hypothesis are numerous studies indicating that spontaneous preterm labor is associated with an early rise in maternal CRH levels (Holzman, 2001; McGrath, 2002; Moawad, 2002, and all their co-workers). Levels of CRH in term and preterm women are similar. However, women destined for preterm labor exhibit a rise in CRH levels 2 to 6 weeks earlier (McLean and co-workers, 1995). This has been described as early as 18 weeks’ gestation, leading some to suggest that CRH determination may provide a useful marker for preterm delivery. Because of large variations in CRH levels among pregnant women, however, a single CRH measurement has low sensitivity (Leung and colleagues, 2001; McGrath and associates, 2002). It may be that the rate of increase in maternal CRH levels may be a more accurate predictor of preterm birth. Confounding factors include CRH variability among ethnic groups. Another is that placental CRH enters the fetal circulation—albeit at lower levels than in the maternal circulation. In vitro studies have shown that CRH can directly stimulate fetal adrenal production of DHEA-S and cortisol (Parker and colleagues, 1999; Smith and co-workers, 1998).

If preterm delivery is associated with early activation of the fetal adrenal-placental endocrine cascade, maternal estrogen levels would likely be prematurely elevated. This is true, and an early rise of serum estriol concentrations is noted in women with subsequent preterm labor (Heine and co-workers, 2000; McGregor and associates, 1995). Physiologically, this premature rise in estrogens may alter myometrial quiescence.

Taken together, these observations suggest that preterm birth is associated, in many cases, with a maternal-fetal biological stress response. The nature and variety of the stressors that activate this cascade likely are broad. For example, CRH or estriol levels are prematurely elevated in preterm birth due to infection and multifetal pregnancies (Gravett and colleagues, 2000; Warren and co-workers, 1990). Thus, activation of this axis may be considered a common feature for initiation of phase 1 of parturition.

**Infection and Preterm Labor**

There is great interest in the role of infection as a primary cause of preterm labor in pregnancies with intact membranes. Many cases of preterm labor may result from intrauterine infection. This concept has been promoted because of widespread suspicion that subclinical infection is a common accompaniment and cause of preterm labor. The term “subclinical” has been used to describe infection that is accompanied by little or no clinical evidence of infection (Goncalves and co-workers, 2002; Iams and colleagues, 1987).

Certainly microorganisms are not recovered from the amniotic fluid in all women with preterm labor. In fact, the incidence of positive cultures varies from 10 to 40 percent and averages 15 percent (Goncalves and co-workers, 2002). Importantly, these women were more likely to develop clinical chorioamnionitis and preterm PROM than women with sterile cultures. Their neonates are also more likely to have complications (Hitti and co-workers, 2001). Although more severe when intra-amniotic infection is detected, intra-amniotic inflammation in the absence of detectable microorganisms is also a risk factor for the development of a fetal inflammatory response (Lee and associates, 2007, 2008). The earlier the onset of preterm labor, the greater is the likelihood of documented amniotic fluid infection (Goldenberg and associates, 2000; Watts
and colleagues, 1992). At the same time, however, the incidence of culture-positive amniotic fluids collected by amniocentesis during spontaneous term labor is similar or even greater than it is during preterm labor (Gomez and colleagues, 1994; Romero and co-workers, 1993). It has been suggested that at term, amniotic fluid is infiltrated by bacteria as a consequence of labor, whereas in preterm pregnancies, bacteria represent an important cause of labor. Although plausible, this explanation questions the contribution of fetal infection as a major contributor to preterm birth.

Certainly, there are considerable data that associate chorioamnionitis with preterm labor (Goldenberg and associates, 2002; Üstün and colleagues, 2001). In such infections, the microbes may invade maternal tissue only and not amniotic fluid. Despite this, endotoxins can stimulate amniotic cells to secrete cytokines that enter amniotic fluid. This scenario may serve to explain the apparently contradictory observations concerning an association between amniotic fluid cytokines and preterm labor, in which microbes were not detectable in the amniotic fluid.

**Sources for Intrauterine Infection.** The patency of the female reproductive tract, although essential for achievement of pregnancy and delivery, is theoretically problematic during phase 1 of parturition. It has been suggested that bacteria can gain access to intrauterine tissues through: (1) transplacental transfer of maternal systemic infection, (2) retrograde flow of infection into the peritoneal cavity via the fallopian tubes, or (3) ascending infection with bacteria from the vagina and cervix. The lower pole of the fetal membrane–decidual junction is contiguous with the orifice of the cervical canal, which in turn is patent to the vagina. This anatomical arrangement provides a passageway for microorganisms, and ascending infection is considered to be the most common. A thoughtful description of the potential degrees of intrauterine infection has been provided by Goncalves and co-workers (2002). They categorize intrauterine infection into four stages of microbial invasion that include bacterial vaginitis—stage I, decidual infection—stage II, amniotic infection—stage III, and finally, fetal systemic infection—stage IV. As expected, progression of these stages is thought to increase the effects on preterm birth and neonatal morbidity.

Based on these insights, it is straightforward to construct a theory for the pathogenesis of infection-induced preterm labor (Fig. 6-25). Ascending microorganisms colonize the decidua and possibly the membranes, where they then may enter

**FIGURE 6-25** Potential pathways for infection-induced preterm birth. Exposure to bacterial endotoxins causes an early initiation of the normal processes associated with parturition, including cervical ripening, loss of uterine quiescence, and increased production of uterotropins. (CRH = corticotropin-releasing hormone; DHEA-S = dehydroepiandrosterone sulfate; HPA = hypothalamic–pituitary–adrenal; PPROM = preterm prematurely ruptured membranes.)
the amnionic sac. Lipopolysaccharide or other toxins elaborated by bacteria induce cytokine production in cells within the decidua, membranes, or fetus itself. Both lipopolysaccharide and cytokines then provoke prostaglandin release from the membranes, the decidua, or both. These influence both cervical ripening and loss of myometrial quiescence (Challis, 2002; Keelan, 2003; Loudon, 2003; Olson, 2003; and all their associates).

Microbes Associated with Preterm Birth. Some microorganisms—examples include Gardnerella vaginalis, Fusobacterium, Mycoplasma hominis, and Ureaplasma urealyticum—are detected more commonly than others in amnionic fluid of women with preterm labor (Gerber, 2003; Hillier, 1988; Romero, 1989; Yoon, 1998, and all their co-workers). This finding was interpreted by some as presumptive evidence that specific microorganisms are more commonly involved as pathogens in the induction of preterm labor. Another interpretation, however, is that given direct access to the membranes after cervical ripening and loss of myometrial quiescence (Challis, 2002; Keelan, 2003; Loudon, 2003; Olson, 2003; and all their co-workers). Immunohistochemical studies have shown in the term laboring uterus that both invading leukocytes and certain parenchymal cells produce cytokines. These leukocytes appear to be the primary source of myometrial cytokines, including IL-1, IL-6, IL-8, and TNF-α (Young and co-workers, 2002). By contrast, in the decidua, both stromal cells and leukocytes are likely to contribute because they have been shown to produce these same cytokines. In the cervix, glandular and surface epithelial cells appear to produce IL-6, IL-8, and TNF-α. Of these, IL-8 is considered a critical cytokine in cervical dilation, and it is produced in both cervical epithelial and stromal cells.

Intrauterine Inflammatory Response to Infection. The initial inflammatory response elicited by bacterial toxins is mediated, in large measure, by specific receptors on mononuclear phagocytes, decidual cells, and trophoblasts. These toll-like receptors represent a family of receptors that has evolved to recognize pathogen-associated molecules (Janssens and Beyaert, 2003). Toll-like receptors are present in the placenta on trophoblast cells as well as on fixed and invading leukocytes (Chuang and Ulevitch, 2000; Gonzalez and colleagues, 2007; Holmlund and co-workers, 2002). Under the influence of ligands such as bacterial lipopolysaccharide, these receptors increase release of chemokines, cytokines, and prostaglandins as part of an inflammatory response. One example is IL-1β, which is produced rapidly after lipopolysaccharide stimulation (Dinarello, 2002). This cytokine in turn acts to promote a series of responses that include: (1) increased synthesis of others, that is, TNF-α, IL-6, and IL-8; (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 and colleagues, 2000). Also, IL-1 promotes prostaglandin formation in many tissues, including myometrium, decidua, and amnion (Casey and co-workers, 1990). Thus, there appears to be a cascade of events once an inflammatory response is initiated that can result in preterm labor.

Origin of Cytokines in Intrauterine Infection. Cytokines within the normal term uterus are likely important for normal and preterm labor. The transfer of cytokines such as IL-1 from decidua across the membranes into amnionic fluid appears to be severely limited. Thus, it is likely that cytokines produced in maternal decidua and myometrium will have effects on that side, whereas cytokines produced in the membranes or in cells within the amnionic fluid will not be transferred to maternal tissues. In most cases of inflammation resulting from infection, resident and invading leukocytes produce the bulk of cytokines. Indeed, leukocytes—mainly neutrophils, macrophages, and T lymphocytes—invade the cervix, lower uterine segment, and fundus at the time of labor. It was also shown that with preterm labor, leukocytes invade both membranes and cervix. Thus, invading leukocytes may be the major source of cytokines at the time of labor. Along with proinflammatory cytokines recent studies in women and animal models highlight the importance of the anti-inflammatory limb of the immune response in the parturition process (Gotsch and colleagues, 2008; Timmons and co-workers, 2009).

Intravenous studies have shown in the term laboring uterus that both invading leukocytes and certain parenchymal cells produce cytokines. These leukocytes appear to be the primary source of myometrial cytokines, including IL-1, IL-6, IL-8, and TNF-α (Young and co-workers, 2002). By contrast, in the decidua, both stromal cells and leukocytes are likely to contribute because they have been shown to produce these same cytokines. In the cervix, glandular and surface epithelial cells appear to produce IL-6, IL-8, and TNF-α. Of these, IL-8 is considered a critical cytokine in cervical dilation, and it is produced in both cervical epithelial and stromal cells.

The presence of cytokines in amnionic fluid and their association with preterm labor has been well documented. But their exact cellular origin—with or without cultivable microorganisms—has not been well defined. Although the rate of IL-1 secretion from forebag decidual tissue is great, Kent and colleagues (1994) found that there is negligible in vivo transfer of radiolabeled IL-1 across the membranes. Amnionic fluid IL-1 probably does not arise from amnion tissue, fetal urine, or fetal lung secretions. It most likely is secreted by mononuclear phagocytes or neutrophils activated and recruited into the amnionic fluid. Therefore, IL-1 in amnionic fluid likely is generated in situ from newly recruited cells. This scenario is supported by immunohistochemical studies (Young and co-workers, 2002). Thus, the amount of amnionic fluid IL-1 would be determined by the number of leukocytes recruited, their activational status, or the effect of amnionic fluid constituents on their rate of IL-1 secretion.

Leukocyte infiltration may be regulated by fetal membrane synthesis of specific chemokines. In term labor, there are increased amnionic fluid concentrations of the potent chemot tractant and monocyte-macrophage activator, monocyte chemotactic protein-1 (MCP-1). As is true for prostaglandins and other cytokines, the levels of MCP-1 are much higher in the forebag compared with the upper compartment (Esplin and co-workers, 2003). Levels in preterm labor were significantly higher than those found in normal term amnionic fluid (Jacobsson and colleagues, 2003). It has been proposed that MCP-1 may be the factor that initiates fetal leukocyte infiltration of the placenta and membranes. In addition, the production of MCP-1 may act as a marker for intra-amnionic infection and inflammation.
Summary of Preterm Labor

Preterm labor is a pathological condition with multiple etiologies and has recently been termed the *preterm parturition syndrome* (Romero and associates, 2006). Most research in this field has been focused on the role of infection in mediating preterm birth. It is possible that intrauterine infection causes some cases currently categorized as idiopathic spontaneous preterm labor. There are a variety of sites for intrauterine infection—maternal, fetal, or both—and increasing evidence that the inflammatory response may have distinct and compartment-specific functions that differ between uterus, fetal membranes, and cervix in normal birth. Thus, determining the proportion of pregnancies that end prematurely because of infection is difficult. That said, it is clear that infection does not explain all causes of preterm birth.

In recent years, our understanding of other influences on the parturition process such as maternal nutrition before or during pregnancy, genetics, and dynamic regulation of changes in the extracellular matrix have led to new avenues of research and a broader understanding of this complicated and multifactorial process. The current and future application of genomic and bioinformatics as well as molecular and biochemical studies will shed light on pathways involved in term and preterm labor and identify processes critical to all phases of cervical remodeling and uterine function.

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In 2006, the Centers for Disease Control and Prevention defined preconceptional care as “a set of interventions that aim to identify and modify biomedical, behavioral, and social risks to a woman’s health or pregnancy outcome through prevention and management.” In addition, it established the following goals for improving preconceptional care:

1. Improve knowledge, attitudes, and behaviors of men and women related to preconceptional health.
2. Assure that all women of childbearing age receive preconceptional care services—including evidence-based risk screening, health promotion, and interventions—that will enable them to enter pregnancy in optimal health.
3. Reduce risks indicated by a previous adverse pregnancy outcome through interconceptional interventions to prevent or minimize recurrent adverse outcomes.
4. Reduce the disparities in adverse pregnancy outcomes.

The American College of Obstetricians and Gynecologists (2005a) also has reinforced the importance of preconceptional and interpregnancy care. Moreover, recent data from the Centers for Disease Control and Prevention describe the health status of women who gave birth to live-born infants in the United States in 2004 (Table 7-1). This table demonstrates the high prevalence of many conditions that may be amenable to intervention during the preconceptional and interpregnancy periods (D’Angelo and associates, 2007).

Randomized trials that evaluate preconceptional counseling efficacy are scarce, partly because withholding such counseling would be unethical. In addition, because maternal and perinatal outcomes are dependent on the interaction of various maternal, fetal, and environmental factors, it is often difficult to ascribe salutary outcomes to a specific intervention (Moos, 2004). That said, there are a few prospective and case-control studies that clearly demonstrate the successes of preconceptional counseling.

Unplanned Pregnancy

Counseling about potential pregnancy risks and preventative strategies must be provided before conception. By the time most women realize they are pregnant—1 to 2 weeks after the first missed period—the fetal spinal cord has already formed and the heart is beating. Thus, many prevention strategies, for example folic acid to prevent neural-tube defects, are ineffective if initiated at this time. It is estimated that up to half of all pregnancies are unplanned, and that these may be at greatest risk (American College of Obstetricians and Gynecologists, 2006; Finer and Henshaw, 2006). Women with unintended pregnancy are more likely to be young or single; have lower educational attainment; use tobacco, alcohol, or illicit drugs; and not supplement with folate (Cheng, 2009; Dott, 2009; Postlethwaite, 2009, and all their associates).

To assess the effectiveness of preconceptional counseling to reduce unintended pregnancies, Moos and colleagues (1996) studied the effects of a preconceptional care program instituted in a health department clinic. The 456 women given preconceptional counseling had a 50-percent greater likelihood of describing their subsequent pregnancies as intended compared
with 309 women with health care but no counseling, and a 65-percent greater likelihood compared with women with no healthcare prior to pregnancy. Family planning and contraception are discussed in Chapter 32.

**CHRONIC MEDICAL DISORDERS**

### 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 52. Most important, many of these complications can be avoided if glucose control is optimized before conception. The American College of Obstetricians and Gynecologists (2005c) has concluded that preconceptional counseling for women with pregestational diabetes mellitus is both beneficial and cost-effective and should be encouraged.

Recommendations of the American Diabetes Association (2004) for the content of preconceptional care are listed in Table 7-2. Importantly, it advises that the preconceptional goal is to obtain the lowest hemoglobin A1c level possible without undue risk of hypoglycemia in the mother. In addition to assessing diabetic control during the preceding 6 weeks, hemoglobin A1c measurement can also be used to compute risks for major anomalies (Fig. 7-1). Although these data are from women with severe diabetes, the incidence of fetal anomalies in women who have gestational diabetes and fasting hyperglycemia is increased fourfold compared with that in normal women (Sheffield and associates, 2002).

**Efficacy of Counseling in Diabetic Women**

Preconceptional counseling has been shown to decrease diabetes-related complications at all stages of pregnancy. For example, Leguizamón and colleagues (2007) identified 12 clinical studies comparing the incidence of major congenital anomalies in a combined total of 1618 women with insulin-dependent diabetes mellitus who received preconceptional care with a combined total of 1599 who did not. The rates of congenital anomalies in the two groups were 2.7 and 8.3 percent, respectively. Importantly, 10 of the 12 studies showed that preconceptional care is associated with significantly fewer malformations.

Dunne and co-workers (1999) reported that diabetic women who received counseling sought prenatal care earlier, had lower hemoglobin A1c levels, and were less likely to smoke during pregnancy. Of the women who received counseling, none were delivered before 30 weeks compared with 17 percent in an uncounseled cohort. Finally, counseled women had fewer macrosomic infants—25 versus 40 percent; they had no growth-restricted infants compared with 8.5 percent; they had no neonatal deaths compared with 6 percent; and their infants had half as many admissions to the intensive care nursery—17 versus 34 percent. Similarly, Temple and associates (2006) found lower rates of adverse pregnancy outcome and preterm delivery in those receiving prepregnancy care.

It follows that preconceptional counseling reduces healthcare costs in diabetic women. Indeed, based upon their literature review, Reece and Homko (2007) found that for every dollar spent on a preconceptional care program for diabetic women between $1.86 and $5.19 was saved in direct medical costs averted. Surprisingly, despite such benefits, the proportion of diabetic women receiving preconceptional care remains low. In a study of approximately 300 women with diabetes enrolled in a managed-care plan, Kim and colleagues (2005) found that only about half reported receiving preconceptional counseling. Among the uninsured, the rates are undoubtedly even lower.

---

**TABLE 7-1.** Prevalence of Prepregnancy Maternal Behaviors, Experiences, Health Conditions, and Previous Poor Birth Outcomes in the United States in 2004

<table>
<thead>
<tr>
<th>Factor</th>
<th>Prevalence (percent)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tobacco use</td>
<td>23.2</td>
</tr>
<tr>
<td>Alcohol use</td>
<td>50.1</td>
</tr>
<tr>
<td>Multivitamin use</td>
<td>35.1</td>
</tr>
<tr>
<td>Contraceptive nonuse&lt;sup&gt;a&lt;/sup&gt;</td>
<td>53.1</td>
</tr>
<tr>
<td>Dental visit</td>
<td>77.8</td>
</tr>
<tr>
<td>Health counseling</td>
<td>30.3</td>
</tr>
<tr>
<td>Physical abuse</td>
<td>3.6</td>
</tr>
<tr>
<td>Stress</td>
<td>18.5</td>
</tr>
<tr>
<td>Underweight</td>
<td>13.2</td>
</tr>
<tr>
<td>Overweight</td>
<td>13.1</td>
</tr>
<tr>
<td>Obesity</td>
<td>21.9</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.8</td>
</tr>
<tr>
<td>Asthma</td>
<td>6.9</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2.2</td>
</tr>
<tr>
<td>Heart problem</td>
<td>1.2</td>
</tr>
<tr>
<td>Anemia</td>
<td>10.2</td>
</tr>
<tr>
<td>Prior low-birthweight infant</td>
<td>11.6</td>
</tr>
<tr>
<td>Prior preterm infant</td>
<td>11.9</td>
</tr>
</tbody>
</table>

<sup>a</sup>Among women who were not trying to become pregnant. Data from D’Angelo and associates (2007).

**FIGURE 7-1.** Relationship between first-trimester glycosylated hemoglobin values and risk for major congenital malformations in 320 women with insulin-dependent diabetes. (Data from Kitzmiller and associates, 1991.)
SECTION 3

Epilepsy

It is indisputable that women with epilepsy are two to three times more likely to have infants with structural anomalies than unaffected women (Wide and associates, 2004). Some reports indicate that epilepsy increases this risk, independent of the effects of antiseizure medication. This view is not held by all. Holmes and colleagues (2001) compared pregnancy outcomes in 509 epileptic women who took antiseizure medication with 606 who did not. They found that fetuses exposed to one drug had significantly fewer malformations than those exposed to two or more drugs—21 versus 28 percent. By contrast, the incidence of fetal defects of epileptic mothers who did not take medication was 8.5 percent—the same as in fetuses of women without seizure disorders.

Preconceptional counseling usually includes efforts to achieve control with monotherapy and with medications considered least teratogenic (Adab, 2004; Aguglia, 2009; Tomson, 2009, and all their associates). As shown in Table 7-3, some regimens used individually are less teratogenic than others. Results of a prospective registry, for example, indicate that the overall risk of major malformations associated with lamotrigine monotherapy is comparable with that of the general population. The risks of antiseizure medication are described in detail in Chapter 14 (p. 317). According to Jeha and Morris (2005), the American Academy of

<table>
<thead>
<tr>
<th>TABLE 7-2. American Diabetes Association Recommendations for the Preconceptional Care of Women with Diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Medical and obstetrical history</strong></td>
</tr>
<tr>
<td>- Duration and type of diabetes</td>
</tr>
<tr>
<td>- Acute complications, including history of infections, ketoacidosis, and hypoglycemia</td>
</tr>
<tr>
<td>- Chronic complications, including retinopathy, nephropathy, hypertension, atherosclerotic vascular disease, and neuropathy</td>
</tr>
<tr>
<td>- Diabetes management, including insulin regimen, use of glucose lowering agents, self-glucose monitoring regimens and results, nutrition, and physical activity</td>
</tr>
<tr>
<td>- Concomitant medical conditions</td>
</tr>
<tr>
<td>- Menstrual and pregnancy history, contraceptive use</td>
</tr>
<tr>
<td>- Support systems</td>
</tr>
<tr>
<td><strong>Physical examination</strong></td>
</tr>
<tr>
<td>- Blood pressure, including testing for orthostatic changes</td>
</tr>
<tr>
<td>- Retinal examination with pupillary dilatation</td>
</tr>
<tr>
<td>- Cardiovascular examination for evidence of cardiac or peripheral vascular disease—if present, screen for evidence of coronary artery disease</td>
</tr>
<tr>
<td>- Neurological examination</td>
</tr>
<tr>
<td><strong>Laboratory evaluation</strong></td>
</tr>
<tr>
<td>- Hemoglobin A₁c</td>
</tr>
<tr>
<td>- Serum creatinine</td>
</tr>
<tr>
<td>- Urine protein: protein excretion &gt;190 mg/24 hours may increase the risk for hypertensive disorders during pregnancy (see Chap. 34, p. 719); protein excretion &gt;400 mg/24 hours may increase the risk for fetal-growth restriction (see Chap. 38, p. 843).</td>
</tr>
<tr>
<td>- Thyroid function tests: 5- to 10-percent coincidence of type 1 diabetes and thyroid dysfunction (see Chap. 53, p. 1134).</td>
</tr>
<tr>
<td><strong>Initial management plan</strong></td>
</tr>
<tr>
<td>- Counseling</td>
</tr>
<tr>
<td>- Risk and prevention of congenital anomalies</td>
</tr>
<tr>
<td>- Fetal and neonatal complications of maternal diabetes (see Chap. 52, p. 1113)</td>
</tr>
<tr>
<td>- Effects of pregnancy on maternal diabetic complications (see Chap. 52, p. 1116)</td>
</tr>
<tr>
<td>- Risks of obstetrical complications that occur with increased frequency in diabetic pregnancies (see Chap. 52, p. 1113)</td>
</tr>
<tr>
<td>- Need for effective contraception until glycemia is well controlled</td>
</tr>
<tr>
<td>- Insulin regimen selected to achieve the following goals:</td>
</tr>
<tr>
<td>- Capillary plasma glucose before meals = 80–110 mg/dL</td>
</tr>
<tr>
<td>- Capillary plasma glucose 2 hours after meals less than 155 mg/dL</td>
</tr>
<tr>
<td>- Monitor hemoglobin A₁c levels at 1- to 2-month intervals until stable with the goal to achieve a concentration less than 1 percent above the normal range</td>
</tr>
</tbody>
</table>

There are no data to suggest that postmeal glucose monitoring has a specific role in preconception diabetes care beyond what is needed to achieve the target hemoglobin A₁c. Thus, a focus on preprandial monitoring is recommended initially to assist patients in self-selection of insulin doses.

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Neurology recommends consideration for discontinuation of antiseizure medication in select women, including those who:

1. Have been seizure-free for 2 to 5 years
2. Have a single seizure type
3. Have a normal neurological examination and normal intelligence
4. Have an electroencephalogram that has normalized with treatment.

Epileptic women also are advised to take supplemental folic acid. Biale and Lewenthal (1984) performed a case-control study to evaluate effects of periconceptional folate supplementation in women taking anticonvulsants. Although 10 of 66 (15 percent) unsupplemented pregnancies resulted in offspring with congenital malformations, none of 33 neonates of supplemented women had anomalies. Similarly, in a case-control study using the Hungarian National Birth Registry, Kjær and colleagues (2008) concluded that risk of congenital abnormalities in fetuses exposed to carbamazepine, phenobarbital, phenytoin, and primidone is reduced—but not eliminated—by folic acid supplementation.

Vajda and colleagues (2008) recently reported results from the Australian Register of Antiepileptic Drugs in Pregnancy. They found that the risk of seizures during pregnancy was 50 to 70 percent less if the prepregnancy year was seizure free. Once one year without seizures had elapsed, there seemed to be relatively little further advantage in deferring pregnancy to avoid seizures during pregnancy.

### Other Chronic Diseases

Cox and co-workers (1992) reviewed pregnancy outcomes of 1075 high-risk women who received preconception counseling. The 240 women with hypertension, renal disease, thyroid disease, asthma, or heart disease had significantly better outcomes than with their previous pregnancies. Indeed, 80 percent of those counseled were delivered of normal infants, compared with only 40 percent in the previous gestation which lacked prepregnancy counseling.

### GENETIC DISEASES

The incidence of these defects is 1 to 2 per 1000 live births, and they are second only to cardiac anomalies as the most frequent structural fetal malformation (see Chap. 12, p. 281). Some NTDs, as well as congenital heart defects, are associated with a specific mutation in the methylene tetrahydrofolate reductase gene (677C → T). Adverse effects of this appear to be largely overcome by periconceptional folic acid supplementation (Ou and colleagues, 1996). Although its role is still controversial, low levels of vitamin B<sub>12</sub> preconceptionally, similar to folate, may increase the risk of neural-tube defects (Molloy and co-workers, 2009; Thompson and colleagues, 2009).

The Medical Research Council on Vitamin Study Research Group (1991) conducted a randomized double-blind study of preconceptional folic acid therapy at 33 centers in seven European countries. Women with a previous affected child who took supplemental folic acid before conception and throughout the first trimester reduced their NTD recurrence risk by 72 percent. Perhaps more importantly, because 90 to 95 percent of infants with NTDs are born to women with no prior family history, Czeizel and Dudas (1992) showed that supplementation reduced the <i>a priori</i> risk of a first NTD occurrence.

Despite such benefit, in recent years, only 40 to 50 percent of women have taken folic acid supplementation during the periconceptional period (de Jong-van den Berg and co-workers, 2005; Goldberg and colleagues, 2006). The strongest predictor of use appears to be consultation with a health-care provider before conception. To improve supplementation, many countries fortify wheat and maize flour with folic acid to lower rates of NTDs (Bell and Oakley, 2008; Hamner and associates, 2009).

### Neural-Tube Defects (NTDs)

The incidence of these defects is 1 to 2 per 1000 live births, and they are second only to cardiac anomalies as the most frequent structural fetal malformation (see Chap. 12, p. 281). Some NTDs, as well as congenital heart defects, are associated with a specific mutation in the methylene tetrahydrofolate reductase gene (677C → T). Adverse effects of this appear to be largely overcome by periconceptional folic acid supplementation (Ou and colleagues, 1996). Although its role is still controversial, low levels of vitamin B<sub>12</sub> preconceptionally, similar to folate, may increase the risk of neural-tube defects (Molloy and co-workers, 2009; Thompson and colleagues, 2009).

### Phenyketonuria (PKU)

This inherited disorder of phenylalanine metabolism is an example of a disease in which the fetus is not at risk to inherit the disorder, but may be damaged by maternal disease. Specifically, individuals with PKU who eat an unrestricted diet have abnormally high blood phenylalanine levels. As discussed in Chapter 12 (p. 277), this amino acid readily crosses the placenta and can damage developing fetal organs, especially neural and cardiac tissues (Table 7-4). With appropriate preconception counseling and adherence to a phenylalanine-restricted diet before pregnancy,
TABLE 7-4. Frequency of Complications in the Offspring of Women with Untreated Phenylketonuria (Blood Phenylamine >1200 μmol/L)

<table>
<thead>
<tr>
<th>Complication</th>
<th>Frequency in Affected Pregnanacies (percent)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spontaneous abortions</td>
<td>24</td>
</tr>
<tr>
<td>Mental retardation</td>
<td>92</td>
</tr>
<tr>
<td>Microcephaly</td>
<td>73</td>
</tr>
<tr>
<td>Congenital heart disease</td>
<td>12</td>
</tr>
<tr>
<td>Intrauterine growth restriction</td>
<td>40</td>
</tr>
</tbody>
</table>


the incidence of fetal malformations is dramatically reduced (Guttler, 1990; Hoeks, 2009; Koch, 1990, and all their associates).

The Maternal Phenylketonuria Collaborative Study confirmed the effectiveness of preconceptional care in almost 300 women with this disorder (Rouse and co-workers, 1997). Compared with infants whose mothers had poor dietary control, infants of those women with a low phenylalanine diet had a lower incidence of microcephaly—6 versus 15 percent, neurological abnormalities—4 versus 14 percent, and cardiac defects—none versus 16 percent. Similarly, Lee and colleagues (2005) found improved fetal birthweights, head circumferences, and intelligence quotient (IQ) scores in 110 newborns whose mothers began a phenylalanine-restricted diet before conception.

Thalassemias

These disorders of globin-chain synthesis are the most common single-gene disorders worldwide. 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. 51, p. 1090). In endemic areas such as Mediterranean and Southeast Asian countries, counseling and other prevention strategies have reduced the incidence of new cases by at least 80 percent (Angelini and Modell, 1998). The American College of Obstetricians and Gynecologists (2007) recommends that individuals of such ancestry be offered carrier screening to allow them to make informed decisions regarding reproduction and prenatal diagnosis. Preimplantation genetic diagnosis of thalassemia is available for candidate patients (Chen and associates, 2008; Mohd Nasri and colleagues, 2009).

Experiences with a long-standing counseling program aimed at Montreal high school students at risk were summarized by Mitchell and colleagues (1996). During a 20-year period, 25,274 students of Mediterranean origin were counseled and tested for β-thalassemia. Within a few years of initiating the preconceptional program, all high-risk couples who requested prenatal diagnosis had already been counseled, and no affected children were born during those times.

Genetic Diseases More Prevalent in Individuals of Eastern European Jewish Descent

Most individuals of Jewish ancestry in North America are descended from Ashkenazi Jewish communities and are at an increased risk for having offspring with one of the autosomal recessive disorders listed in Table 7-5. The American College of Obstetricians and Gynecologists (2004) recommends preconceptional care for these women:

- The family history of individuals considering pregnancy—or who are already pregnant—should determine whether either member of the couple is of Eastern European (Ashkenazi) Jewish ancestry or has a relative with cystic fibrosis or a genetic condition listed in Table 7-5.
- Carrier screening for Tay-Sachs disease, Canavan disease, cystic fibrosis, and familial dysautonomia should be offered to Ashkenazi Jewish individuals before conception.
- Carrier screening is also available for mucolipidosis IV, Niemann-Pick disease type A, Fanconi anemia group C, Bloom syndrome, and Gaucher disease.
- When only one partner is of Ashkenazi Jewish descent, that individual should be screened first. If this individual is a carrier, the other partner is offered screening. The couple should be informed that the carrier frequency and detection rate in non-Jewish individuals is unknown for all of these disorders except Tay-Sachs disease and cystic fibrosis (see Table 7-5). Therefore, it is difficult to predict the couple’s risk of having a child with the disorder.
- Individuals with a positive family history of one of these disorders should be offered carrier screening for the specific disorder and may benefit from genetic counseling (see Chap. 8, p. 200).
- When both partners are carriers of one of these disorders, they should be referred for genetic counseling and offered prenatal diagnosis.
- When an individual is found to be a carrier, he or she should be encouraged to inform relatives that they are at risk for carrying the same mutation.

Tay-Sachs Disease

The effectiveness of preconceptional counseling in reducing genetic disease has been most clearly demonstrated in Tay-Sachs disease. This disease is a severe, autosomal-recessive neurodegenerative disorder that leads to death in early childhood. In the early 1970s, there were approximately 60 new cases in the United States each year, primarily in individuals of Jewish heritage. An intensive worldwide campaign was initiated to counsel Jewish men and women of reproductive age to identify carriers through genetic testing, to provide prenatal testing for high-risk couples, and even to help heterozygote carriers choose unaffected mates. Within 8 years of the inception of this campaign, nearly 1 million young adults around the world had been tested and counseled. The incidence of new Tay-Sachs cases has plummeted to only approximately five new cases per year (Kaback and colleagues, 1993). Currently, most new cases are in the non-Jewish population.
<table>
<thead>
<tr>
<th>Disorder</th>
<th>Disease Incidence</th>
<th>Carrier Frequency(^a)</th>
<th>Detection Rate(^a)</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tay-Sachs disease</td>
<td>1/3000</td>
<td>1/30</td>
<td>Varies(^b)</td>
<td>Caused by hexosaminidase A deficiency. Neurological motor and mental dysfunction with childhood death. No effective treatment</td>
</tr>
<tr>
<td>Canavan disease</td>
<td>1/6400</td>
<td>1/40</td>
<td>98%</td>
<td>Caused by aspartoacylase deficiency. Neurological disorder with developmental delay, hypotonia, large head, seizures, blindness, gastrointestinal reflux, and childhood death. No effective treatment</td>
</tr>
<tr>
<td>Cystic fibrosis</td>
<td>1/2500–3000</td>
<td>1/29</td>
<td>97%</td>
<td>See p. 178</td>
</tr>
<tr>
<td>Familial dysautonomia</td>
<td>1/3600</td>
<td>1/32</td>
<td>99%</td>
<td>Caused by mutations in IKBKAP gene. Neurological disorder with poor feeding, abnormal sweating, pain and temperature insensitivity, labile blood pressure, and scoliosis. No cure, but some treatments lengthen and improve quality of life</td>
</tr>
<tr>
<td>Fanconi anemia group C</td>
<td>1/32,000</td>
<td>1/89</td>
<td>99%</td>
<td>Usually caused by recessive mutation of any of several genes. Severe anemia, pancytopenia, developmental delay, failure to thrive, and later-childhood death. Congenital anomalies, microcephaly, and mental retardation may be present. Bone-marrow transplantation may be successful</td>
</tr>
<tr>
<td>Niemann-Pick disease type A</td>
<td>1/32,000</td>
<td>1/90</td>
<td>95%</td>
<td>Caused by sphingomyelinase deficiency. Neurodegenerative disorder with childhood death. No effective treatment</td>
</tr>
<tr>
<td>Mucolipidosis IV</td>
<td>1/62,500</td>
<td>1/127</td>
<td>95%</td>
<td>Neurodegenerative lysosomal storage disorder with growth failure, marked psychomotor retardation, and retinal degeneration. Life expectancy may be normal. There is no effective treatment</td>
</tr>
<tr>
<td>Bloom syndrome</td>
<td>1/40,000</td>
<td>1/100</td>
<td>95–97%</td>
<td>Increased chromosome breakage, susceptibility to infections and malignancies, growth deficiency, skin findings, and mental retardation. Death usually in 20s and related to cancer. No effective treatment</td>
</tr>
<tr>
<td>Gaucher disease (Type 1)</td>
<td>1/900</td>
<td>1/15</td>
<td>95%</td>
<td>Caused by (\beta)-glucosidase deficiency. Affects the spleen, liver, and bones. Develops at any age with a wide clinical spectrum including anemia, bruising and bleeding, hepatosplenomegaly, and osteoporosis. Enzyme therapy improves quality of life</td>
</tr>
</tbody>
</table>

\(^a\)Non-Jewish carrier frequency and detection rates are unknown except for Tay-Sachs disease: 1 in 30 if French Canadian or Cajun ancestry and 1 in 300 for others, with a 98-percent carrier detection rate by Hex-A test.

\(^b\)Detection is 98 percent by Hex-A test, 94 percent by DNA-based test.

Data from the American College of Obstetricians and Gynecologists (2004, 2005d) and the National Institute of Neurological Disorders and Stroke (2007a–d).

The American College of Obstetricians and Gynecologists (2005d) recommends the following regarding Tay-Sachs disease:

- Screening be offered before pregnancy if both members of a couple are of Ashkenazi Jewish, French-Canadian, or Cajun descent. Those with a family history consistent with Tay-Sachs disease should also be offered screening.

- When one member of a couple is at high risk as described above, but the other partner is not, the high-risk partner should be offered screening, especially if there is uncertainty about ancestry or if there is a consistent family history. If the high-risk partner is determined to be a carrier, the other partner also should be offered screening.
• Biochemical analysis by determining hexosaminidase A serum levels should be used for individuals in low-risk populations. Leukocyte testing must be used if the woman is already pregnant or taking oral contraceptives.
• Ambiguous or positive screening test results should be confirmed by biochemical and DNA analysis for the most common mutation. This will detect patients who carry genes associated with mild disease or pseudodeficiency states.
• If both partners are determined to be carriers of Tay-Sachs disease, genetic counseling and prenatal diagnosis should be offered.

PRECONCEPTIONAL COUNSELORS

Practitioners providing routine health maintenance have the best opportunity to provide preventive counseling. Gynecologists, internists, family practitioners, and pediatricians can do so at periodic health examinations. The occasion of a negative pregnancy test is an excellent time for counseling. Jack and associates (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. These included medical or reproductive problems—52 percent, family history of genetic diseases—50 percent, increased risk of human immunodeficiency virus (HIV)—30 percent, increased risk of hepatitis B and use of illegal substances—25 percent, alcohol use—17 percent, and nutritional risks—54 percent.

Basic advice regarding diet, alcohol and illicit drug use, smoking, vitamin intake, exercise, and other behaviors can be provided. Pertinent medical records should be reviewed. Counselors should be knowledgeable about relevant medical diseases, prior surgery, reproductive disorders, or genetic conditions, and must be able to interpret data and recommendations provided by other specialists. If the practitioner is uncomfortable providing counseling, the woman or couple should be referred to an appropriate counselor.

PRECONCEPTIONAL COUNSELING VISIT

Personal and Family History
A thorough review is taken of the medical, obstetrical, social, and family histories. Useful information is more likely to be obtained by asking specific questions about each history and about each family member than by asking general, open-ended questions. The interview may take 30 minutes to an hour. Some important information can be obtained by questionnaire, ideally at a routine prepregnancy visit. Prepared questionnaires are also available that address these topics. Answers are reviewed with the couple to ensure appropriate follow-up, including obtaining relevant medical records.

Medical History
Preconceptional counseling addresses all risk factors pertinent to mother and fetus. General points include how pregnancy will affect maternal health, and how a high-risk condition might affect the fetus. Finally, advice for improving outcome is provided. Almost any medical, obstetrical, or genetic condition warrants some consideration prior to pregnancy. These are discussed in terms of general maternal and fetal risks, and suggestions for preconception evaluation are offered. More detailed information on specific diseases is found in their relevant chapters.

Genetic Diseases
Women whose ethnic background, race, or personal or family history places them at increased risk to have a fetus with a genetic disease should receive appropriate counseling. This includes the possibility of prenatal diagnosis as discussed in Chapter 13. These women may require additional counseling visits to a trained genetic counselor. They also may benefit from consultation with other specialists, for example, anesthesiologists, cardiologists, or surgeons.

Reproductive History
Questions are asked regarding infertility; abnormal pregnancy outcomes, including miscarriage, ectopic pregnancy, and recurrent pregnancy loss; and obstetrical complications such as preeclampsia, placental abruption, and preterm delivery (Stubblefield and co-workers, 2008). Regarding this last complication, most studies to date have not disclosed significant benefits of proposed prophylactic regimens such as treatment of bacterial vaginosis or other interconceptional antimicrobial regimens to prevent spontaneous preterm birth (Andrews and colleagues, 2006; Allsworth and Peipert, 2007).

History of a prior stillborn infant is especially important. This was recently reviewed by Silver (2007).

When identified, specific complications can be managed as outlined in discussions of these topics, which are found in later chapters of this text.

Social History

Maternal Age
Women at both ends of the reproductive-age spectrum have unique outcomes that are considered.

Adolescent Pregnancy. According to the Centers for Disease Control and Prevention, 7.6 percent of births in 2002 in the United States were in women between the ages of 15 and 19 years. Although this represented a 9-percent decline since 2000, the adolescent pregnancy rate remains among the highest of all industrialized nations (Ventura and colleagues, 2006). Adolescents are more likely to be anemic, and they are at increased risk to have growth-restricted infants, preterm labor, and a higher infant mortality rate (Fraser and associates, 1995; Usta and co-workers, 2008). The incidence of sexually transmitted diseases—common in adolescents—is even higher during pregnancy (Nicolai and colleagues, 2003).

Because most of their pregnancies are unplanned, adolescents rarely seek preconception counseling. These young women usually are still growing and developing and thus have greater caloric requirements than older women. The normal or underweight adolescent should be advised to increase caloric intake by 400 kcal/day. Alternatively, as discussed in Chapter 43, the obese adolescent likely does not need additional calories. Nonjudgmental questioning may elicit a history of substance abuse.
Pregnancy after Age 35. Currently, about 10 percent of pregnancies occur in women within this age group. The older woman is more likely to request preconceptional counseling, either because she has postponed pregnancy and now wishes to optimize her outcome, or because she plans to undergo infertility treatment. Some studies—including data from Parkland Hospital presented in Figure 7-2—indicate that after age 35, there is an increased risk for obstetrical complications as well as perinatal morbidity and mortality (Cunningham and Leveno, 1995; Huang and associates, 2008). 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 much lower than previously reported.

The maternal mortality rate is higher in women aged 35 and older. Compared with women in their 20s, women aged 35 to 39 are 2.5 times more likely and women aged 40 or more are 5.3 times more likely for pregnancy-related mortality (Geller and colleagues, 2006). According to Buehler and colleagues (1986), improved medical care may ameliorate these risks. They reviewed maternal deaths in the United States from 1974 through 1982. Through 1978, older women had a fivefold increased relative risk of maternal death compared with that of younger women. By 1982, however, the mortality rates for older women had decreased by 50 percent.

Maternal age-related fetal risks primarily stem from: (1) indicated preterm delivery for maternal complications such as hypertension and diabetes, (2) spontaneous preterm delivery, (3) fetal growth disorders related to chronic maternal disease or multifetal gestation, (4) fetal aneuploidy, and (5) pregnancies resulting from use of assisted reproductive technology.

Most researchers have found that fetal aneuploidy is the only congenital abnormality related to maternal age. A study of 577,000 births in British Columbia by Baird and co-workers (1991) and another of 574,000 live births in Sweden by Pradat (1992) found no association between nonaneuploid structural defects and maternal age. An exception was the study by Hollier and colleagues (2000) of nearly 103,000 pregnancies that included 3885 infants with congenital malformations delivered at Parkland Hospital. They reported that the incidence of nonaneuploid structural abnormalities increased significantly with maternal age. Some contend, however, that ascertainment bias was likely because older mothers commonly underwent targeted sonographic examination but not amniocentesis, and the study population was enriched with regional referrals for women with malformed fetuses.

**Assisted Reproductive Techniques.** Recall that older women have subfertility problems. And although the incidence of dizygotic twinning increases related to maternal age, the more important cause of multifetal gestation in older women follows the use of assisted reproductive technology and ovulation induction. Indeed, according to the Centers for Disease Control and Prevention, 40 percent of triplet and 17 percent of twin births in the United States in 2004 were the result of assisted reproductive technologies (Martin and associates, 2007). As discussed in Chapter 39 (p. 859), multifetal pregnancies account for much of the morbidity and mortality from preterm delivery (Schieve and colleagues, 2002; Strömberg and associates, 2002).

Over the past decade, experience has accrued that links assisted reproductive techniques to increased major congenital malformations. Hansen and co-workers (2002) reported that 9 percent of 837 infants conceived by in vitro fertilization and 8.6 percent of 301 infants conceived using intracytoplasmic sperm injection and had major birth defects—this compared with 4.2 percent in 4000 control women.

**Paternal Age.** Although there is an increased incidence of genetic diseases in offspring caused by new autosomal-dominant mutations in older men, the incidence is still low (see Chap. 12, p. 276). Accordingly, whether targeted sonographic examinations should be performed solely for advanced maternal or paternal age is controversial.

**Recreational Drugs and Smoking**

Fetal risks associated with alcohol, marijuana, cocaine, amphetamines, and heroin are discussed in Chapter 14 (see p. 326). The first step in preventing drug-related fetal risk is for the woman to honestly assess her usage. Questioning should be nonjudgmental. Alcoholism can be identified by asking the well-studied TACE questions, which correlate with DSM-IV criteria (Chang and associates, 1998). TACE is a series of four questions concerning tolerance to alcohol, being annoyed by comments about their drinking, attempts to cut down, and a history of drinking early in the morning—the “eye opener.”

In a Canadian study of more than 1000 postpartum patients, Tough and colleagues (2006) found that a high percentage of women reported alcohol use while trying to conceive. Specifically, nearly half of those planning for pregnancy reported a mean of 2.2 drinks daily during early gestation before they recognized that they were pregnant. Of note, Bailey and co-workers (2008) found that rates of binge drinking and marijuana use by men were unaffected by their partner’s pregnancy. The frequency and pattern of such behaviors clearly underscore the opportunity for preconceptional counseling.

In 2005, approximately 10 percent of women giving birth in the United States smoked cigarettes, and this rate was roughly

**FIGURE 7-2.** Incidence of selected pregnancy complications in relation to maternal age among 235,329 women delivered at Parkland Hospital, 1988–2007. (Used with permission from Dr. Donald McIntire.)