Prenatal and Postnatal Care

A Woman-Centered Approach

Second Edition

Robin G. Jordan
Cindy L. Farley
Karen Trister Grace

WILEY Blackwell

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This book is dedicated to women who persist.

To the wide circle of women in my life who help keep me physically strong, intellectually growing, and emotionally sustained.
And laughing the whole time.
~Robin~

To my granddaughter, Isabel Brown, from Brooklyn Town.
My wish for you is expressed in the Girl's Globe Manifesto and my hope is that this book contributes in small part toward a healthy life for women and their families:
"A girl should be free to live to her full potential, to live a healthy life, free from violence and discrimination. To get educated and access her right to go to school. To choose when, if and whom to marry and have children when she is ready. Simple, these are her rights. With them she can change the world."
~With love, Nana Cindy~

To my husband, Peter, whose love, support, and co-parenting makes it all possible.
~Karen~

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About the Editors

Robin G. Jordan, PhD, CNM, FACNM, studied midwifery at the University of Medicine and Dentistry of New Jersey, after earning her MSN from Case Western Reserve University. She earned a PhD in Health Sciences from Touro University. Dr. Jordan started the first hospital-based nurse-midwifery service in the greater Northern Michigan area. During her clinical practice career, she has attended childbearing women in hospital, birth center, and home settings. Dr. Jordan was a long-standing faculty member of Frontier Nursing University, developing and teaching the Antepartum Care course series for midwifery and nurse practitioner students. She has also served as adjunct faculty at Georgetown University in the Nurse-Midwifery/Women's Health Nurse Practitioner (WHNP) programs teaching antepartum care. She is coauthor of *Clinical Practice Guidelines for Midwifery and Women's Health*. Dr. Jordan currently serves her community as a member of the board of directors of the local women's safe home, and is active in state politics with a focus on improving health care for women and girls.

Cindy L. Farley, PhD, CNM, FACNM, studied midwifery at Emory University. She earned her BSN and PhD from The Ohio State University and her MSN from Emory University. She is an associate professor at Georgetown University in the Nurse-Midwifery/WHNP programs. She serves as a locum tenens midwife for Mount Eaton Care Center, an Amish birth center, and Pomerene Hospital, a rural hospital in Millersburg, Ohio. Dr. Farley works as a legal expert on selected cases involving midwifery regulatory issues and clinical care. She is co-author of *Clinical Practice Guidelines for Midwifery and Women's Health.* Dr. Farley has been instrumental in organizing groups of midwifery students to visit their federal legislators and advocate for positive change in important maternal health policies and legislation. Making midwives to improve the health of women and their families is Dr. Farley's passion.

Karen Trister Grace, PhD(c), MSN, CNM, has been a midwife for 18 years. She earned a BA in sociology at Barnard College, a BSN and MSN from the University of Pennsylvania, a Certificate in Health Disparities and Health Inequality from Johns Hopkins Bloomberg School of Public Health, and she is currently a PhD candidate at Johns Hopkins University School of Nursing. Her research focuses on unintended pregnancy and reproductive coercion. Ms. Grace has also been a nursing and midwifery educator for 10 years, and is currently an Adjunct Instructor at Georgetown University in the Nurse-Midwifery/WHNP program. She practices clinically at Mary's Center, a FQHC in the metropolitan Washington, DC, area.

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Preface

Pregnancy and the birth of a baby are significant life-changing events for a woman and her family. A woman transforms into a mother, and a family is created. Optimal care not only focuses on the physical process but also on the emotional experience of pregnancy and the postpartum period. The context of a woman's culture, life experiences, social roles, and physical and mental health status on the childbearing experience influence her options, choices and outcomes.

This book both describes and challenges current prenatal and postnatal care practices. Prenatal care visits within the current pathology-centered model of care are brief and focused on testing, legalities, and reimbursement. Too often this approach emphasizes the needs of the provider within the office setting rather than the woman's needs during pregnancy. Postnatal care is often limited in scope and connection at a time when the new family needs guidance and support from professionals as well as family members. This is a disservice to women and their families. Opportunities to promote health and well-being for the woman and her family during pregnancy, birth, and beyond are being missed in contemporary practice. These missed opportunities are reflected in the rising maternal mortality rate in the United States.

The woman herself and her unique needs are the rightful focus of prenatal and postnatal care. *Woman-centered care* is the term used to describe a philosophy of maternity care that is based on the needs and preferences of the woman. This care emphasizes the importance of informed choice, continuity of care, active participation, best care practices, provider responsiveness, and accessibility. Pregnancy, childbirth, and the postpartum period are the start of family life. A full account of the meaning and values that each woman brings to her experience of pregnancy and motherhood should be included in care.

The fundamental principles of woman-centered care encompass the following tenets:

- Women are co-creators of their maternity care with their healthcare providers.
- Women have the right to informed choice in the options available to them during pregnancy, labor, birth, and the postnatal period, including the place of birth, who provides care, and where care is provided.
- Women have the ultimate authority over the key decisions that affect the content and progress of their care.
- Women have the moral and legal right to decisions regarding their bodily integrity.
- Women have the right to care that supports their optimal health and that of their baby.

Prenatal and postnatal care provided within the context of the woman's own experience, focused on both the life-changing nature of the pregnancy experience as well as physical adaptations and needs, leads to improved maternal and infant outcomes. The views, beliefs, and values of the woman, her partner, and her family in relation to her care and that of her baby are sought and respected at all times. Adequate time is spent in providing optimal prenatal and postnatal care with kindness, respect, and dignity.

The Need for This Text

A growing body of scientific evidence supports physiological childbearing for healthy pregnant women at low risk for complications. Several decades of escalating pregnancy and birth medicalization have shown that interventions applied on a large scale and without medical indication lead to significant negative iatrogenic consequences. However, care supporting physiological labor and birth does not begin with the first contraction; rather, it begins with the first prenatal appointment and continues into the postpartum period. Too much faith is placed in technology and too little faith is placed in human connection and caring. This book brings balance to the fore; it adds a holistic framework from which to enter into dialogue with the woman who presents for care. Midwives, nurse practitioners, physicians, physician assistants and other prenatal and postnatal healthcare providers, and students with common practice foundations in providing holistic care, emphasizing patient education and health maintenance in the context of an ongoing relationship, will find this book useful.

The editors of this book are experienced clinicians and educators of midwives, nurse practitioners, medical students, and other healthcare providers. We have found that many available obstetrical and maternity care texts offer limited content on prenatal and postnatal care. Additionally, an appreciation of the effects of the

mind–body connection and the background social dynamics of the pregnant woman and her family on her overall health and childbearing experience has been lacking. This appreciation, in addition to a solid understanding of normal childbearing processes, will increase healthcare providers' competency in supporting the normal and recognizing the abnormal. This text provides a breadth and depth of knowledge on normal pregnancy and postpartum processes and care not found in other texts.

New in the Second Edition

This edition has been updated in all chapters to reflect current standards and care recommendations. An intentional focus is placed on the needs of diverse populations. The following new chapters have been added:

- Prenatal Ultrasound
- Oral Health
- Diversity and Inclusiveness in the Childbearing Year
- Preparing for Birth
- Triage during Pregnancy
- Pregnancy after Infertility

Additional highlights include new and updated content on pregnant women in the workplace, prenatal genetic testing, trauma-informed care, and transgender pregnancy care. The second edition also includes commonly used complementary therapies and offers more detailed information on planning for birth and on select prenatal and postpartum complications. Faculty resources have been expanded within the electronic text version.

Gender and Language

The editors recognize that some readers may take strong exception to and may feel marginalized by the use of the term *woman* throughout this textbook, including in its title. In our clinical practices and in our scholarly work, it is our aim to honor the full range of gender identities of the pregnant people who we and other prenatal care providers care for. And as writers, we are especially attuned to the politics and the power of language. We recognize that some providers care for people who were assigned female at birth but who seek pregnancy and identify as male or gender nonconforming, and that the language in this book may leave them wondering if their patients and their clinical experiences are represented here. We have added content in this edition about prenatal and postnatal care for transgender individuals that we feel is important for all prenatal care providers to know. We aimed for the most inclusive language possible without losing the "woman-centered" focus we originally set out to provide. We wish to state, in unequivocal terms, our unwavering support for pregnant people of all genders, and the providers who offer a person-centered approach to caring for this vulnerable population.

We are pleased that the first edition has been well received by clinicians and faculty in educational programs of various health professions. The first edition was honored with the 2015 Book of the Year award from the American College of Nurse Midwives. We are extremely fortunate to have many highly regarded contributors to the second edition and to mentor some talented new writers. All contributing authors have a background in clinical practice and are established content experts in their field. Most of our contributors are also educators, bringing an understanding of the needs of students to the text. We want to acknowledge our co-editors of the first edition, Julie A. Marfel and Janet L. Engstrom, and their work in launching the first edition. We are excited to welcome Karen Trister Grace to our editorial team for the second edition.

Just as second labors differ from the first when considering pregnancy and birth, so too do second editions differ from first edition texts. We knew what to expect and were prepared, but met a few surprises along the way. Throughout the process, we held true to our goal—to give birth to a text that will assist clinicians and students to provide exemplary prenatal and postnatal care. We hope our efforts on this second edition will inform and inspire you as you serve the childbearing women and families of your community.

This book was written as a resource for all those interested in providing woman-centered prenatal and postnatal care. While aspects of this care are timeless and do not change, certain elements of prenatal and postnatal care are refined as new evidence is incorporated into existing bodies of knowledge. Healthcare providers are responsible for their ongoing learning in the field and should read critically and widely among the many resources available to them. Evidence-based health care encompasses psychosocial and cultural aspects of care applied in a mutual dialogue and determination with each individual woman.

The authors, editors, and publisher have made every effort to assure accuracy of information as this book goes to press. Nevertheless, they are not responsible for errors, omissions, or outcomes related to the application of this information in the clinical setting. This is at the healthcare provider's own discretion.

Robin G. Jordan
Cindy L. Farley
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About the Companion Website

This book is accompanied by a companion website:

www.wiley.com/go/jordan/prenatal

The website includes:

- Case studies
- Multiple Choice Questions

Prenatal and Postnatal Care

A Woman-Centered Approach

Part I

Physiologic Foundations of Prenatal and Postnatal Care

1

Reproductive Tract Structure and Function

Patricia W. Caudle

Relevant Terms

Adrenarche—initiation of increased adrenal androgens
Ampulla—wider end of the fallopian tube
Atresia—degeneration and absorption of immature follicles
Bartholin glands—pea sized bilateral vulvar glands that secrete fluid to lubricate the vagina
Cervix—lower portion of the uterus
Chadwick's sign—bluish color to the cervix, vagina and labia due to increased blood flow in pregnancy, can be seen as early as 6-8 weeks gestation
Clitoris—erogenous organ with erectile tissue covered by labia minora
Cornua—both sides of the upper outer area of the uterus where the fallopian tubes join the uterus
Ectropion—visible columnar cells at the cervical os
Endocervical canal—passageway within the cervix to the inner uterus
Endometrium—lining of the uterus
Escutcheon—pubic hair
Fimbriae—fingerlike projections that move the egg toward and into the fallopian tube
First polar body—other half of the product of division of the primary oocyte
Fornix (fornices)—spaces around the cervix in the vagina
Fourchette—area immediately below the introitus
Gonadarche—period when ovaries begin to secrete sex hormones
Gonadostat—gonadotropin-releasing hormone pulse generator
Granulosa cells—cells lining an ovarian follicle that become luteal cells after ovulation
Ground substance—mucopolysaccharide between smooth muscle and collagen of the cervix
Hart's line—line of change where skin transitions to smoother, moist skin
Hegar's sign—softening and compressibility of the uterine isthmus
Hymen—membranous ring of tissue at the introitus
Introitus—opening to the vagina
Isthmus—uterine "neck" between cervix and body
Labia majora—two rounded folds of adipose tissue covered with pubic hair
Labia minora—folds of tissue between the labia majora
Lactobacilli—normal bacterial flora of the vagina
Leptin—hormone secreted by fat cells that plays a key role in appetite and metabolism
Meatus—opening of the urethra
Menarche—initiation of menses
Metaplasia—normal replacement of one cell type with another
Mittelschmerz—pain upon ovulation
Myometrium—middle, muscular layer of the uterus
Mucin—glycosylated proteins that form mucus that acts as lubricant and protectant
Nulliparous—a woman who has never had a child
Oogenesis—transformation of oogonia into oocytes
Oogonia—primordial female germ cells
Os—opening of the cervix
Parous—woman who has had a child
Peritoneum—thin membrane around abdominal organs that covers the bladder, uterus, and rectum
Rectouterine pouch—fold of peritoneum between the uterus and the rectum
Rectovaginal septum—tissue between the rectum and vagina
Rugae—thin ridges of tissue like an accordion that allow for expansion in the vagina
Squamocolumnar junction (SCJ)—where squamous cells and columnar cells meet on the cervix
Skene glands—small bilateral vulvar glands that secrete fluid to lubricate the urethra
Thelarche—breast development
Vasovagal response—bradycardia and syncope caused by stretching the cervical canal
Vesicouterine pouch—fold of peritoneum between the bladder and the uterus
Vesicovaginal septum—tissue between the bladder and the vagina
Vestibule—area inside the labia minora where openings of the urethra and the vagina are found
Zona pellucida—membrane surrounding the plasma membrane of the oocyte

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Companion website: www.wiley.com/go/jordan/prenatal

Anatomy of the Female Reproductive System

An understanding of the anatomy of the female reproductive system is essential in caring for women. It is important to be able to recognize normal structures and to appreciate that there is a wide variation of normal among women.

External Genitalia

The vulva is a term designated for the external genitalia of the female. The vulva includes the mons pubis, **labia majora** and **minora**, **clitoris**, **vestibule**, **hymen**, urinary **meatus**, and Skene and Bartholin glands. Figure 1.1 and Figure 1.2 illustrate the external genitalia and its development from embryonic structures.

The mons pubis is the cushion-like area over the pubic bone. In adult woman, the mons is covered with curly, coarse pubic hair called the **escutcheon**. The pubic hair distribution is usually triangular but may extend up toward the umbilicus in a diamond shape in women who have higher levels of serum androgens.

The labia majora consist of two rounded folds of adipose tissue covered with pubic hair that extend from the mons to the perineum on either side of the vaginal opening. The labia minora, found between the majora, are thinner, pinkish in color, and hairless (Bickley & Szilagyi, 2013). The labia majora have the same position and general structure as the male scrotum and arise from the same tissues during embryonic development.

The labia minora have two folds above where they divide to descend on either side of the vestibule, ending at the **fourchette** just below the **introitus**, or the opening to the vagina. The upper fold forms the prepuce over the clitoris and the lower fold is the frenulum of the clitoris. The clitoris is an erogenous organ with erectile tissue. The clitoris is exquisitely sensitive in most women and is the primary source of sexual pleasure.

The vestibule is that area inside the labia minora where the openings to the urethra, vagina, and Skene and Bartholin gland ducts are found. The urethra is just above the vaginal opening and below the pubic arch. The vaginal introitus is rimmed with the hymen or its tags. **Bartholin glands** are located at either side of the lower portion of the introitus. The ducts for these glands open near the hymenal ring at 5 o'clock and 7 o'clock. **Skene glands** and ducts are found near the urethral meatus.

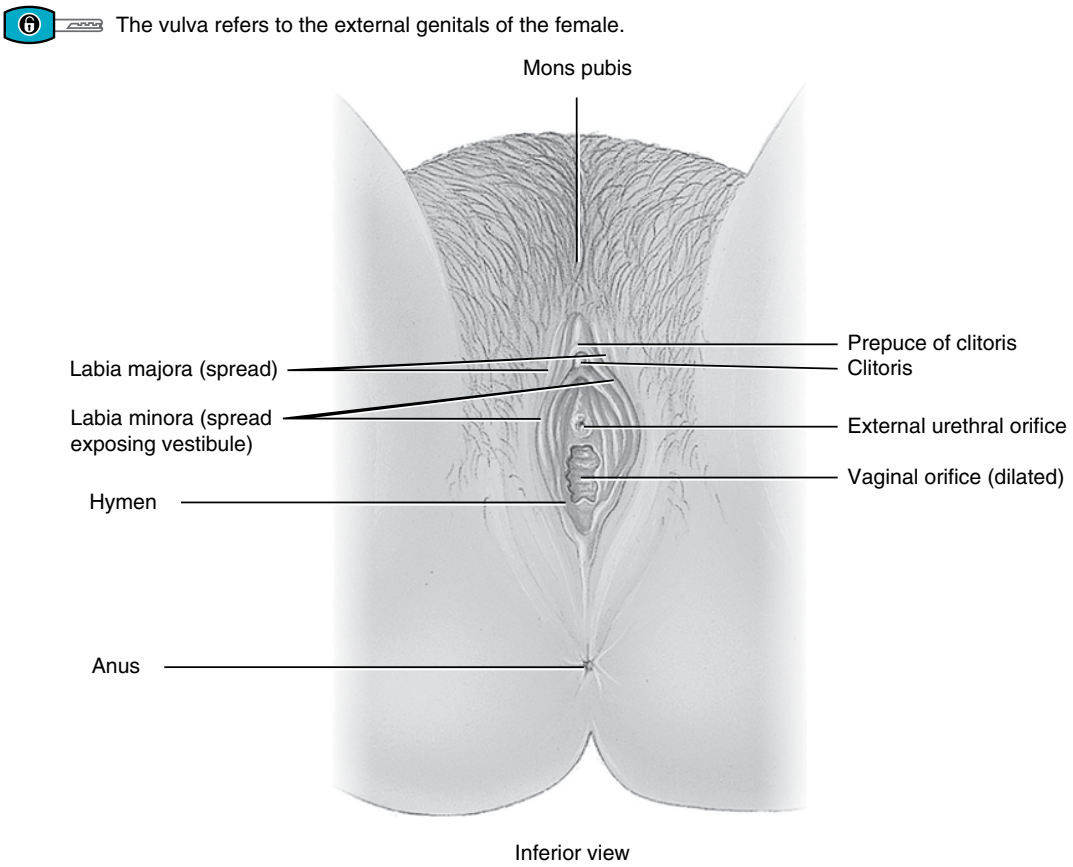

Figure 1.1. External female genitalia. From Tortora & Derrickson (2017). Used with permission.

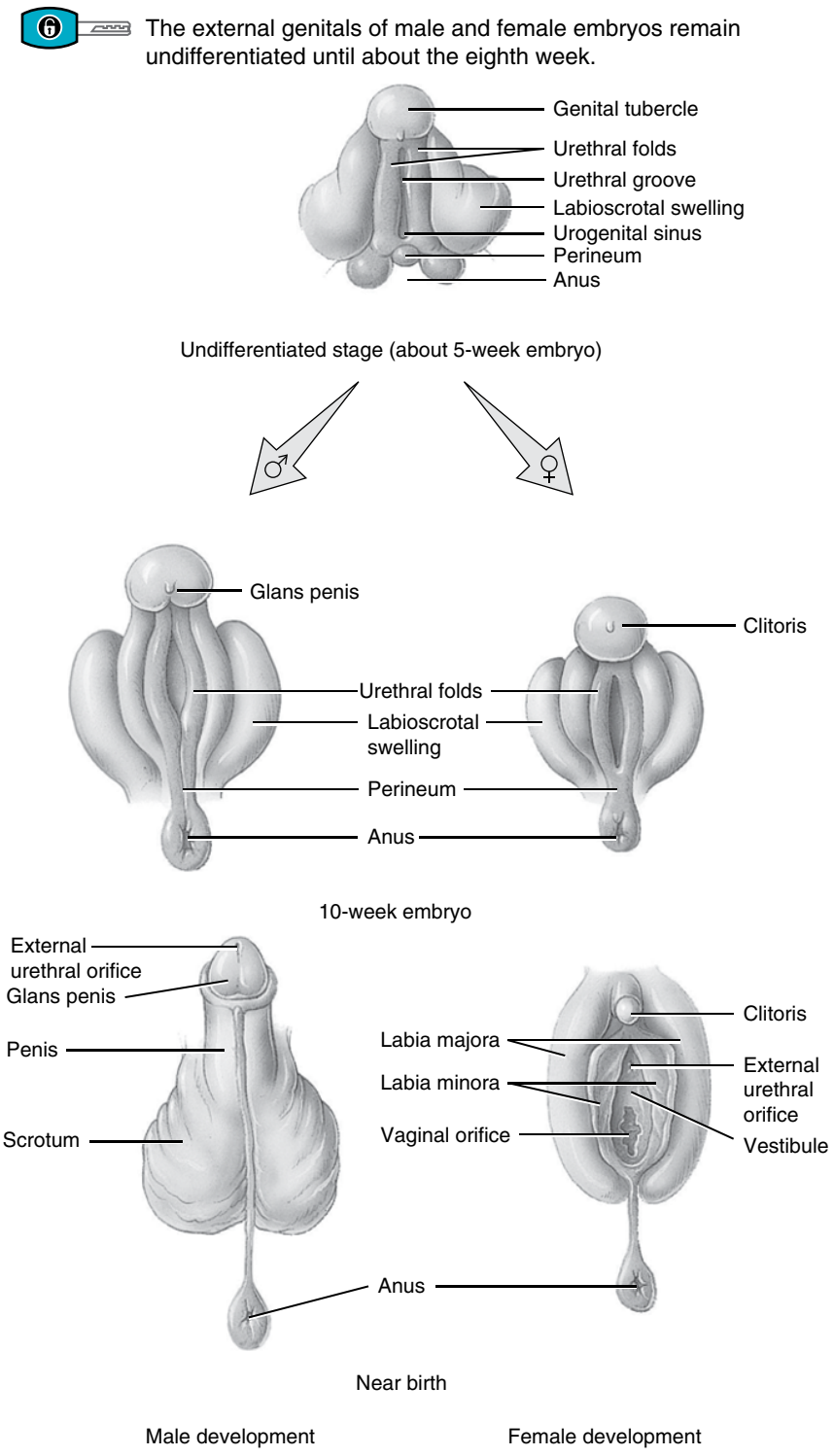

Figure 1.2. Development of external genitalia from embryonic structures. From Tortora & Derrickson (2017). Used with permission.

Hart's line is the line of change in the vestibule where vulvar skin transitions to smoother, moister skin around the urethral meatus and the introitus.

Below the vulva is the perineal body and anal opening. These structures are examined as part of the external genitalia examination. Underlying these structures are the superficial muscles of the perineum and anal sphincter. The superficial muscles most often affected by childbirth include the bulbocavernosus muscle, the superficial transverse perineal muscle, and the external and internal

The perineum is a diamond-shaped area that includes the urogenital triangle and the anal triangle.

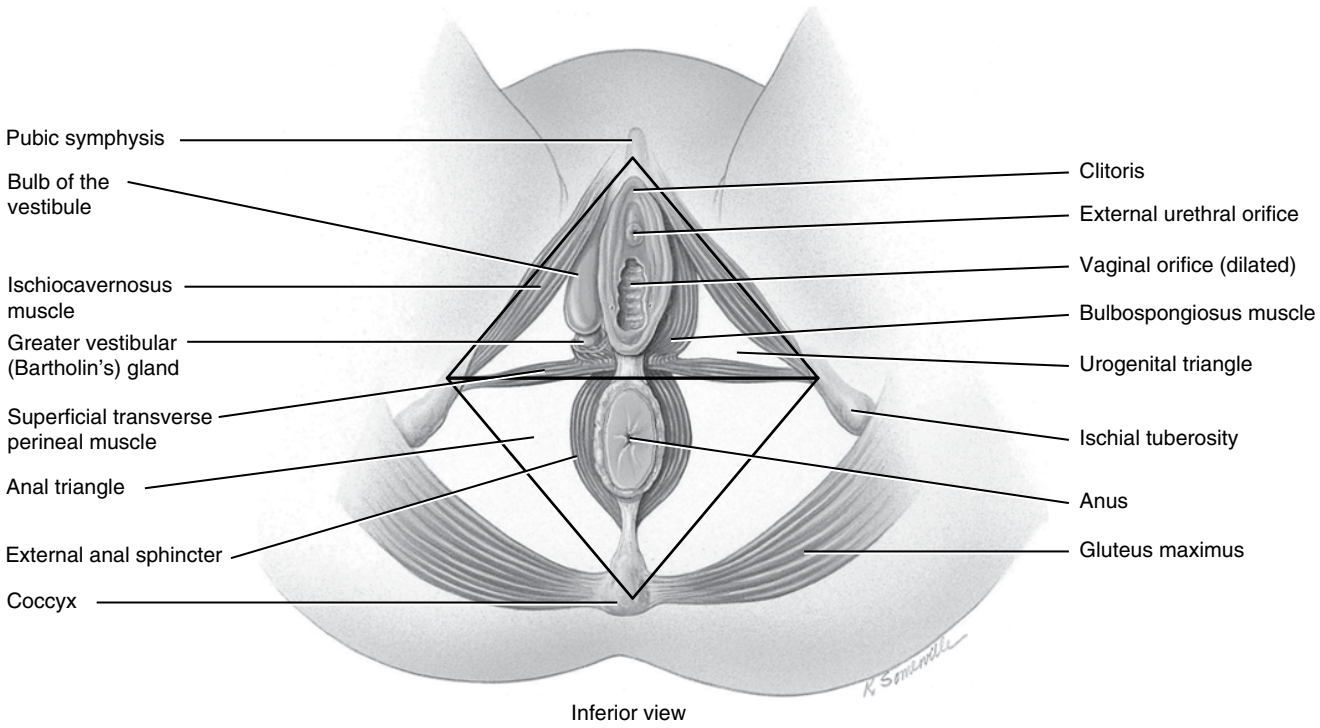

Figure 1.3. Superficial muscles of the perineum. From Tortora & Derrickson (2017). Used with permission.

anal sphincters. These structures, with the exception of the internal anal sphincter, converge on the central tendon of the perineum found between the introitus and the anus. The central tendon is part of the perineal body that may tear or be cut by episiotomy during birth (Figure 1.3).

Internal Genitalia

The vagina is a musculomembranous tube that gives access to the **cervix** for coitus and serves as the birth canal. The lower third of the vagina is supported and fixed by the pubococcygeus muscles of the levator ani group. The upper portion of the vagina and the cervix are supported by the cardinal and uterosacral ligaments. This portion of the vagina is capable of amazing expansion to accommodate birth. Vaginal **rugae** allow for elasticity and expansion. Vaginal length varies with genetics, parity, age, and estrogen effect. On average, the length of the vagina is about 6–8 cm anteriorly and 7–10 cm along the posterior wall (Cunningham et al., 2014). The elastic vagina elongates during intercourse and stretches widely during birth. The spaces around the cervix within the vagina are called the anterior, posterior, and lateral **fornices**.

The rectum supports the middle of the posterior vaginal wall. The anterior vaginal wall offers some support to the bladder (Phillippi, Latendresse, McCance, 2014). The principle innervations for the vagina are the pudendal nerve and the inferior hypogastric plexus, both of which derive from sacral nerve (S) 2–4. Lymph drainage for the vagina is to the para-aortic nodes.

The vagina is lubricated by an epithelial glycoprotein coat and transudate, cervical mucus from the endocervical columnar epithelium, and fluids from the Bartholin and Skene glands (Tufts et al., 2014). The milieu of the vagina is acidic and presents a barrier to many bacteria. The pH is normally between 4.0 and 4.5 in women of childbearing age and is maintained by the estrogen effect on the epithelial glycoprotein coat and **lactobacilli** (normal bacterial flora of the vagina). Vaginal secretions increase during pregnancy due to increased vascularity.

The lower portion of the vagina is separated from the urinary bladder by the **vesicovaginal septum**, and is separated from the rectum by the **rectovaginal septum**. The rectovaginal septum is at risk for lacerations and tears in the event of an operative birth. The upper vagina, around the cervix, is separated from the rectum via a fold of the **peritoneum** (thin membrane around abdominal organs that covers the uterus, bladder, and rectum) called the **rectouterine pouch** or pouch of Douglas. There is a similar, smaller pouch in front of the cervix and behind the bladder called the **vesicouterine pouch**. This area must be incised and the bladder brought forward during cesarean birth (Cunningham et al., 2014).

After ovulation, a secondary oocyte and its corona radiata move from the pelvic cavity into the infundibulum of the uterine tube. The uterus is the site of menstruation, implantation of a fertilized ovum, development of the fetus, and labor.

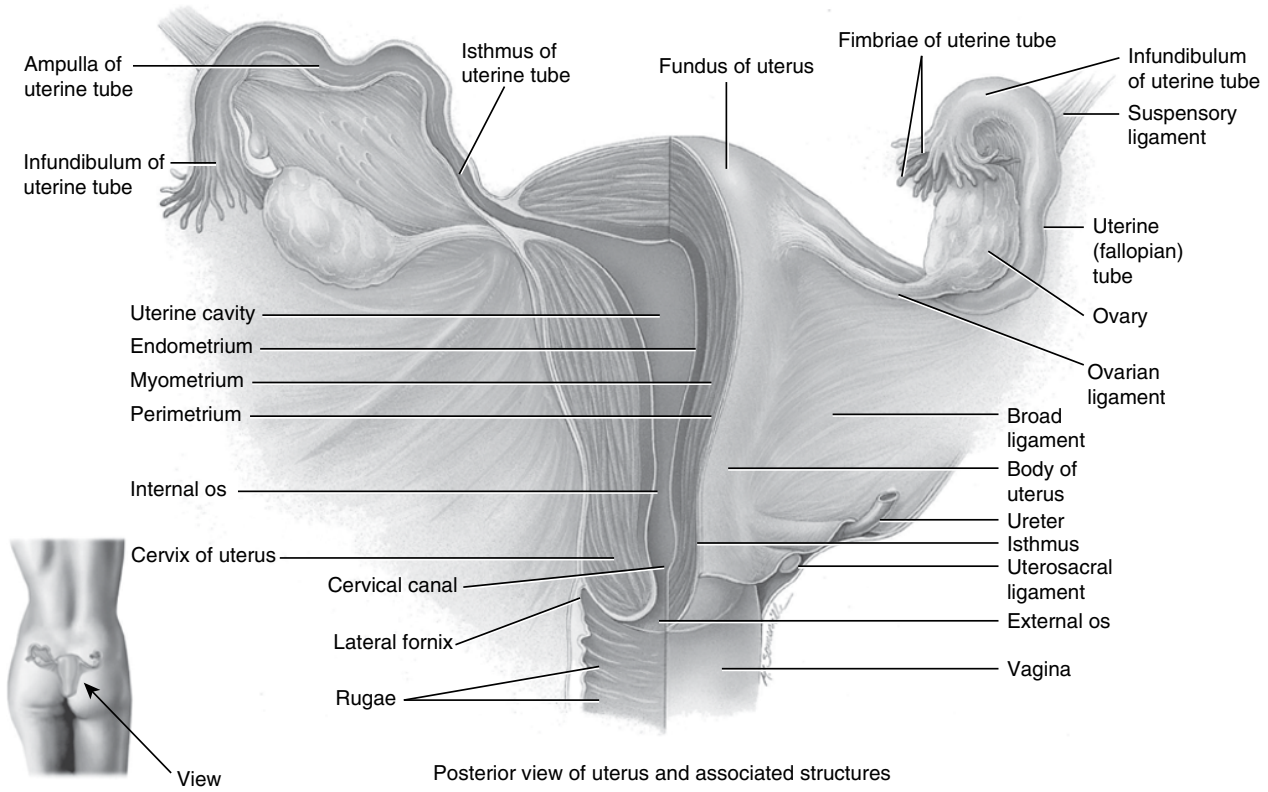

Figure 1.4. The uterus and associated structures. From Tortora & Derrickson (2017). Used with permission.

The cervix is the lower, narrow part of the pear-shaped uterus that protrudes into the vagina (Figure 1.4). About half of the cervix is within the vaginal canal. This part of the cervix has an external **os** followed by a passageway to the uterus called the **endocervical canal**. The canal ends at the internal os that opens into the uterine cavity. The size and shape of the cervix varies with parity, age, and the amount of estrogen and progesterone available. The cervix of a **nulliparous** woman is smaller and the external os is smaller and more circular than the cervix of a **parous** woman, which is wider and the external os is slit-like and more open. The length of the cervix plays a role in cervical integrity during pregnancy.

The blood supply to the cervix arrives via the uterine arteries that derive from the internal iliac arteries. The cervical branches of the uterine arteries are located at 3 o'clock and 9 o'clock to the cervical os. Venous blood drains to the hypogastric venous plexus.

The cardinal and uterosacral ligaments support the cervix and upper vagina. The cardinal ligament to attaches either side of the cervix and extends laterally to attach to connective tissue called the parametrium. The uterosacral ligament attaches to the posterior cervix and extends posteriorly to attach to the fascia of the sacrum. The main nerve supply to the cervix derives from the hypogastric plexus and follows the uterosacral ligament to the posterior cervix. Since there are sensory, sympathetic, and parasympathetic nerve fibers within the endocervical canal, any instrumentation through the cervical os has the potential for causing a **vasovagal response** in some women. Conversely, the external cervix has fewer sensory nerve endings, making small external biopsies less painful for women.

The structure of the cervix is complex. It is composed of collagenous connective tissue (smooth muscle and elastic tissue) and **ground substance**, a mucopolysaccharide. There is a much smaller percentage of smooth muscle in the cervix than in the uterine fundus. The cervix during pregnancy is extraordinarily strong and remains closed as the uterine contents increase in size and volume. Near the end of the pregnancy, the cervix softens and becomes distensible, allowing the fetus to be expelled. This dramatic change requires enzyme activity, an increase in cervical water content, hormonal changes, and an increase in

prostaglandins (Blackburn, 2013). After birth, the dilated cervix will shorten and become firmer, so that by 1 week postpartum, the os is dilated to only 1 cm.

Histologically, the cervix has two cell types: the columnar cells that line the endocervical canal and the opening of the cervix, and the squamous epithelium that covers the outside of the cervix. Most lower genital tract cancers occur where these two cell layers meet at the **squamocolumnar junction** (SCJ) (Phillippi, et al., 2014).

Columnar cells secrete **mucin** (a glycosylated protein that forms mucus that acts as lubricant and protectant) and have a reddened papillary appearance. The squamous epithelium is smooth and pink. At **menarche**, higher levels of estrogen cause glycogenation and other changes in the squamous epithelium. These changes and the increasing acidity in the vagina cause the squamous cells to migrate and cover the columnar cells. **Metaplasia** of the squamous and columnar cells occurs at the SCJ. This makes this area highly susceptible to invasion by human papilloma virus, hyperplasia, and dysplasia. Metaplasia occurs throughout a woman's childbearing years; over time, the SCJ will migrate into the endocervical canal. The SCJ is the most important area for collection of cell samples for the Pap test.

Columnar cells are visible at the cervical os during adolescence, pregnancy, and when women use oral contraceptive pills because of the higher levels of estrogen during these events. This is often referred to as **ectropion**. Columnar cells produce cervical mucus that changes according to the hormones secreted during the menstrual cycle. During the late follicular phase and ovulation, when estrogen levels are highest, the mucus is clear, stretchy, slick, thin, and abundant. These characteristics of the mucus facilitate sperm passage from the vagina, through the cervix, and into the uterus. Under the influence of progesterone during the luteal phase, the mucus becomes scant, thick, pasty, and opaque. One of the important effects of progestin-only contraceptives is the thickening of the cervical mucus that serves as a barrier to sperm (Lewis et al., 2010).

Mucus from the columnar cells of the endocervical canal becomes thick and forms a mucous plug during pregnancy. This plug helps to prevent the passage of bacteria into the uterus. Increased vascularity and swelling of the cervix during early pregnancy will cause a bluish coloring called **Chadwick's sign**.

The uterine cervix is connected to the body of the uterus by the **isthmus**. This segment of the uterus will soften and become compressible during early pregnancy, a feature specific to pregnancy known as **Hegar's sign**.

The body or corpus of the uterus (Figure 1.4) is the most dynamic portion of the uterus. Here, the innermost lining, or **endometrium**, responds to ovarian hormones every month, building in preparation for implantation, then sloughing as menses if pregnancy does not occur (Behera, 2016). This is also where implantation and gestation take place and where the powerful forces of labor are generated. An adult woman's uterus is about 3–4 inches long before any pregnancies have occurred. After pregnancy and postpartum involution, the range is 4.5–5 inches. The weight of the nonpregnant uterus is about 60 grams if never pregnant, heavier depending numbers of pregnancies (Cunningham et al., 2014). During pregnancy, the muscles of the uterus hypertrophy and the weight will increase to about 38.8 oz by 40 weeks' gestation. This hypertrophy does not extend to the cervix, which contains much less muscle tissue.

Attached to both sides of the upper, outer portion of the uterus, known as the **cornua**, are the fallopian tubes, round ligaments, and ovarian ligaments. The body of the uterus, unlike the cervix, is mostly muscle tissue. Inside the uterus, the anterior and posterior walls lie very close to each other, forming a slit-like space (Cunningham et al., 2014). Within this space is the very active endometrium, the first of three layers within the uterine corpus (Behera, 2016). The endometrial cyclic response to hormones is explained later in this chapter.

The middle layer of the uterus is the **myometrium**. This layer is composed of smooth muscle united by connective tissue and makes up most of the uterine bulk. The outermost layer is the perimetrium, a thin layer of epithelial cells. The myometrium contains four layers of muscles with blood vessels coursing through each layer. The inner layer of muscle fibers is composed of spirals on the long axis of the uterus. The middle layers of muscle fibers have interlacing fibers that form a figure eight around the many blood vessels. When the placenta is expelled after birth, the empty uterus contracts and the muscles of this layer become "living ligatures" that help halt the blood flow. The outer two layers of muscle fibers are smooth muscle in bundles of 10 to 50 overlapping cells interspersed with connective tissue and ground substance that transmit contractions during labor (Blackburn, 2013, p. 115). Interestingly, the layers of the myometrium arise from different embryonic locations, so they respond to uterine stimuli in different ways. The result is a rhythmic contractile force that propels the fetus toward the cervical opening regardless of the fetal presentation.

The uterine blood supply comes to the uterus from the internal iliac artery via the ovarian and uterine arteries. These arteries feed the arcuate, radial, basal, and spiral arteries. The spiral arteries of the endometrium change during the menstrual cycle. If pregnancy does not occur during the cycle, the spiral arteries constrict, the endometrial matrix breaks down, and menses occurs. There is extensive collateral circulation that is

enhanced during pregnancy. This arterial system is very efficient in supplying nutrients and oxygen to the growing uteroplacental unit and fetus, but if hemorrhage occurs, this interconnected system of vessels makes control of the bleeding difficult.

There are two sets of lymphatics within the uterine body. One set drains into the internal iliac nodes and the other ends in the para-aortic lymph chain (Cunningham et al., 2014). The nerve supply to the uterus is derived mostly from the sympathetic nervous system and partly from the parasympathetic system. The parasympathetic system fibers derive from sacral nerves 2, 3, and 4. The sympathetic system ultimately comes from the aortic plexus just below the sacral promontory. Sensory fibers from the uterus derive from the 11th and 12th thoracic nerve root and carry the pain signals from contractions of labor to the central nervous system. The sensory nerves from the cervix and upper vagina move through the pelvic nerves to sacral nerves 2, 3, and 4. The primary nerve of the lower vagina is the pudendal nerve.

The fallopian tubes (Figure 1.4) extend from the upper sides the uterus. These oviducts vary from 8–14 cm in length. There are three parts: the **fimbria**, **ampulla,** and the isthmus. The fimbria opens into the abdominal cavity and have finger-like, ciliated projections, with one longer projection that reaches closer to or touches the ovary, which capture the ovum from the surface of the ovary. The ampulla is the widest section of the uterine tubes. The smooth muscle and ciliated cells within the tubes contract rhythmically all the time. At ovulation, these contractions become stronger and more frequent in order to move the ovum toward the uterine lining. Fertilization, if it occurs, will typically occurs in the ampulla (Blackburn, 2013). The isthmus is the narrowest section of the tubes, connecting the ampulla to the uterine cavity

The ovaries reside on either side of the uterus and are attached to the ovarian ligament that extends to and attaches to the cornua. Other ligaments help support the ovaries and serve as conduits for vessels and nerves. The top layer of the ovary contains oocytes and developing follicles. The core of the ovary is composed of connective tissue, blood vessels, and smooth muscle. Ovaries vary in size but typically are approximately 2.5–5 cm long and 1.5–3 cm wide, giving them an almond shape. Ovaries are sometimes palpable during the bimanual examination of the adnexa during pelvic examination (Bickley & Szilagyi, 2013).

Menstrual Cycle Physiology

The menstrual cycle occurs regularly in most women from menarche to menopause with some expected irregularity during the first year after menarche and the years of perimenopause. It is regulated by complex interactions between the hypothalamus, the pituitary gland, the ovaries, and the uterus. This section will highlight the hormonal changes and how these changes affect the ovary and the uterine lining.

Beginnings

The gender of an embryo is determined at the time of fertilization. The male contribution of an X chromosome combined with the female-contributed X chromosome produce the basis for a unique female human. Before the seventh week of gestation, the gonads of male and female embryos look the same. It is not until the sixteenth week after fertilization that primordial germ cells called **oogonia** can be detected along the genital ridge in females (Moore, Persaud, & Torchia, 2016). By 7 months of gestation, all of the oogonia have been transformed into primary oocytes and no new oogonia are formed. At birth, a female newborn will have an average of 200,000–400,000 follicles on the two ovaries. Each follicle contains a primary oocyte that has already begun the first meiotic division (Moore et al., 2016). At puberty, only about 10%, or 40,000, of these early follicles will remain due to **atresia**. Of these, only about 400–500 will develop into a primary and secondary follicles.

Oogenesis is the sequence of events that transforms the oogonia into an oocyte ready to be fertilized. In early fetal life, oogonia divide via mitosis to form primary oocytes. By birth, the primary oocytes have begun the first meiotic division but the process is arrested and remains that way until just before ovulation, when the first meiotic division is completed. At this division, a secondary oocyte receives the bulk of the cytoplasm and the **first polar body** is formed. At ovulation, the secondary oocyte begins its second meiotic division, but the process halts and does not resume unless the secondary oocyte is fertilized by a sperm (Moore et al., 2016). The process of oogenesis is depicted in Figure 1.5.

At term, the gonadotropin-releasing hormone pulse generator, or **gonadostat**, is at work in the fetus. The gonadostat responds to high levels of maternal estrogen by releasing small amounts of gonadotropin-releasing hormone. After birth, when maternal estrogens are removed, the gonadotropins follicle-stimulating hormone (FSH) and luteinizing hormone (LH) are released from the newborn's pituitary gland (Tufts et al., 2014). During infancy and childhood, estrogen levels are very low and gonadotropin secretion is restrained in a positive feedback fashion.

Onset of Puberty

When a girl is 8–12 years old, the gonads begin to produce estrogen and puberty begins with **thelarche** (breast development). Estrogen production begins in

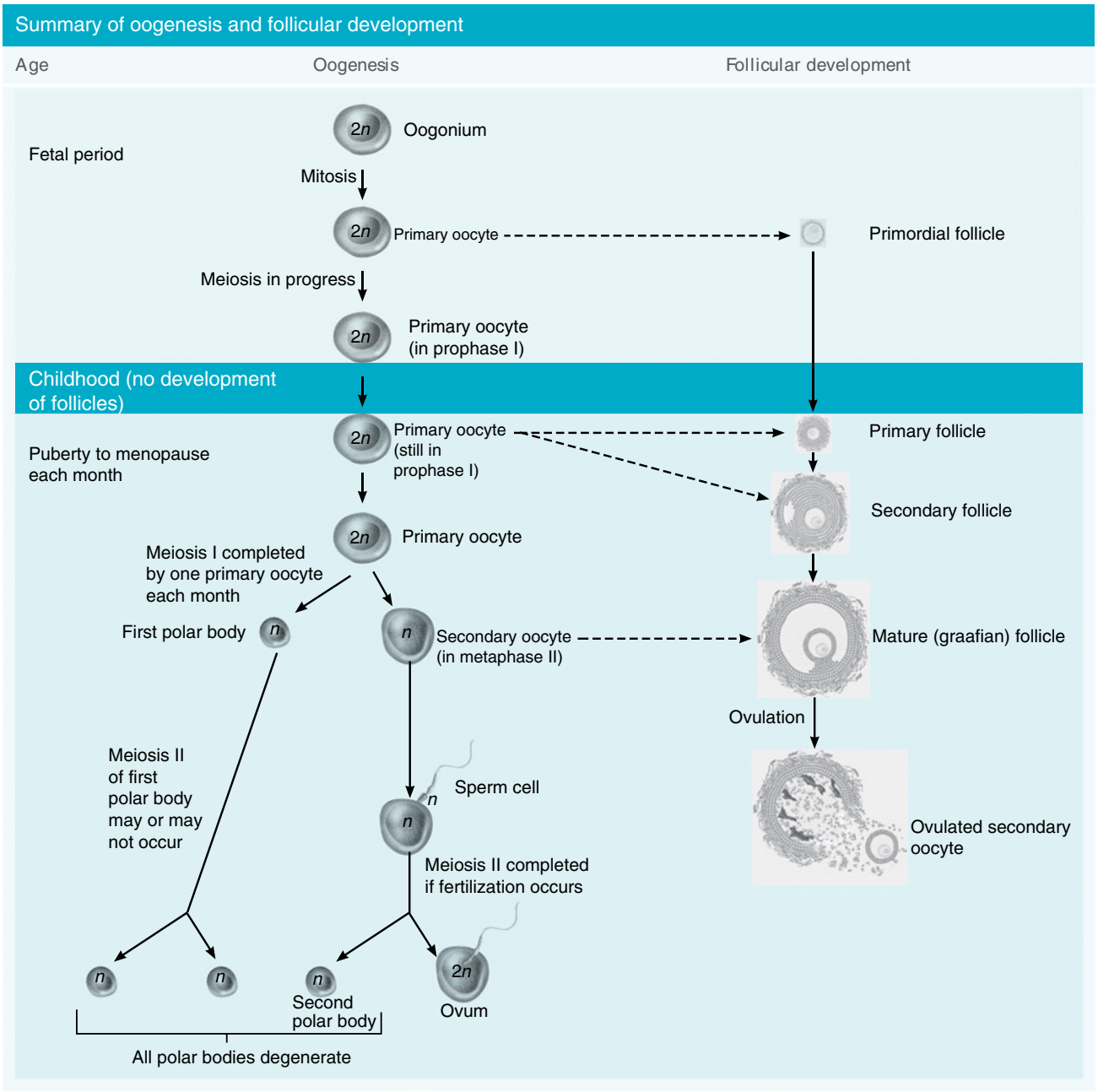

Figure 1.5. Oogenesis. From Tortora & Derrickson (2017). Used with permission.

response to complex interrelated changes involving the central nervous system, hypothalamus, pituitary, and ovary. Onset of these changes is influenced by genetics, general health, nutrition, geographic location, exposure to light, and body weight (Tufts et al., 2014; Silverthorn, 2016). It is thought that increasing body fat and the adipose hormone **leptin** facilitate maturation, and both are important to the onset of menses. Reproductive maturation involves the central nervous system and the endocrine system in a sequence of changes that will lead to menarche.

The first in the sequence of events that will lead to reproductive maturation is the release of gonadotropin-releasing hormone from the hypothalamus that will cause the release of FSH and LH from the pituitary. These hormones will induce **gonadarche** and **adrenarche**, and the hormones from the gonads and adrenal glands stimulate the development of secondary

Hormones from the anterior pituitary regulate ovarian function, and hormones from the ovaries regulate the changes in the endometrial lining of the uterus.

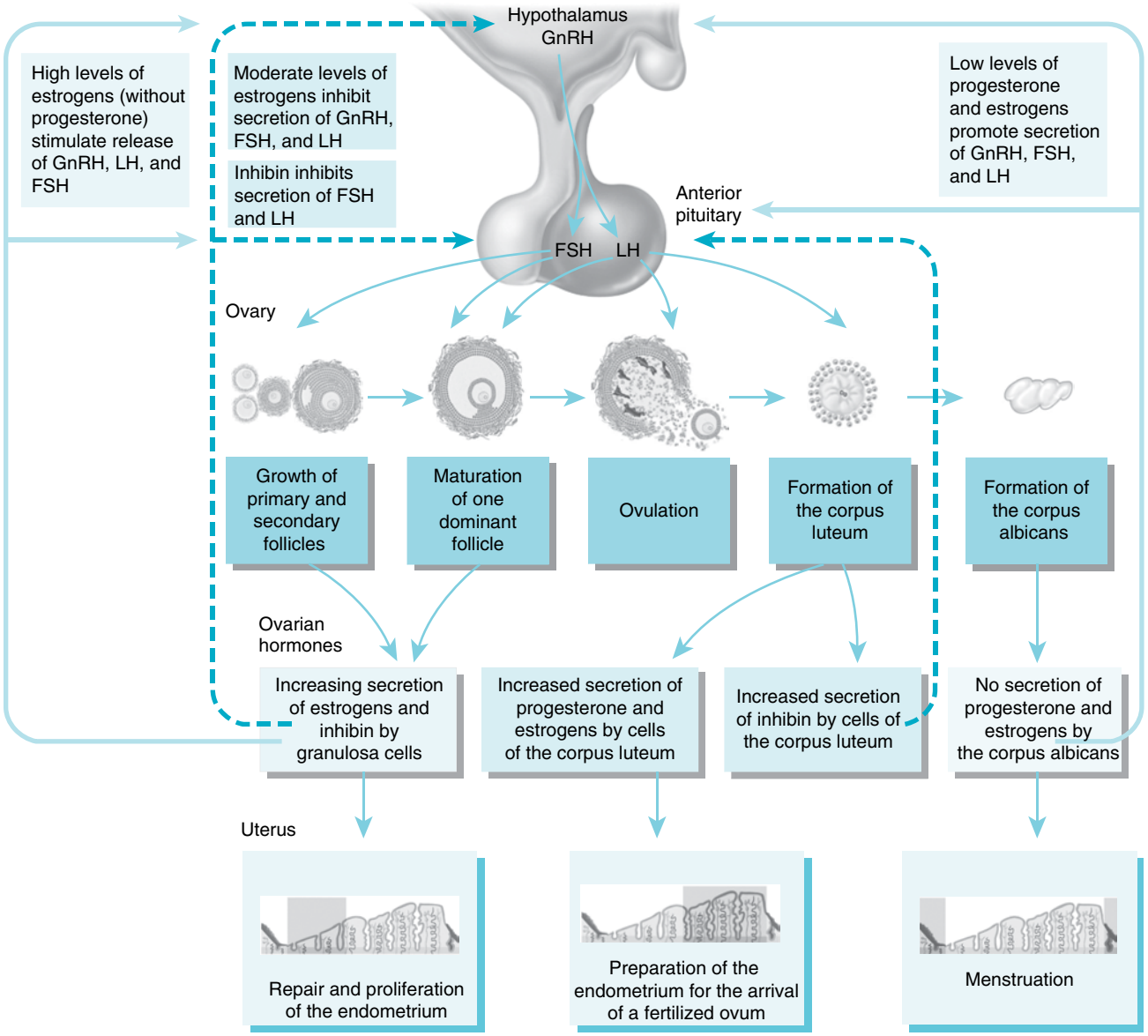

Figure 1.6. Hormonal stimulation of the gonads and feedback loops. GnRH, gonadotropin-releasing hormone. From Tortora & Derrickson (2017). Used with permission.

sexual characteristics such as breast growth, pubic and axillary hair growth, and changes in the vagina (Bickley & Szilagyi, 2013; Tufts et al., 2014). These changes also set the stage for the first ovulation and first ovulatory menstrual period. Figure 1.6 illustrates the sequence for the beginning of hormonal stimulation of the ovary and the beginning negative and positive feedback loops.

The average age for menarche in the United States varies according to population, race, socioeconomic conditions, and nutrition. Among well-nourished white females, the average age at menarche is 12.43 (ACOG, 2015). Black females begin about 5 or 6 months earlier. Table 1.1 describes the characteristics of the normal menstrual cycle.

Once menarche and ovulatory cycles are established, puberty is complete and the female is able to reproduce physiologically; however, social and cultural norms influence reproductive behaviors and

Table 1.1 Normal menstrual cycle characteristics

Menarche (average age)	
White	12.43 years
Black	~11.5 years
Menstrual cycle length	
First year of menses	32.2 days (range 20–60 days)
Typical menstrual cycle length during the years between menarche and menopause	21–45 days (only 9%-15% are 28 days in length)
Flow length	
First year	2–7 days
Typical length	4–6 days (less than 2 or more than 8 considered abnormal)
Flow amount	20–80 mL (second day heaviest)

Adapted from: American College of Obstetricians and Gynecologists (ACOG). (2015); Blackburn (2013); and Shulman (2011).

choices once physical reproductive maturity is achieved. Throughout the childbearing years, the hypothalamic–pituitary–ovarian (HPO) axis and the uterus go through cycles in production of hormones and changes in the endometrial lining.

The Hypothalamic–Pituitary–Ovarian Axis

Once established, the menstrual cycle continues based on feedback mechanisms between the hypothalamus, pituitary, and the ovary. The hypothalamus is a pearl-sized organ at the base of the brain near the optic chiasm. The cells of the hypothalamus synthesize and secrete many releasing hormones that act on the pituitary and other endocrine glands. It is responsible for regulating thirst, sleep, hunger, libido, and many endocrine functions (Tufts et al., 2014). The hypothalamus responds to lower serum levels of estrogen near the end of a cycle by secreting an FSH-releasing factor that will travel to the nearby pituitary gland and stimulate the release of FSH. FSH will stimulate the growth of follicles on the ovary, with one follicle becoming dominant for each cycle. Later, when the follicle releases enough estrogen, the hypothalamus will secrete an LH-releasing hormone that will travel to the pituitary and stimulate the release of LH.

The pituitary gland is located in the sella turcica, below the hypothalamus and optic chiasm. It has a stalk connecting it to the hypothalamus and two lobes, anterior and posterior. The anterior lobe synthesizes and secretes FSH, LH, and many other hormones that affect specific target organs. Figure 1.6, depicts the early HPO axis with feedback loops.

The ovaries are the target organs for the gonadotropins secreted by the anterior pituitary. They are located on either side of the uterus, suspended by the ovarian ligament. They are covered in follicles, each with the potential for growing and releasing an ovum. Figure 1.7 shows the ovarian surface and the stages of the follicle.

The functioning of the HPO axis is dependent on feedback loop control. The most common form of feedback control is negative feedback. This occurs when rising hormone serum levels cause a decrease in another hormone. The other form of feedback control is positive feedback, where rising levels of one hormone causes a rise in another. These feedback mechanisms help to keep the hormones within normal ranges.

The hormones involved in the menstrual cycle include the gonadotropin-releasing hormones from the hypothalamus, the gonadotropin-stimulating hormones from the pituitary, and the ovarian hormones from the ovary (Table 1.2).

Menstrual Cycle Phases

There are two parts to the menstrual cycle that occur simultaneously. To help clarify what is happening in each part, this section will separate the ovarian cycle and the endometrial cycle.

Ovarian cycle

There are three phases of the ovarian cycle: the follicular phase, ovulation, and the luteal phase. The follicular phase begins on the first day of menses and is more variable in length than the luteal phase. It may last anywhere from 10 to 21 days (Silverthorn, 2016). The luteal phase is the most predictable in length because of the life span of the corpus luteum. It lasts 13–15 days unless pregnancy occurs and the life of the corpus luteum continues (Shulman, 2011).

The follicular phase actually begins during the last days of the previous cycle when decreasing estrogen and inhibin deliver a negative feedback signal to the hypothalamus and pituitary. This signal stimulates the hypothalamus to release an FSH-releasing factor that stimulates the anterior pituitary to release FSH. The primordial follicles on the ovary each contain an oocyte and a layer of **granulosa cells** that will respond to the FSH. It is thought that there is at least a 3-month period of stimulation to recruit a dominant follicle for one ovulation (Blackburn, 2013). It is this one primed follicle that responds to the FSH first and begins to grow before

The ovaries are the female gonads; they produce haploid oocytes.

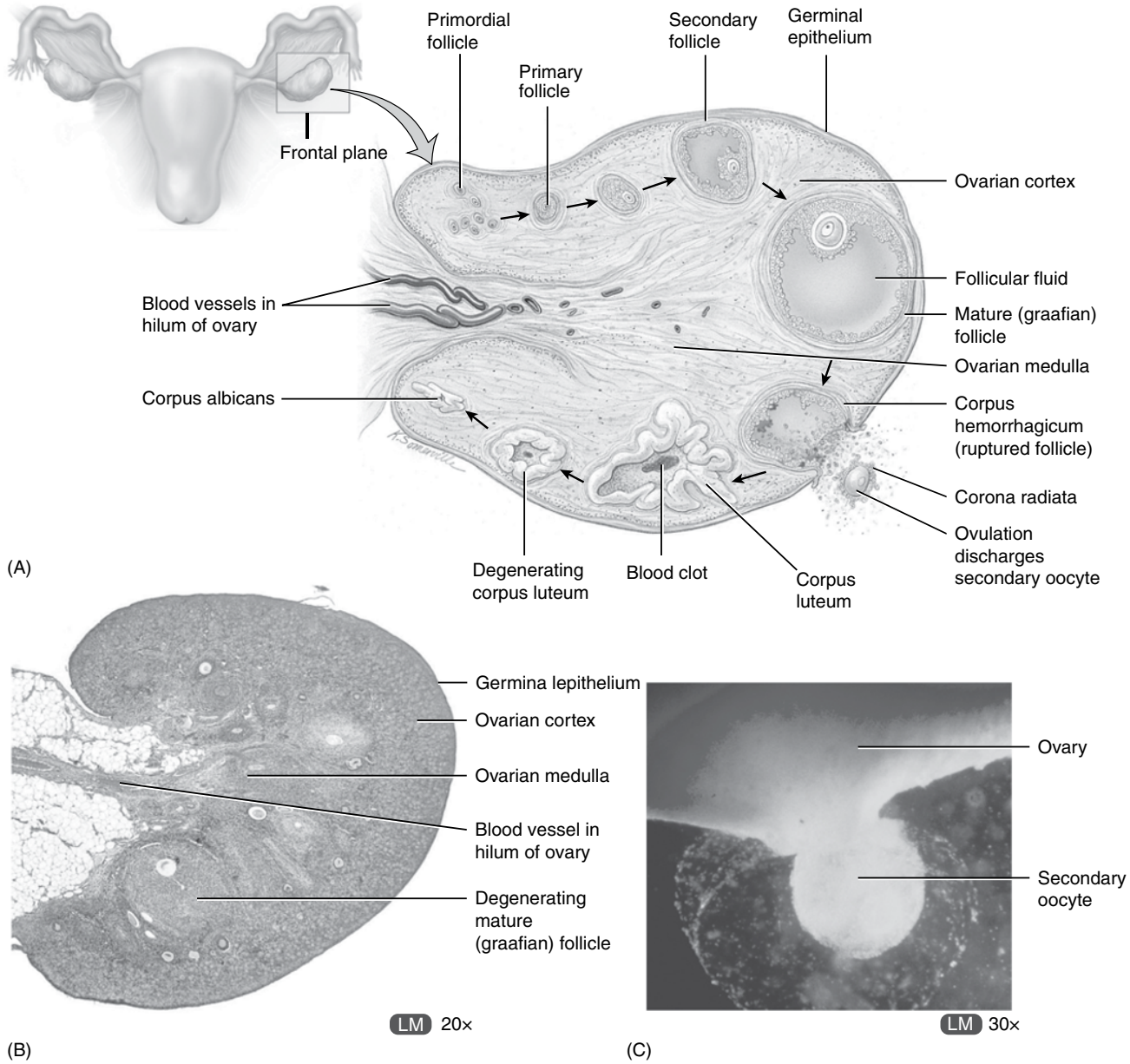

Figure 1.7. Cross section of the ovary during the reproductive years. (A) Frontal section. (B) Hemisection. (C) Ovulation of a secondary oocyte. From Tortora & Derrickson (2017). Used with permission.

other follicles on the ovaries that may respond. This follicle takes in more FSH than the others and grows more rapidly. Within this dominant or primary follicle, the oocyte begins to grow and the **zona pellucida** is formed and grows between the oocyte and the granulosa cells (Tufts et al., 2014). Just before ovulation, the corona radiata will form around the zona pellucida. As these changes progress, some of the follicles that had started to respond to FSH but did not fully mature undergo atresia (Shulman, 2011).

During the follicular phase, the ovary and the primary follicle are secreting both estrogen and progesterone, with estrogen being produced in higher amounts. FSH stimulates the granulosa cells of the dominant follicle to produce much higher levels of estrogen and to upregulate LH receptors within the follicle cells (Tufts et al., 2014). The higher levels of estrogen cause positive feedback stimulation of the hypothalamus and pituitary that result in a rise in LH. Near the end of the follicular phase, estrogen will peak, causing LH to surge and reach its highest

Table 1.2 Hormones of the menstrual cycle

Hypothalamus	Follicle-stimulating hormone releasing factor Gonadotropin-releasing factor Luteinizing hormone-releasing factor
Pituitary	Follicle-stimulating hormone Luteinizing hormone
Ovary	Progesterone Estrogen Testosterone Inhibin Activin Follistatin

Adapted from: Tufts, Rodway, Huether, & Deneris (2014).

level about 12–24 hours before ovulation (Blackburn, 2013). The higher levels of LH are a very reliable signal of impending ovulation. LH detection kits are available to help couples determine when ovulation occurs (US Food and Drug Administration (FDA), 2014).

LH has other functions. It stimulates ovarian tissue in a way that increases androgen levels and enhances the libido (Shulman, 2011). It stimulates the remaining granulosa cells of the ruptured follicle to become lutein cells so that the corpus luteum is formed. LH is also responsible for stimulating the oocyte to resume meiosis (Silverthorn, 2016).

Ovulation occurs after a surge and peak level of LH, but there are several factors that facilitate the extrusion of the ovum from the follicle. As the follicle and oocyte have grown, the oocyte has shifted to one side of the follicle. When estrogen begins to decrease, the follicle swells and prostaglandins, proteolytic enzymes, and smooth muscle contractions cause the follicular wall to burst open and the ovum is extruded (Blackburn, 2013). The phenomenon of **mittelschmerz** or pain upon ovulation is thought to be due to the rupture of the follicle and the release of the ovum and surrounding fluid that can irritate the abdominal lining.

After ovulation, the remaining cells of the follicle are re-vascularized and transformed into the corpus luteum by taking up hormones and lutein pigment that gives it a yellow color (Shulman, 2011). The corpus luteum continues to secrete estrogen and progesterone, but now progesterone is produced in higher amounts. Progesterone will cause changes in the endometrium and suppress new follicular growth. It will peak between 7 and 8 days after the rapid increase of LH. This highest level of progesterone corresponds with the time of implantation, if fertilization has occurred. If implantation occurs, the corpus luteum is maintained by the human chorionic gonadotropin secreted by the conceptus so that progesterone levels are maintained.

If fertilization has not occurred, the corpus luteum begins involution and estrogen, progesterone, and inhibin levels will fall. Cellular changes during involution will result in a small scar on the ovary called the corpus albicans (Silverthorn, 2016). The decrease in the ovarian hormones causes a negative feedback stimulation of the hypothalamus and pituitary and the process begins all over again.

Endometrial cycle

The endometrial cycle has three phases: proliferative, secretory, and menstrual. These phases correspond with events occurring in the ovarian cycle. Proliferative changes in the endometrial lining occur under the influence of estrogen during the corresponding follicular phase. During this phase, there is hyperplasia of the endothelial cells and growth of the stroma within the endometrium (Silverthorn, 2016). The endometrial height will reach 0.5–5 mm during this phase.

After ovulation, when the corpus luteum begins producing more progesterone, the secretory phase begins. During this time, the epithelial cells accumulate glycogen, become more tortuous, the spiral arteries coil, and capillary permeability of the stroma increases (Cunningham et al., 2014). If fertilization occurs, the secretory endometrium begins transformation to decidual tissue and will be 5–10 mm deep when implantation begins (Blackburn, 2013).

If fertilization does not occur, then the endometrium degenerates and the menstrual phase begins. The corpus luteum atrophies, estrogen and progesterone production decreases, and prostaglandins are released. Prostaglandins cause vasoconstriction and other changes that lead to ischemia and necrosis of the secretory structures. At the same time, there is the breakdown of proteins within the superficial layer and sloughing. Rupture of capillaries during sloughing leads to bleeding. Bleeding and myometrial contractions help remove the degenerated endometrium (Tufts, et al., 2014).

Menses typically lasts 4–6 days, but may be considered normal if all of a woman's bleeding is consistently between 2 and 8 days in length. The prostaglandins released will cause contractions, ischemia, and pain in some women. These contractions, along with increasing levels of estrogen, which encourage clot formation, eventually stop the bleeding (Shulman, 2011). Figure 1.8 illustrates the endocrine changes, ovarian cycle, and endometrial cycle in one chart.

The menstrual cycle is a complex and wondrous phenomenon that ensures the continuation of the human

Estrogens are the primary ovarian hormones before ovulation; after ovulation, both progesterone and estrogens are secreted by the corpus luteum.

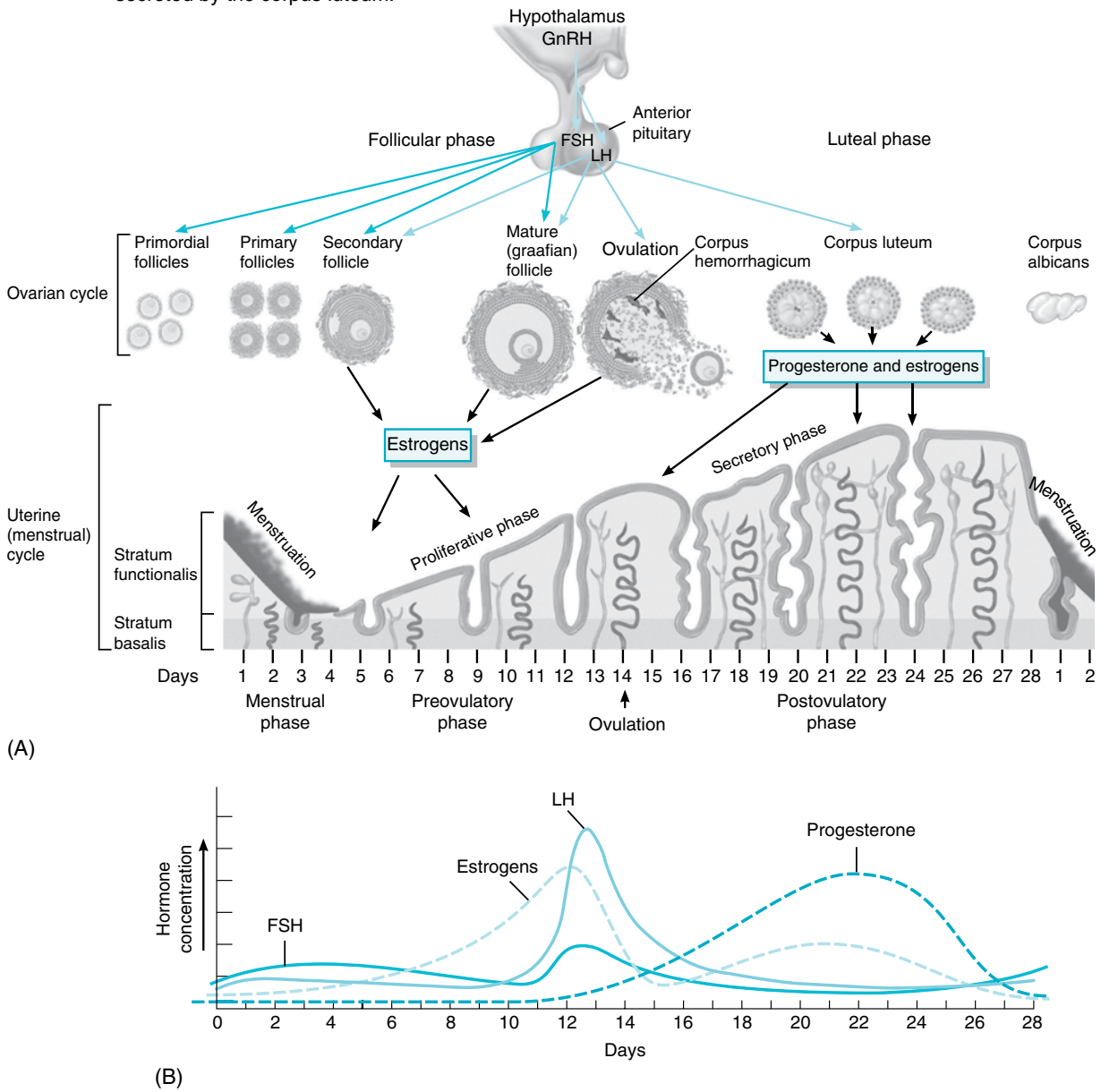

Figure 1.8. Changing hormone levels during the menstrual cycle. (A) Hormonal regulation of changes in the ovary and uterus. (B) Changes in concentration of anterior pituitary and ovarian hormones. From Tortora & Derrickson (2017). Used with permission.

race. Most of the time, all of the components work in harmony and there is no need to intervene. The story of embryonic and fetal development that occurs in the uterus is continued in Chapter 2.

Resources for Women

Menstruation and the Menstrual Cycle Fact Sheet: https://www.womenshealth.gov/publications/our-publications/fact-sheet/menstruation.html

Resources for Healthcare Providers

Association of Reproductive Health Professionals: http://www.arhp.org/topics/pregnancy

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2

Conception, Implantation, and Embryonic and Fetal Development

Patricia W. Caudle

Relevant Terms

Acrosome reaction—a process that exposes small openings in the head of the sperm that allows it to penetrate the ovum membrane and release its contents
Active transport—movement across a semipermeable membrane against a concentration gradient
Allantois—small appendage of the umbilical vesicle
Angiogenesis—process by which new vessels form from existing vessels
Apoptosis—programmed cell death
Blastocyst—third stage of the conceptus development; postmorula
Capacitation—removal of the glycoprotein coat from the head of the sperm
Chorion—outer membrane that surrounds the embryo/fetus and becomes the fetal part of the placenta
Chorion frondosum—villi at embryonic pole that extend into the decidua; will develop into the placenta
Chorion laeve—smooth chorion that will fuse and disappear
Chorionic villi—projections from the cytotrophoblast to the syncytiotrophoblast that eventually become an arteriocapillary venous network that supplies the embryo
Cleavage—replication process of cells
Cloacal membrane—future site of the anal opening in the embryo
Coelom—cavity that fills with a nutrient lake for molecular exchange between the woman and the embryo
Corona radiata—first layer of the ovum
Cytotrophoblast—inner layer of the trophoblast
Decidual reaction—cellular and vascular changes in the endometrium at implantation
Diploid—contains 46 chromosomes
Ectoderm—outermost layer of the developing embryo
Endoderm—innermost layer of the developing embryo
Extraembryonic somatic mesoderm—layer of mesoderm that will combine with trophoblast to form the chorion
Facilitated diffusion—movement across a semipermeable membrane that needs a transporter but no energy
Gametes—ovum and sperm
Gastrulation—formation of the germ layers of the embryo
Haploid—contains 23 chromosomes
Hydatidiform mole—abnormal proliferation of the conceptus that can become malignant
Implantation bleeding—loss of a small amount of blood from the uterine lining during implantation
Lacunae—small spaces or "lakes" within the syncytiotrophoblast
Lanugo—fine, soft hair that covers the fetus
Lipolysis—breakdown of fat molecules
Mesenchymal—cells that can differentiate into many different cell types
Mesoderm—middle layer of the developing embryo
Morula—mulberry-like group of cells, second phase of conceptus cellular development, postzygote
Neurulation—formation of the neural tube
Notochordal—rodlike structure that helps organize the nervous system and becomes part of the vertebra and axial skeleton
Oligohydramnios—less than normal amount of amniotic fluid
Oocyte—ovum
Oogonia—primitive ovum
Organogenesis—process by which endoderm, mesoderm, and ectoderm develop into internal organs
Peptide—synthesized from protein
Pinocytosis—carrier molecule is required to engulf molecules and move it across the placental barrier
Placenta accreta—abnormal attachment of the trophoblast to the endometrium
Polyhydramnios—excessive amniotic fluid
Precursors—building blocks or chemicals used to make another chemical
Primitive streak—line of epiblast cells through the middle of the back of the embryo
Pulmonary hypoplasia—poor fetal lung growth
Quickening—fetal movement first felt by the woman

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Sacrococcygeal teratoma—cystic tumor with tissue from all three embryonic germ layers
Simple diffusion—movement across a semipermeable membrane from higher to lower concentration
Somites—segmental mass of mesoderm occurring in pairs along the notochord, which develop into vertebrae and muscles
Steroid—synthesized from cholesterol
Syncytiotrophoblast—outer layer of the conceptus that sends out fingerlike extensions that take in uterine cells as it invades the endometrium
Teratogen—any substance that can disrupt the development of an embryo
Velamentous insertion—umbilical blood vessels insert into the placenta via the amniotic membrane and are not protected by Wharton's jelly
Vernix caseosa—cheesy coating on the fetus that protects the skin
Wharton's jelly—gelatinous connective tissue of the umbilical cord
Zona pellucida—second layer of the ovum
Zygote—first cell created by fusion of ovum and sperm

Introduction

Estrogen produced by the ovarian follicle begins the preparation of the endometrial lining for a potential pregnancy. When the follicle extrudes the ovum, the *corpus luteum* develops and begins to produce more progesterone (literally, progestation). This hormone causes the endometrium to become very receptive to implantation should conception occur. This chapter will outline conception, implantation of the *conceptus* into the receptive uterine lining, and the development of the embryo/fetus and placenta. For purposes of consistency, embryonic and fetal age is based on the estimated time of fertilization unless otherwise stated.

Conception and Implantation

Conception or fertilization occurs in the ampulla of the fallopian tube typically within 24 hours of ovulation. In order for conception to occur, about 300 to 500 sperm must be in the fallopian tube when the ovum arrives. It takes that many sperm to produce the enzymes needed for one sperm to fertilize the egg (Blackburn, 2013). During the journey through the cervix and uterus to the fallopian tube, the sperm undergoes **capacitation** so that when it passes through the **corona radiata** (the first layer of the ovum), it can begin the **acrosome reaction** (small openings of the head that releases the contents) and bind to the **zona pellucida**, which is the second layer of the ovum. The enzymes that have been released by the other sperm help to remove obstructing cells and allow one sperm to penetrate the zona pellucida and enter the ovum. The entire sperm will be taken into the **oocyte** or ovum. Once the sperm has entered the ovum cytoplasm, a zonal reaction occurs to prevent another sperm from entering. The sperm will determine the sex of the embryo by contributing either an X (for female) or a Y (for male) sex chromosome.

Within a few hours, the **haploid** (containing 23 chromosomes) **gametes** (ovum and sperm) will unite within the ovum to form a complete **diploid** (containing 46 chromosomes) cell called the **zygote**, the first cell of a human being. All the information to make a human being is within the zygote. Each cell that develops from this first cell will move and take shape according to the programming of the DNA (deoxyribonucleic acid) from each parent. Cells will change in order to make different tissues and changing cells will influence each other. There will be migrations of cells to form different organs. **Apoptosis** will occur so that cavities are formed and excessive growth does not occur (Beery & Workman, 2012). It is a complex and marvelous chain of events.

The zygote begins to move toward the uterus and the cell begins the replication process, or **cleavage**. In about 30 hours, there are two cells (Benirschke, 2014). By about 3 days, a morula made of 12–32 cells enters the uterine cavity (Moore, Persaud, & Torchia, 2016). Fluid accumulates in the **morula**, forming a **blastocyst**. The blastocyst is protected from the woman's immune system by the *zona pellucida*, the covering for the blastocyst (Blackburn, 2013). About 5 days after fertilization, a 58-cell blastocyst will shed the zona pellucida and secrete substances that help to make the uterine lining even more receptive to implantation. These substances include human chorionic gonadotropin (hCG).

Spontaneous pregnancy losses that occur during the first two weeks are typically caused by chromosomal abnormalities or by failure of the blastocyst and the **syncytiotrophoblast** to produce enough hCG to maintain the corpus luteum as it produces progesterone. Figure 2.1 depicts the cleavage and travel of the conceptus through the fallopian tube to the uterine implantation site.

About 6 to 10 days after ovulation, implantation of the blastocyst into the estrogen- and progesterone-primed endometrium begins (Liu, 2014). Most implantations occur on the upper posterior uterine segment closest to the follicle that released the egg. The blastocyst will adjust itself so that the embryonic pole is closest to the endometrial lining (Blackburn, 2013). It will embed entirely into the endometrium where it has adhered itself.

Fertilization usually occurs in the uterine tube.

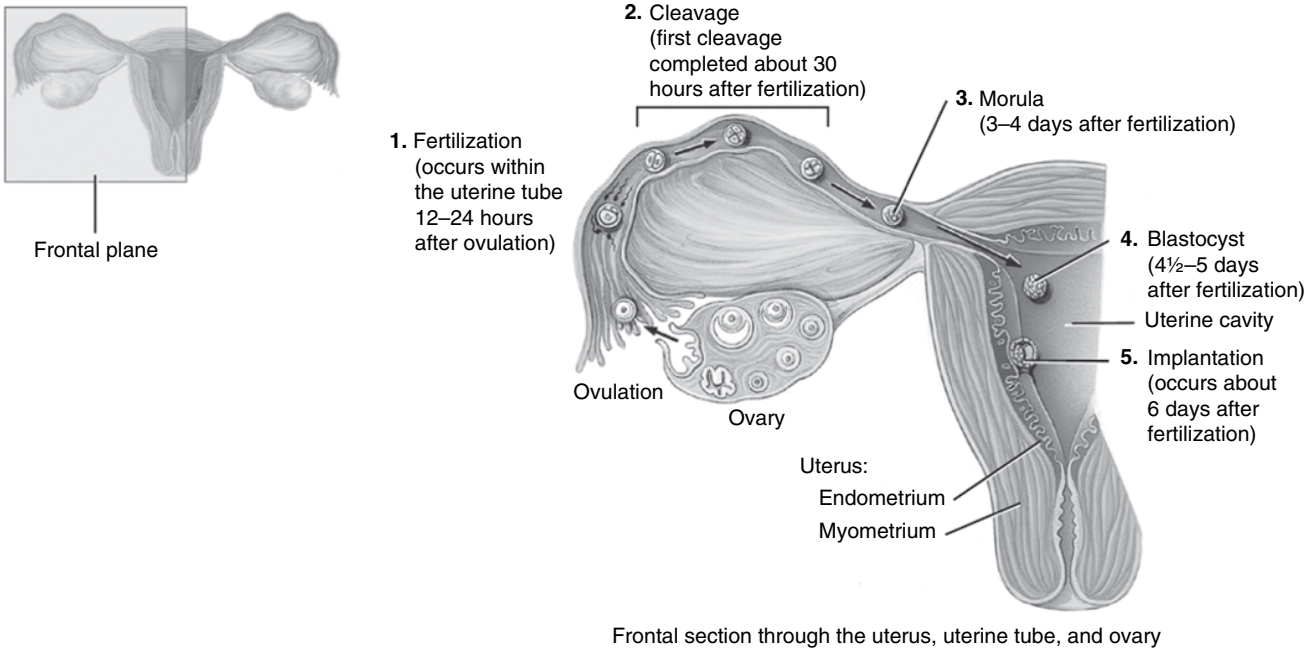

Figure 2.1. Cleavage and travel of the conceptus to the uterus.

The embryonic disc appears and during the second week, it will develop the **ectoderm**, **endoderm**, and **mesoderm** layers that will later form all the body systems of the embryo. Structures outside the embryonic disc form the amniotic cavity, the amnion, the umbilical cord beginnings, and the chorionic sac.

The Placenta

Beginnings and Structure

Encircling the blasotocyst are trophoblast cells that begin the invasion process by projecting into the uterine lining to reach maternal blood vessels. These cells will form the placenta. Once adhered to the endometrium, the trophoblast cells differentiate into two layers. The outer layer is the syncytiotrophoblast, which is a multinuclear protoplasm mass that sends out the fingerlike extensions that take in uterine cells as it invades the endometrium. This layer of the trophoblast secretes both **peptide** and **steroid** hormones important to the maintenance of the pregnancy. The inner layer of the trophoblast has distinct cells and is called the **cytotrophoblast**. These cells secrete peptide hormones needed for the pregnancy.

The syncytiotrophoblast grows and begins to develop small spaces called **lacunae** that will fill with serum from woman's spiral arteries as the invasion progresses. This fluid will nourish the trophoblast. The maternal arteries become fully dilated and a low-resistance, low-pressure continuous flow is established (Cunningham et al., 2014). Communication between the lacunae and uterine vessels begins uteroplacental circulation. The remodeling of the spiral arteries is an important step in establishing optimal circulation and nourishment for the embryo/fetus. Chronic disorders of pregnancy, such as preeclampsia or intrauterine fetal growth restriction, or both, can result from incomplete dilation of the spiral arteries at this stage in development (Blackburn, 2013).

The projections from the cytotrophoblast into the syncytiotrophoblast mass become chorionic villi. These protrusions develop through three stages to become a functioning arteriocapillary venous network that supplies the embryo. Fetal blood begins to circulate by about 21 days after fertilization within the villi. An exchange via diffusion between the maternal and embryonic circulations begins, but the blood from each does not combine or meet. More about the cardiovascular development and transfer of nutrients and gases between woman and fetus is presented later in this chapter.

Recall that the endometrium is changing under the influence of the progesterone that has been secreted by the corpus luteum. This secretory endometrial lining must be primed for the conceptus to be able to implant. Correct timing is essential. At midway in the secretory phase, the endometrium develops protrusions and chemical changes that enhance the acceptance of the blastocyst (Cunningham, et al., 2014).

A **decidual reaction** (cellular and vascular changes in the endometrium at implantation) occurs around the conceptus after it has embedded into the primed endometrium. This reaction provides an area for the conceptus that is protected from the maternal immune system (Moore, Persaud, & Torchia, 2016). If this reaction is abnormal, then ***placenta accreta*** (abnormal attachment of the trophoblast to the myometrium) or ectopic pregnancy may occur. The *decidua basalis* is directly under the trophoblast and is compressed. The villi at the embryonic pole extend into the decidua basalis and become the **chorion frondosum** that develops into the placenta. The *decidua capsularis* and *decidua vera* (or *parietalis)* are over the trophoblast. The decidua capsularis will disappear as the embryo develops. The decidua vera will fuse with the **chorion laeve** (smooth chorion) and disappear as products of conception fill the uterine cavity.

Implantation bleeding, the loss of a small amount of blood from the uterine lining at implantation, occurs when the invasion of the uterine lining causes an abrupt opening in arterioles or veins. Many pregnant women experience this episode of bleeding, and it is considered physiological or a normal variant. The appearance of this bleeding occurs at about the same time a menstrual period is anticipated and can be incorrectly interpreted as the last menstrual period. This can affect how the pregnancy is dated, so a careful menstrual history is warranted.

The placenta at term is round and disk-shaped, about 9 in. or 22 cm in diameter and 2 to 4 cm thick (Cunningham, et al., 2014). The maternal surface is formed by about 20 cotyledons (lobes) attached to the decidua via septa connected to the grooves between the cotyledons. Each lobe contains one main stem villi and its many branches. The fetal side is grayish white and covered by the amnion membrane.

Chorionic and Amnionic Membranes

At about 14 days post conception, the implanted ovum is visible on the endometrium as a polyp-like protrusion. The embryo, amnion, and yolk sac cavities are within the cytotrophoblast layer. The developing embryo at about 14 days is connected inside the trophoblast via a stalk that will become part of the umbilical cord. The stalk is part of the mesoderm, one of three layers of the developing embryo. The ectoderm is part of the amniotic sac epithelium. The endoderm is opposite the ectoderm and beside the yolk sac (Benirschke, 2014). As the embryo grows, it will fold, making the endoderm the innermost portion of the embryo. Eventually, the embryo is surrounded by the amnion and the amniotic fluid (AF).

The yolk sac provides nutrition for the early embryo. As the embryo folds, the yolk sac is enclosed and becomes the primitive gut, nourishing the conceptus (Benirschke, 2014). The cytotrophoblast cells encircle the extraembryonic **coelom**, a cavity that fills with a nutrient lake for molecular exchange between the woman and the embryo (Ross & Beall, 2014). The coelom disappears by the end of the first trimester and the amniotic fluid-filled cavity surrounds the fetus.

One layer of the extraembryonic mesoderm is the **extraembryonic somatic mesoderm**. This layer will combine with the two layers of the trophoblast to form the chorion and the chorionic sac. Within the chorion, the embryo, amniotic sac, and umbilical vesicle are attached to the chorion by the connecting stalk that will become the umbilical cord.

The amniotic sac will enclose the embryo and cells from the amniotic membrane will eventually cover the umbilical cord (Benirschke, 2014). The amniotic sac lies against but does not normally adhere to the entire chorionic membrane by about 12 weeks. There are no blood vessels in the amnion except in rare instances of **velamentous insertion** (where blood vessels insert or grow into the amniotic membrane). The amniotic membrane is made up of ectodermal epithelial cells, thin connective tissue, and macrophages.

AF fills the amniotic sac around the embryo. It protects the embryo/fetus from trauma and most bacteria, allows for fetal movement and growth, and facilitates lung and limb development (Ross & Beall, 2014). The amount of AF increases steadily between 10 and 30 weeks, then slows. Between 36 and 38 weeks, AF begins to decrease normally. At 41 weeks of gestation, AF begins to decrease more rapidly.

Excessive AF, known as **polyhydramnios**, can occur when the fetus has anencephaly or esophageal atresia, which prevents swallowing of AF, or when the woman has diabetes. Complications of polyhydramnios include placental abruption, uterine dysfunction, and postpartum hemorrhage.

Oligohydramnios, or below normal AF, can occur when there is an obstruction to fetal urine flow, renal agenesis, or other fetal anomalies; chronic leakage of AF; or rupture of the amniotic membrane. Chronic reduction in AF can cause fetal **pulmonary hypoplasia** or can increase the risk for infection.

Functions of the amniotic fluid

- Protects the embryo/fetus from trauma
- Is a barrier to most bacteria
- Allows for fetal movement and growth
- Facilitates lung and limb development
- Reflects fetal kidney function
- Provides thermoregulation
- Aids in gastrointestinal maturation

The Umbilical Cord

The connecting stalk is the earliest appearance of the umbilical cord. As the embryo folds during the fourth week, the umbilical cord begins to form and the amnion cells near it develop into the covering for the cord (Moore, Persaud, & Torchia, 2016). Once fetoplacental circulation is established, two umbilical arteries within the cord carry deoxygenated blood away from the fetus to the placenta and woman. The placental barrier between the woman and the fetus is very thin and allows substances, but not blood, to move back and forth. One umbilical vein within the cord brings oxygen and nutrients back to the fetus from the placenta and woman. These three umbilical vessels are surrounded by **Wharton's jelly**, a gelatinous connective tissue. This protective coating does not cover the entire umbilical cord when there is a velamentous insertion.

The umbilical cord is usually between 12 and 35 in. (30 and 90 cm) long (Moore, Persaud, & Torchia, 2016). If it is too long, there is danger that it will coil around the fetus, tighten, and cut off oxygen and nutrient flow. A true knot in the umbilical cord can be created through fetal movement and is found in about 1 in 100 pregnancies, but only causes problems for 1 in 2000. A longer cord can prolapse with the rupture of amnionic membranes, be occluded by the fetal presenting part, and cause loss of oxygen and nutrients to the fetus. About 1 in 20 umbilical cords are abnormally short (Beall, 2015). The cause of shorter cords is unknown; however, shortened cords may cause decreased fetal movement, placental abruption, or disruption in a part of the cord. A shortened cord can affect fetal descent and expulsion, although there are data that indicate that a vaginal delivery can happen if the cord is as short as 5.125 in. (13 cm).

Placental Functions

The placenta and umbilical cord move substances such as nutrients, gases, drugs, and wastes between the woman and the fetus. In addition to the transport of substances, the placenta serves as the organ for gas exchange and waste removal and as an endocrine gland for the fetus. It metabolizes glycogen, cholesterol, and fatty acids for energy, and synthesizes and secretes both steroid and peptide hormones (Moore, Persaud, & Torchia, 2016). The placenta can metabolize some drugs via specific enzyme action. In addition, placental cells produce P-glycoprotein, a substance that can pump some drugs away from the fetus (Lassiter & Manns-James, 2017). Shortly after the baby is born, the extraordinary placenta is expelled from the uterus as waste.

Sociocultural Uses of the Placenta

The American health care system has often treated the placenta as biohazardous waste material, although some placentas have been harvested for medical or commercial use. In some cultures, the placenta is used in rituals designed to honor or protect the mother and the baby, such as burying it under a tree. Two alternative trends are emerging with regard to the placenta: (1) lotus birth, in which the umbilical cord is not severed at birth and the cord and placenta are kept with the baby until natural separation occurs; and (2) placental encapsulation in which the placenta is steamed, dehydrated, ground, and placed into capsules for ingestion in the postpartum period by the mother with reputed effects of enhancing milk supply and preventing depression. Health care providers should discuss the woman's preferences for the disposal or use of the placenta in the prenatal period.

Placental Transport

By the third week after fertilization, the embryo has developed a vascular network and fetal circulation begins and the heart begins to beat by about day 21 (Moore, Persaud, & Torchia, 2016). The embryonic circulation is separated from maternal circulation by a thin membrane often called the placental barrier.

The four main modes of transport for substances across the placental membrane are **simple diffusion** (movement from higher to lower concentration), facilitated diffusion (movement that needs a transporter but no energy), **active transport** (movement against a concentration gradient that requires energy), and **pinocytosis** (carrier molecule is required to engulf the molecule and move it across the placental barrier) (Blackburn, 2013; Moore, Persaud, & Torchia, 2016). Most drugs cross the placenta via simple diffusion (Lassiter & Manns-James, 2017). Table 2.1 lists the four modes of transport and gives a few examples of substances that are transported via each mode.

Table 2.1 Four main transport mechanisms

Mode of Transport	Examples
Simple diffusion	Oxygen, CO_2, carbon monoxide, H_2O, most drugs, steroids, electrolytes, anesthetic gases
Facilitated diffusion	Glucose (facilitated by insulin), cholesterol, triglycerides, phospholipids
Active transport	Amino acids, vitamins, transferrin (carries iron to fetus), iodine, calcium
Pinocytosis	Immunoglobulin G

Adapted from: Adams & Urban (2016); and Blackburn (2013).

Seven factors affect substance transfer across the placenta (Adams & Urban, 2016):

1. High maternal plasma level of the specific substance can affect transfer. Higher maternal plasma levels will mean that more of the substance is available for transfer to the fetus.
2. Lipid-soluble substances cross the placental barrier better and more rapidly than do water-soluble substances.
3. The smaller the molecule, the more readily it crosses the placenta. Alcohol, for instance, is a very small molecule and crosses readily. Heparin is a very large molecule and does not cross.
4. Protein binding can make the substance too large to cross.
5. Ionized drugs do not cross as easily as nonionized drugs. An example of this is how nicotine crosses and reaches higher concentrations in the fetus. Nicotine is a weak base and maternal serum is slightly more acid than fetal serum. Once in the fetus, nicotine becomes ionized in a higher pH environment and will not cross the placenta back to woman. So, plasma levels of nicotine are higher in the fetus than in the woman.
6. If uteroplacental blood flow is compromised, drugs or other substances can stay in the fetus for a long time. This increases the risk for more serious fetal side effects. In fact, the rate of maternal or fetal blood flow through the villous spaces will affect diffusion.
7. The stage of fetal development makes a difference. Before implantation, drug exposure will either destroy the blastocyst or it will not be affected at all. During organ development between weeks 3 and 8, the developing organs may be damaged by drugs. This is also the time when the risk for drug-related spontaneous abortion is highest. During the fetal phase, weeks 9–40, drugs will be in the fetal system for a longer period of time due to immature metabolism and excretion processes. Exposure at this time, however, does not cause severe malformations. Instead, there may be delayed growth or organ function problems.

Some viruses, bacteria, and protozoa cross the placenta to infect the fetus. Table 2.2 lists the infectious agents that may cross the placental barrier and affect the fetus.

Table 2.2 Transplacental infections

Viruses	Varicella zoster, Coxsackie, parvovirus (B19), cytomegalovirus, rubella, human immunodeficiency virus, polio virus, zika virus
Bacteria	*Treponema pallidum* (syphilis), listeriosis, Borrelia (Lyme disease)
Protozoa	Toxoplasmosis

Adapted from: Centers for Disease Control and Prevention. (2016, November 18); Cunningham et al. (2013); and Moore, Persaud, & Torchia (2016).

Placental Endocrine Synthesis and Secretion

The placenta uses **precursors** such as cholesterol, estrogen, or protein to synthesize both peptide and steroid hormones. The peptide hormones include, but are not limited to, hCG, human placental lactogen (also called human chorionic somatomammotropin), human chorionic adrenocorticotropin (ACTH), corticotropin-releasing hormone, relaxin, and inhibin. The steroid hormones include estrogen and progesterone.

The hormone hCG is essential to pregnancy. It is produced by both the syncytiotrophoblast and cytotrophoblast for the first 5 weeks of pregnancy, thereafter, by the syncytiotrophoblast and fetal kidneys. It is detectible in maternal serum and urine by 7–9 days after ovulation and is used for pregnancy tests. Maternal plasma levels of hCG double every 31–35 hours until around 63–70 days (Liu, 2014). Plasma levels then decline until about 16 weeks to remain the same until birth.

Maternal serum levels of hCG are used clinically for pregnancy testing and for diagnosis of various pregnancy abnormalities in the early weeks of pregnancy. Levels of hCG that are too high indicate multiple fetuses, fetal hemolytic disease, **hydatidiform mole**, or Down syndrome. Levels that are too low or that do not double in 2 days can indicate spontaneous abortion or ectopic pregnancy. hCG is also used in combination with other substances such as estriol and alpha-fetoprotein to screen for other fetal abnormalities.

The functions of hCG include maintenance of the corpus luteum; maintenance of the development of spiral arteries in the myometrium and formation of syncytiotrophoblast; acting as a luteinizing hormone to stimulate the male embryonic/fetal testicle to secrete testosterone; stimulation of the maternal thyroid gland; and promotion of secretion of relaxin (peptide hormone) from the corpus luteum. It might also promote vasodilation and smooth muscle relaxation of the uterus (Moore, Persaud, & Torchia, 2016; Blackburn, 2013). In maintaining the corpus luteum, hCG also prevents menses. It is synthesized without any contribution from the fetus, so maternal serum levels will remain high long after fetal demise (Blackburn, 2013).

Human placental lactogen is synthesized in the syncytiotrophoblast and can be measured in maternal serum at about 4 weeks. Its actions include maternal **lipolysis** (breakdown of fat for energy), increased maternal insulin resistance that facilitates protein synthesis

and availability of amino acids and glucose to the fetus, **angiogenesis** (embryo blood vessel formation), and increased synthesis and availability of lipids (Blackburn, 2013). This is the placental hormone most involved in keeping a constant flow of glucose and amino acids going to the fetus.

ACTH is important for fetal lung maturation and plays a role in the timing of labor and birth. Corticotropin-releasing hormone (CRH) is produced in the placenta, membranes, and decidua. CRH acts to increase ACTH secretion from the trophoblast, causes smooth muscle relaxation in blood vessels and in the uterus until late in pregnancy, and facilitates maternal immunosuppression. Near term, a rise of CRH from the fetus and the placenta contributes to the genesis of labor.

Relaxin is produced in the corpus luteum, decidua, and the placenta. It acts to quiet the myometrium, facilitate the decidual reaction, remodel collagen, and soften the cervix (Blackburn, 2013). Relaxin also mediates hemodynamic changes of pregnancy and softens ligaments and cartilage in the skeletal system.

Inhibin is another glycoprotein produced by the trophoblast. It acts with sex steroid hormones to decrease the secretion of follicle-stimulating hormone from the pituitary, thereby stopping ovulation during pregnancy.

There are three major estrogens: estrone, estradiol, and estriol. In pregnancy, estriol is the major estrogen. Estriol is synthesized in the placenta from precursors from the maternal and fetal adrenal glands. Dehydroepiandrosterone sulfate (DHEA-S) is synthesized from cholesterol in the fetal adrenal glands, and it is an essential precursor to placental synthesis of estriol (Blackburn, 2013). During pregnancy, estriol production increases about 1000 times that seen in nonpregnant women at ovulation (Cunningham et al., 2013). Lower than normal maternal serum levels of estriol are seen when the fetus is anencephalic or has adrenal hypoplasia. Additionally, fetal demise can occur because the fetal pituitary is not releasing ACTH or the fetal adrenal glands are not functioning (Blackburn, 2013). Maternal serum and AF estriol levels, along with other substances, are also used to screen for Down syndrome, trisomy 18, and neural tube defects.

Estrogen in pregnancy has many functions. Estrogens induce the proliferation and secretory phase of the endometrium, stimulate phospholipid synthesis, enhance prostaglandin production, and trigger uterine contractions. Estrogens also promote myometrial vasodilation, increase uterine blood flow, prepare the breasts for breastfeeding, affect the maternal renin–angiotensin system, stimulate the liver to produce globulins, and increase fetal lung surfactant production (Blackburn, 2013; Liu, 2014).

Progesterone is secreted by the corpus luteum early in pregnancy. It is not until about 8–10 weeks that progesterone is synthesized and secreted by the placenta. The precursor for progesterone synthesis is cholesterol. Maternal serum levels of this steroid hormone increase steadily throughout the pregnancy so that by term, 250 mg/day is being produced (Liu, 2014). This is about 10 times the amount produced by the corpus luteum during the luteal phase of the menstrual cycle.

Progesterone has a number of essential functions in pregnancy. Progesterone is needed for preparation of the endometrium for implantation; maintenance of a quiescent uterus through relaxation of the smooth muscle; inhibition of uterine prostaglandin development, thereby delaying cervical softening; inhibition of the cell-mediated immune system to help prevent rejection of the conceptus; reduction of CO_2 sensitivity in the maternal respiratory center; inhibition of prolactin secretion; relaxation of maternal smooth muscle in the gastrointestinal and urinary systems; and elevation of maternal temperature. Additionally, it is important in creating thicker cervical mucus and a mucous plug that serve as a barrier to infectious agents trying to enter the uterus (Blackburn, 2013; Liu, 2014). Unlike estrogen, the fetus is not necessary for the production of progesterone and maternal serum levels of this hormone will remain high long after fetal demise (Blackburn, 2013). Table 2.3 summarizes the placental hormones and their functions.

The Embryo

Gastrulation (formation of germ layers of the embryo) changes the embryo from a two-layer disc to a three-layer disc. The three layers include the ectoderm, mesoderm, and endoderm. These layers form the basis for all tissues and organs that will develop as the embryo grows. Gastrulation begins with the appearance of the **primitive streak** from the tail through the middle of the back of the embryo to the head (Moore, Persaud, & Torchia, 2016). Cells from the primitive streak and its derivatives will migrate away and form the mesoderm until about the fourth week. Near the tail end of the primitive streak, the **cloacal membrane** develops. This is the future site of the anal opening. Figure 2.2 shows how the primitive streak appears and lengthens.

Parts of the primitive streak that do not degenerate can give rise to a **sacrococcygeal teratoma**, a cystic tumor that contains tissues from all three germ layers (Hamilton, 2015). These tumors can be surgically removed from the neonate without any lasting effect.

Mesenchymal cells from the primitive node move toward the head and form the **notochordal** process and

Table 2.3 Placental hormones and their functions

Human Chorionic Gonadotropin (hCG)	Maintains the corpus luteum Promotes vasodilation and relaxation of the uterus Stimulates the male testicle to secrete testosterone Stimulates maternal thyroid Promotes secretion of relaxin
Human placental lactogen (hPL)	Maternal lipolysis Increases maternal insulin resistance Angiogenesis Increases synthesis of lipids
Human chorionic adrenocorticotropin (ACTH)	Promotes fetal lung maturation Plays role in timing of labor
Corticotropin-releasing hormone	Acts to increase ACTH secretion from the trophoblast Causes smooth muscle relaxation in blood vessels and uterus Facilitates maternal immunosuppression Near term, contributes to genesis of labor
Relaxin	Quiets the myometrium Facilitates decidual reaction Remodels collagen Helps soften the cervix Affects cartilage of maternal skeletal system
Inhibin	Acts with other hormones to decrease release of follicle-stimulating hormone, which stops ovulation
Dehydroepiandrosterone sulfate (DHEA-S)	Essential precursor to placental synthesis of estrogen
Estrogen	Acts to prepare the endometrium for pregnancy Stimulates phospholipid synthesis Enhances prostaglandin production Promotes uterine vasodilation Prepares breasts for breastfeeding Increases fetal lung surfactant production
Progesterone	Essential for preparation of the endometrium for implantation Maintains quiescent uterus Inhibits prostaglandin development Inhibits maternal cell-mediated immune system Reduces CO_2 sensitivity in maternal respiratory center Inhibits prolactin secretion Relaxes maternal smooth muscle Causes increase in maternal temperature Increases cervical mucus and formation of mucous plug

Adapted from: Blackburn (2013); Cunningham et al. (2013); and Liu (2014).

canal. The notochord is a rodlike structure that helps organize the nervous system and later becomes part of the vertebral column and axial skeleton. As the vertebra develops around the notochord, it will degenerate until only remnants are left in the nucleus pulposus between bony vertebrae. The notochord grows between the ectoderm and the endoderm and stops at the prechordal plate. Before it degenerates, the notochord will cause a thickening of the ectoderm and the formation of the neural plate by the end of week 4. This is where the central nervous system, including the forebrain, begins (Moore, Persaud, & Torchia, 2016). The neural plate and ectoderm also give rise to the retina, iris, optic nerve, and other eye structures. On either side of the notochord, **somites** (segmental mass of mesoderm occurring in pairs along the notchord) develop, which give rise to the skeleton, muscles, and some of the skin. As the somites develop, they can be used to estimate the age of the embryo (Blackburn, 2013). Figure 2.3 shows the notochord process. Near the prechordal plate, layers of

Gastrulation involves the rearrangement and migration of cells from the epiblast.

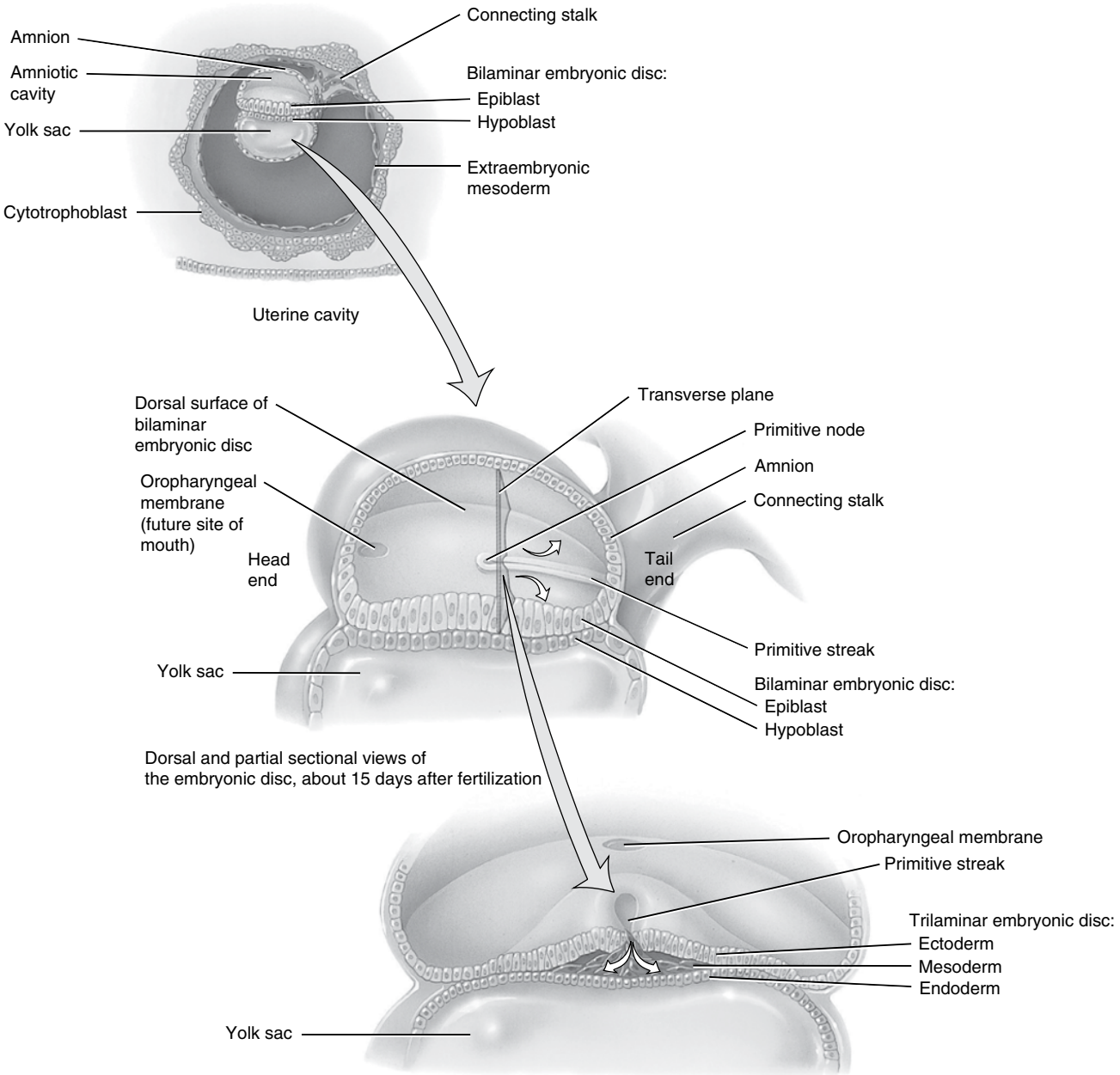

Figure 2.2. Gastrulation and the appearance of the primitive streak.

ectoderm and endoderm meet and form the oropharyngeal membrane, which will become the mouth.

Mesenchymal cells migrate to the sides of the primitive streak and fuse with the extraembryonic mesoderm that is part of the amnion and umbilical vesicle. These cells also migrate toward the head and form the cardiogenic mesoderm where the heart will begin development at the end of the third week. The **allantois** is a small appendage of the umbilical vesicle that attaches to the connecting stalk. It is involved with blood formation and the development of the urinary bladder. The blood vessels of the allantois become the arteries and vein of the umbilical cord (Moore, Persaud, & Torchia, 2016).

Neurulation is complete at the end of week 4. About day 18, a neural groove and neural folds appear in the neural plate. These early neural folds are the first signs of brain development. Later, the neural folds fuse to form the neural tube that will separate from the surface ectoderm. The edges of the ectoderm will then fuse over the neural tube, becoming the skin of the back. A neural

The notochordal process develops from the primitive node and later becomes the notochord.

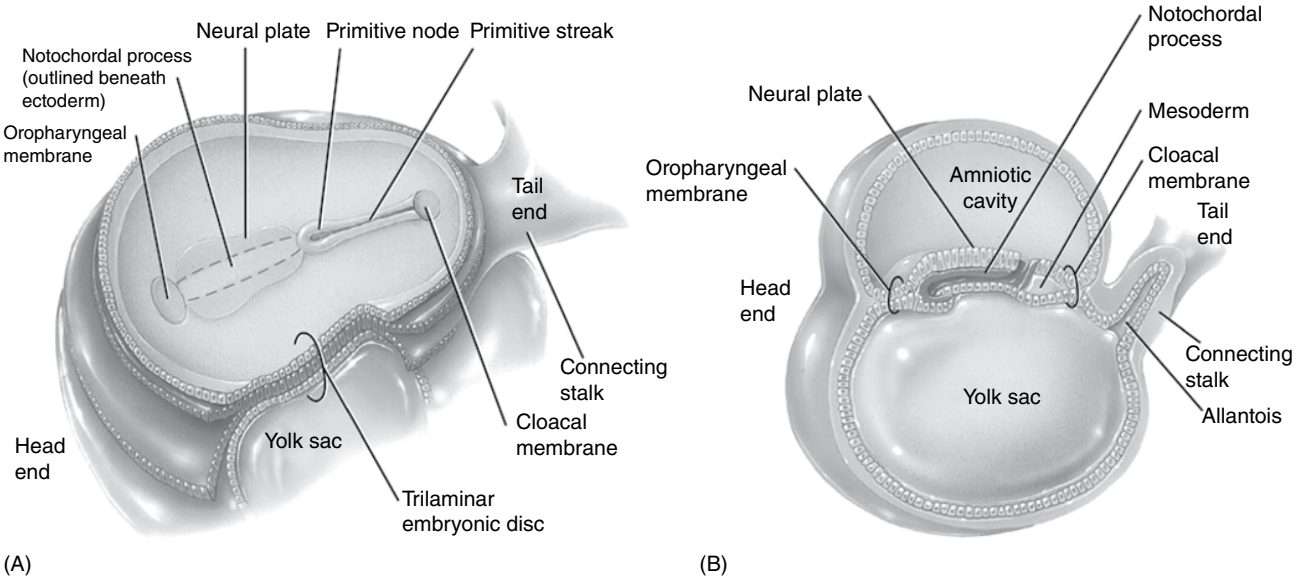

Figure 2.3. Notochord growth. (A) Dorsal and partial sectional views of the trilaminar embryonic disc, about 16 days after fertilization. (B) Sagittal section of the trilaminar embryonic disc, about 16 days after fertilization.

crest forms between the neural tube and the ectoderm (Moore, Persaud, & Torchia, 2016). Neural crest cells migrate and change into spinal ganglia and autonomic nervous system ganglia. These cells also form the ganglia for cranial nerves V, VII, IX, and X; sheaths for peripheral nerves; the pia mater; and arachnoid mater. This is the time that neural tube defects occur, including anencephaly and meningocele due to failure of primary neurulation, and spina bifida due to failure of secondary neurulation (Jallo, 2015).

The embryo's first nourishment is from maternal blood via diffusion through the chorion, extraembryonic coelom, and umbilical vesicle. At the beginning of the third week, blood vessel formation begins in the extraembyonic mesoderm of the umbilical vesicle and connecting stalk (Moore, Persaud, & Torchia, 2016). At the same time, new blood vessels are being formed in the chorion so that by day 21 postfertilization, the early uteroplacental circulation is functional. At about the same time, the intraembryonic coelom is dividing into the pericardial, pleural, and peritoneal cavities.

Blood formation within the embryo does not begin until week 5. The heart and large vessels develop in the pericardial cavity and the heart begins to beat on day 21 or 22 after conception (Moore, Persaud, & Torchia, 2016). The cardiovascular system is the first system in the embryo to function.

Organogenesis

The fourth to eighth week for the embryo is the period of **organogenesis**. All the main organ systems begin to develop during these weeks. This is the time when the embryo is most vulnerable to **teratogens**. As development proceeds, the embryo begins take on more visual characteristics unique to humans.

These transformative 4 weeks begin with the folding of the embryo so that the flat trilaminar disc becomes a curved cylinder (Moore, Persaud, & Torchia, 2016). The curve is toward the connective stalk and umbilical vesicle. Figure 2.4 depicts the folding of the embryo.

Once folding is complete, the three layers—ectoderm, mesoderm, endoderm—begin to divide, migrate, aggregate, and differentiate in precise patterns to form organs.

Germ Layers and Organogenesis

Ectoderm—central and peripheral nervous systems, muscle, the skin, hair and nails, mammary glands, pituitary gland, and tooth enamel
Mesoderm—connective tissue, cartilage, bone, striated and smooth muscle, heart, blood, lymphatic system, kidneys, ovaries, testes, spleen, adrenal glands
Endoderm—lining of the gastrointestinal, urinary and respiratory tracts, linings of the ear, parts of the pancreas, and thyroid

The fourth week of development will produce somites and the neural tube will be open. The pharyngeal arches are visible and the embryo curves more head to tail (Moore, Persaud, & Torchia, 2016). The heart pumps blood even though it has not yet developed chambers. The forebrain causes an elevation of a portion of the head and there is a tail-like structure opposite the head. Arm buds are seen on either side of the upper embryo.

Embryonic folding converts the two-dimensional trilaminar embryonic disc into a three-dimensional cylinder.

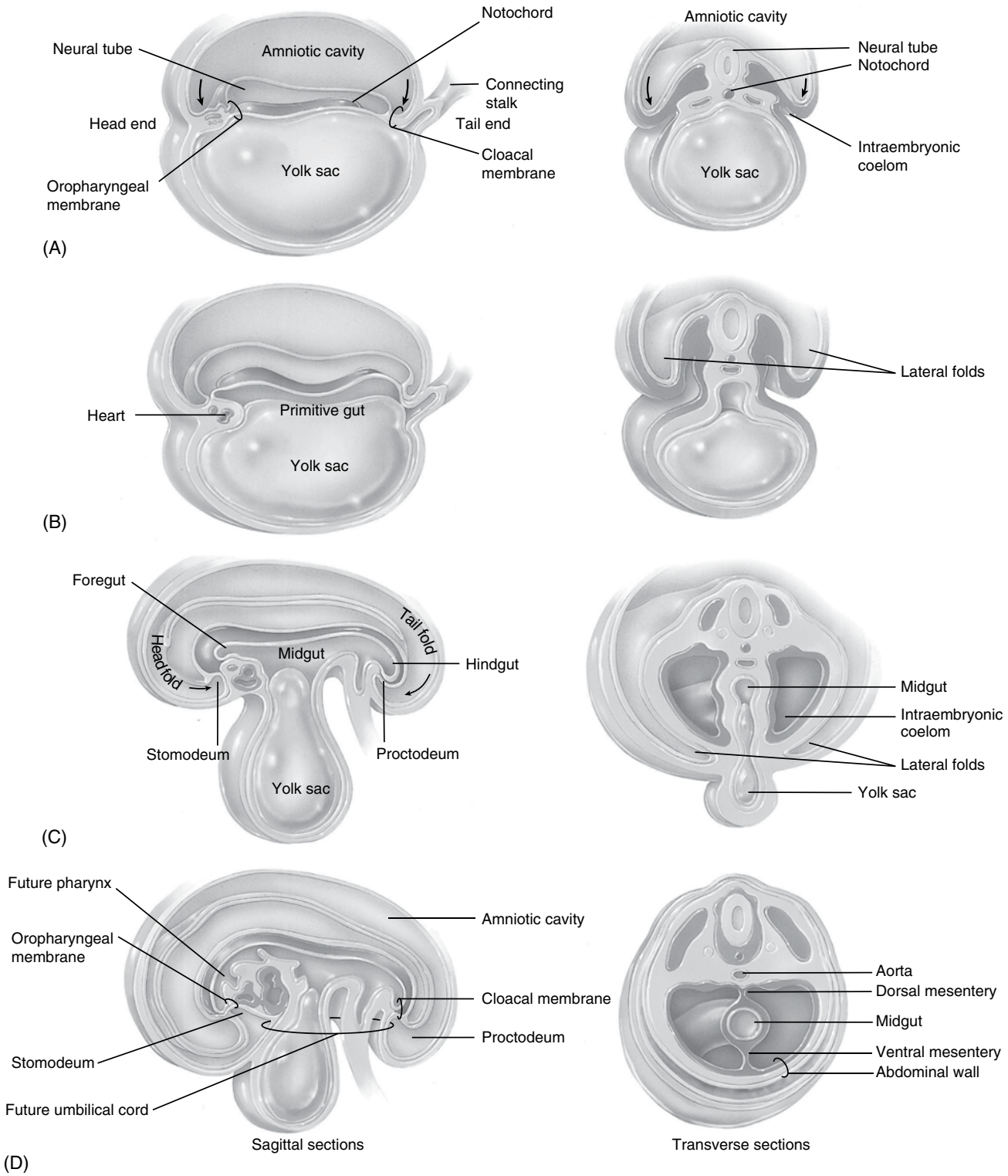

Figure 2.4. Folding of the embryo: (A) 22 days, (B) 24 days, and (D) 28 days.

Otic pits are visible where the ears will be, and a thickening on either side of the head marks where the future eye lenses will be. The leg buds become visible at the end of the fourth week.

During week 5, growth of the head is more rapid than other parts due to the development of the brain and facial features. The embryo is bent in a way that the face will touch the cardiac prominence. Mesonephric ridges appear that will become the kidneys.

The embryo begins slight movements during week 6 and will reflex to touch. Digital rays, the first stages of fingers and hands, appear. The legs develop about 4–5 days after the hands. The auricles for the ears begin to be visible. The retinal pigment for the eyes is present. The head is large and the trunk begins to straighten. The intestines enter the peritoneal cavity near the end of the umbilical cord and an umbilical hernia occurs to give room for the intestine (Moore, Persaud, & Torchia, 2016). At the end of week 6, the embryo is about 22–24 mm in length (Cunningham et al., 2014).

The limbs develop more rapidly during the seventh week. Digital rays become hand plates and the arms and legs become longer. This is also the time when the primordial gut and umbilical vesicle shrink to form the omphaloenteric duct (Moore, Persaud, & Torchia, 2016).

During the last week of organogenesis, fingers are webbed, toes are still digital rays, and the scalp veins become visible and form a band around the head. By the end of the eighth week, digits of the hands and feet have grown longer and the webs are gone. Coordinated movements of all four limbs are seen. The femurs are the first bones to begin to ossify. The tail-like structure has disappeared. The head is still larger than the remainder of the body, but its features are human. The neck is visible, eyelids are closing, and auricles are nearing their final shape. The auricles are low on the head. Sex identification is not yet possible. The fetus will be 10–12 weeks old before it becomes clear that it is either a male or a female. This distinction cannot be made reliably by ultrasound at this stage.

The Fetus

The end of week 8 and the beginning of week 9 mark the beginning of the fetal period. The fetal period is a time of rapid growth and differentiation of the systems that have been formed during the preceding 8 weeks. By convention, the main changes in the fetus are considered to occur every 4–5 weeks (Moore, Persaud, & Torchia, 2016).

From weeks 9–12, the fetus doubles its crown to rump length. At 9 weeks, the eyes are wide set, the ears low on the head, and the eyelids are fused. The legs are short and thighs are small. The intestines are seen at the end of the umbilical cord until week 10. The intestines will be completely in the peritoneal cavity by week 11. Urine formation and micturition begin during this period. The fetus begins to swallow AF that contains the urine. Fetal wastes are passed via fetal blood circulation to the woman through the placental membrane. By the end of week 12, the arm length reaches the proportional length the arms will maintain in relation to the body. The legs are still growing.

During weeks 13–16, the head is smaller in relation to the remainder of the body and the legs are longer. Limb movements as seen via ultrasound are coordinated by week 14. Slow eye movements are seen at 14 weeks and scalp hair has begun to grow. By 16 weeks, ovaries are present in female fetuses and contain ovarian follicles with **oogonia** (primitive ovum). Sixteen weeks is also the time when fetal bones are visible by ultrasound and the eyes are closer together and look forward. At week 14, the fetal crown–rump length has grown to about 7 cm.

The time period between 17 and 20 weeks marks rapid growth. This is the time that fetal movements can be felt by the woman (**quickening**). The skin at this stage is covered with **vernix caseosa**, which protects the skin. The skin is also covered with **lanugo**, which helps hold the vernix caseosa to the skin. Eyebrows are visible. In females, the uterus is differentiated and formed. In the male, the testes have started migrating toward the scrotum from the posterior abdominal wall. Brown fat for heat generation begins to be deposited in the subcutaneous area (Moore, Persaud, & Torchia, 2016).

Increased weight gain and a more proportional fetus are seen in weeks 21–25. Rapid eye movements and blink-startle responses become evident between weeks 21 and 23 (Moore, Persaud, & Torchia, 2016). Lung development is nearing completion. Surfactant begins to be secreted from the walls of the lungs at 24 weeks. This fluid will help maintain open alveoli, and it is essential for newborn breathing to begin and continue after birth. Fingernails are seen at 24 weeks (Moore, Persaud, & Torchia, 2016).

Between 26 and 29 weeks, the fetus has the potential to survive if it is born prematurely. Its central nervous system has matured enough to direct regular breathing motions and to control body temperature (Moore, Persaud, & Torchia, 2016). The eyelids open and close at 26 weeks and toenails are visible. Brown fat has accumulated and skin wrinkles are smoothed.

Fetal pupils react to light at 30–38 weeks, skin is pink and smooth, and arms and legs become plump. By 35 weeks, the grasp reflex is present and the nervous system is mature enough to function. The abdomen is as wide as the head and the breasts protrude from the chest wall in

Table 2.4 Vulnerable periods in embryonic and fetal growth and development

Timing	Physiological Events	Potential Vulnerabilities
Weeks 1 and 2	Dividing zygote, implantation, bilaminar embryo	Not susceptible to teratogenesis; spontaneous loss may occur, often due to genetic malfunction early in process
Week 3	Neurological system and cardiac system development begins	Anencephaly; neural tube defects; truncus arteriosis, atrial septal defect or ventricular septal defects may occur near the end of this week of development
Week 4	Brain and nervous system, arms, and later in the week, legs; end of week: ears, eyes	Neural tube defects, heart defects, upper and lower limb defects; low set or deformed ears and deafness; malformed eyes, cataracts, glaucoma
Week 5	Brain and nervous system, heart, arms, legs, ears, eyes, mouth	Same as week 4 and add cleft lip
Week 6	Same as week 5; add tooth enamel and hard palate near the end of week 6	Same as week 5; add enamel hyperplasia and staining; cleft palate near end of week 6
Week 7	Same as week 6; add genitalia	Masculinization of female genitalia may occur at this point
Week 8	Same as week 7; end of this week marks the end of organogenesis	Ears and hearing at risk; eye deformities at week 4; tooth enamel, hard palate, and female genitalia still at risk
Week 9	Brain, hard palate, female genitalia at risk	Brain development deficiencies major threat; hearing still at risk; other major congenital anomalies become less of a threat; functional defects and minor anomalies still possible
Week 16	Brain	Mental retardation; functional defects and minor anomalies continue
Weeks 32–38	Focus on growth and development	Functional and minor anomalies may occur in the central nervous system, ears, eyes, teeth, palate, and external genitalia

Adapted from: Moore, Persaud, & Torchia (2016).

both boys and girls. Growth begins to slow, although more brown fat is added during the last weeks before birth (Moore, Persaud, & Torchia, 2016). The fetus at 30 weeks weighs about 1800 g, or just under 4 lb (Cunningham et al., 2014). Fetal growth may be assessed by ultrasound, magnetic resonance imaging (MRI), or fetal monitoring.

The baby is expected to be born at about 266 days after fertilization or 280–283 days after the woman's last normal menstrual period (Moore, Persaud, & Torchia, 2016). It is estimated that about 12% of babies are born after the expected date of birth (EDB) (Moore, Persaud, & Torchia, 2016). The average baby will weigh about 3400 g at birth.

Birth defects have the potential for occurring at many times during embryonic growth and development. Table 2.4 lists vulnerable periods and the defects that can occur.

Summary

There is much more to be learned about the development of a human being from the single-celled zygote. The synthesis of the various cells that grow, produce substances that sustain life, migrate to form organs and tissue, or die away to form hollows and spaces is complex and wondrous. It is easy to see that disruption during any stage can cause a cascade of changes that can lead to birth defects or death. It is important that health care professionals respect and protect the woman and the embryo/fetus and educate women and their families to enhance the health of mothers and their growing babies.

Resources for Healthcare Providers

For a detailed week-by-week timeline of human development from a cell to a newborn, use this link: https://embryology.med.unsw.edu.au/embryology/index.php/Timeline_human_development

An interactive visual tool for understanding conception, embryonic, and fetal development, *The Visible Embryo*, is available at http://www.visembryo.com/baby/index.html

Tsiaras, A. (2011). Conception to birth—visualized. YouTube. Retrieved 1/2/17 https://www.youtube.com/watch?v=fKyljukBE70

Khan Academy. (2014). Implantation. YouTube. Retrieved 1/2/17 https://www.youtube.com/watch?v=1KL8HAm3uSY

General Embryology: Detailed Animation on Gastrulation (2014). YouTube. Retrieved 1/2/17 https://www.youtube.com/watch?v=3AOoikTEfeo

Resources for Women, Their Families, and Healthcare Providers

Fetal Development Timeline: http://www.babycenter.com/0_fetal-development-timeline_10357636.bc

This website from the University of Michigan Medical School (1999) depicts the embryonic period during weeks 3–8: http://www.med.umich.edu/lrc/coursepages/m1/embryology/embryo/05embryonicperiod.htm

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3

Maternal Physiological Alterations during Pregnancy

Patricia W. Caudle

Relevant Terms

Accelerated starvation—after a period of fasting, ketonemia, ketonuria and hypoglycemia occur and the body starts to breakdown fat for fuel
Anabolic—construction of molecules for storage
Anagen—growing phase of the hair growth cycle
Angiogenesis—growth of new blood vessels
Apoptosis—cell death by the Fas/FasL ligand system
Catabolism—breakdown of molecules for energy
Cytokines—molecule messengers that regulate responses to inflammation
Epulis—localized vascular swelling of gums between teeth
Fas/FasL—cell membrane proteins that can activate cell death
Fibrinolysis—breakup and removal of excess fibrin
Hyperemia—increased blood flow
Hyperplasia—increased number of normal cells in normal tissue
Linea alba—white fibrous structure running from the umbilicus to the symphysis formed by the fusion of the abdominal muscles, visible through the skin of the anterior abdomen
Linea nigra—darkened skin over the linea alba seen in pregnancy
Lipolytic—breakdown of fat
Lordosis—increased inward curve of the lumbar and cervical spine
Melasma—tan or brown discoloration of areas of the facial skin
Methylation—the process by which methyl groups are added to a DNA molecule, changing the activity of that DNA segment
Neural tube defects—birth defects of the brain and spinal cord
PCO2—partial pressure of carbon dioxide in the blood
Pedunculated—attached via a stalk
Pica—a craving for nonfood substances
Placentation—development of the placenta
Platelet-derived growth factor—protein that regulates blood vessel formation and growth
Ptyalism—excess salivation
Resorption, bone—osteoclasts break down bone and release calcium
Semiallograft—transplanted tissue that is half-host genetic material; in pregnancy, the fetal-placental unit is half maternal genetic material
Telangiectasias—small dilated blood vessels near the skin surface
Telogen—resting phase of the hair growth cycle
Thromboxane—a prostaglandin
Tissue factor—substance that initiates clotting
Trigone—the triangular region of the bladder wall muscle tissue with angles that correspond with ureter and urethra openings

Introduction

This chapter outlines physiological changes and adaptations experienced by the pregnant woman as her body accepts, accommodates, and maintains a pregnancy to term. Virtually every body system is affected by remarkable hormonal, anatomical, physiological, and biochemical changes that occur from fertilization through parturition.

Hematologic System Adaptations

Maternal physiological changes in the hematologic system include increases in blood and plasma volume, and increases in the number of red blood cells (RBCs) and white blood cells (WBCs). These changes lead to increased nutritional requirements for iron and folate. In addition, pregnancy is a hypercoagulable state where

Prenatal and Postnatal Care: A Woman-Centered Approach, Second Edition. Edited by Robin G. Jordan, Cindy L. Farley and Karen Trister Grace.

Companion website: www.wiley.com/go/jordan/prenatal

changes in specific clotting factors and fibrin and fibrinolytic activities occur.

Blood Changes

Blood is composed of plasma, RBCs and WBCs, platelets, and many smaller molecules with numerous functions. During pregnancy, blood volume increases by 30% to 45%, or about 1.5 liters (Blackburn, 2013). The major components, plasma and the RBC mass, increase at different rates and through different mechanisms. The more rapid increase in plasma volume causes hemodilution. This hemodilution lowers the hemoglobin, hematocrit, and RBC count per milliliter. These changes do not affect the mean corpuscular volume or mean corpuscular hemoglobin concentration in a normal pregnancy (Kilpatrick, 2014). Table 3.1 delineates the changes in hematologic laboratory parameters during pregnancy.

Red blood cells

The RBC mass will increase by 20–30% by the end of a normal pregnancy (Monga & Mastrobatista, 2014). This increase occurs because of increased production of RBCs in the bone marrow. Human placental lactogen (hPL), progesterone, and prolactin have been identified as the hormones of pregnancy that stimulate an increase in erythropoiesis (Monga and Mastrobatista, 2014).

White blood cells

Total WBC count increases during pregnancy, ranging from about 5000 to about 15,000 per cubic millimeter (Blackburn, 2013). Most of the increase is in the numbers of neutrophils. Neutrophils function as the first WBC responders in the body's reaction to an infectious or inflammatory process. The WBC count may rise to as high as 30,000 per cubic millimeter during labor and birth without infection. This increase mimics a similar rise in WBCs seen during aerobic exercise.

Table 3.1 Changes in hematologic laboratory parameters during pregnancy

Red blood cells (RBCs)	Increase ~ 20–30%
RBC indices	Unchanged
Hematocrit	Decreases ~ 3–5%
Hemoglobin	Decreases 2–10%
White blood cells	Increase 8% (much higher in labor)
Serum ferritin	Decreases
Serum iron	Decreases
Total iron-binding capacity	Increases
Transferrin saturation	Decreases
RBC folate	Decreases
Iron	Decreases
Transferrin	Increases

Adapted from: Blackburn, S. (2013); Kilpatrick, S. (2014).

Plasma

Plasma volume begins to increase as early as 6–8 weeks' gestation (estimated gestational age [EGA]). By about 32 weeks' EGA, plasma volume will have increased 45–50% higher than nonpregnant levels (Monga and Mastrobatista, 2014). This increase helps to meet heightened maternal metabolic needs, to circulate blood within the dilated uterine vascular system, to provide nutrients to the growing conceptus, and to protect the mother against the consequences of blood loss during labor and birth. Plasma expands because the production of nitric oxide, a potent vasodilator synthesized from the endothelium of the blood vessel walls, is enhanced and leads to vasodilation, causing the renin–angiotensin–aldosterone system (RAAS) to induce sodium and water retention (Monga and Mastrobatista, 2014). In addition, human chorionic gonadotropin (hCG) stimulates the thirst centers of the hypothalamus, leading to an increased sensation of thirst and intake of water and other fluids (Blackburn, 2013).

Plasma volume is higher in multiple gestations, maternal obesity, or when the fetus is larger (Monga and Mastrobatista, 2014). Increased levels of plasma also occur with hydatidiform mole, so the fetus is not the sole reason for plasma increases (Monga and Mastrobatista, 2014). Plasma volume is decreased with preeclampsia.

Iron requirements

An increase in RBC production and a growing fetus and placenta requires increased iron intake and absorption. It is estimated that the pregnant woman needs 500 mg of additional iron during pregnancy. This includes 300 mg that is used by the fetus and about 200 mg that is needed for normal daily use and loss (Monga & Mastrobatista, 2014). To meet this need, maternal iron stores are mobilized and increased absorption of dietary iron from the duodenum occurs. Progesterone mediates a slowed peristalsis in the small intestine and colon, which enhances iron absorption (Kelly & Savides, 2014).

Many women enter pregnancy with micronutrient deficiencies, particularly iron stores, due to inadequate diets and cyclical menstrual blood loss. The demands of pregnancy will further deplete these stores, even though there is no menses during the course of the pregnancy (Kilpatrick, 2014). Routine iron supplementation in the absence of anemia is not recommended by US Preventive

Service Task Force (USPSTF). Studies have shown, however, that prenatal routine iron supplementation is correlated with a decrease in the prevalence of low birth weight (Lassiter & Manns-James, 2017).

The transfer of iron from mother to fetus occurs via active transport through serum transferrin at the placenta. If maternal iron stores are low, then the placenta develops more transferrin receptors (Kilpatrick, 2014). This mechanism helps assure iron transfer to the fetus, even when the woman has limited iron for herself, and further depletes her iron stores.

Folate requirements

Folate is a water-soluble B vitamin that helps tissues grow and function properly. Folate acts as a co-enzyme involved in DNA and RNA synthesis and cell division. Specifically, it is required for the process of **methylation** (Scott et al., 1994). Interruption of DNA synthesis or methylation can prevent the proper closure of the neural tube. During pregnancy, folate requirements increase from 50 to 300–500 μg/day because of the growing fetus, the increased maternal RBC mass, and the increased uterine size (Kilpatrick, 2014). Studies have demonstrated that adequate folate intake, both before and during early pregnancy, will significantly reduce the occurrence of **neural tube defects** (NTDs).

Changes in clotting factors

Blood also contains substances to help prevent hemorrhage through clotting and, at the same time, substances that assure that blood stays in liquid form. During pregnancy, factors that promote hemostasis and **fibrinolysis** are enhanced. This adaptation helps control bleeding when there is an increased risk for hemorrhage with implantation and placental development, and again during the third stage of labor when the placenta detaches from the uterine wall. Paradoxically, prevention of hemorrhage comes with an increased risk for thrombus formation in the uteroplacental and intervillous circulations, and the deep veins of the legs and pelvis.

The changes that occur to enhance hemostasis are many and complex. Not every component of the hemostatic system increases. For instance, the platelet count during pregnancy decreases slightly, but stays within the same normal range as the count for nonpregnant women. This decrease has been attributed to hemodilution and increased platelet aggregation in response to increased production of the prostaglandin **thromboxane** A_2 (Bowersox, 2016). Platelets are non-nucleated cells synthesized by the bone marrow that play an important role in hemostasis. When there is an injury to a blood vessel, platelets are the first to respond. They work through aggregation, adhesion, and through releasing histamine, serotonin, and **platelet-derived growth factor** (PDGF). Once released, these substances enhance the enlargement of the platelet plug, activate the coagulation cascade, support the fibrin mesh that develops to further strengthen the plug, and PDGF stimulates smooth muscle blood vessel walls to help healing (Rodger & Silver, 2014).

Progesterone stimulates an increase in **tissue factor** (TF) (substance that initiates clotting) and plasminogen activator inhibitor type 1 (PAI-1) in the decidua and endometrium (Rodger & Silver, 2014). During pregnancy, fibrinogen doubles, and clotting factors V, VII, VIII, IX, and X and the von Willebrand factor all increase. Prothrombin fragments increase and the prothrombin time decreases. There is decreased anticoagulation and fibrinolysis; however, the bleeding time is about the same. These adaptations serve to control the bleeding that occurs when the placenta detaches. In fact, a fibrin matrix is established in spiral arteries early in pregnancy that will cause a fibrin mesh to form very quickly over the placenta site. Fibrinolytic activity decreases until about an hour after childbirth. These changes and others are summarized in Table 3.2.

Cardiovascular System Adaptations

The heart and vascular system undergo profound changes beginning as early as 5 weeks' gestation. Women with healthy hearts seldom report concerns associated with these changes. There are several signs and symptoms that occur, however, that mimic cardiovascular disease, creating a diagnostic dilemma for the healthcare provider. Up to 4% of pregnant women will have unrecognized cardiovascular disease; this is emerging as a contributor to maternal morbidity and mortality (Mohamad, 2017). Table 3.3 lists the functional cardiovascular signs and symptoms seen in pregnancy.

Anatomical and Functional Cardiac Changes

The ventricular muscle mass increases during the first trimester and the left atrial diameter increases as the blood volume increases (Monga & Mastrobatista, 2014). Cardiac output, a measure of functional capacity of the heart, increases by 30–50%, with about half of this increase occurring by 8 weeks' gestation (Blackburn, 2013). The increase in cardiac output comes from increases in both stroke volume and heart rate. Stroke volume causes most of the early rise in cardiac output and then declines as the pregnancy nears term. Maternal heart rate begins to increase at 5 weeks' gestation and reaches a maximum increase of about 15–20 beats per minute by 32 weeks' gestation. Increased cardiac output is needed to support the 10-fold increase in uterine

Table 3.2 Changes in coagulation factors in pregnancy

Platelets	Decrease slightly but within normal prepregnancy limits
Fibrin deposits	Increased
Tissue factor (TF)	Found in the decidua, and endometrium
Fibrin–fibrinogen complexes	Increased
Plasminogen-activated inhibitors	Increased
Fibrinogen	Increased
Fibrinolysis	Decreased
Coagulation factor I	Increased
Coagulation factor 5 and 9	Increased slightly
Coagulation factor VII	Increased (10 times normal)
Coagulation factor VIII	Increased (doubles)
Coagulation factor X	Increased
von Willebrand factor	Increased
Activated partial thromboplastin time (aPTT)	Decreased
Prothrombin time (PT)	Decreased
Bleeding time	Unchanged
Resistance to activated Protein C	Increased
Protein S (coagulation inhibitor)	Decreased
Fibrin degradation products	Increased
D-dimer (marker for fibrinolysis)	Increased

Adapted from: Blackburn, S. (2013); Cunningham et al (2014); and Rodgers & Silver, 2014.

Table 3.3 Signs and symptoms of a normal pregnancy that mimic heart disease

Dyspnea	Progesterone effect on breathing centers causing increased respiratory rate and increased metabolic demand
Fatigability	Response to increased metabolic demand
Dependent edema	Venous pressure from gravid uterus, lower colloid osmotic pressure
First heart sound louder	Early closure of mitral valve
Split S_2	Expected at about 30 weeks of gestation
S_3	Heard in 90% of pregnant women
Systolic flow murmur	Heard in 95% of pregnant women; begins ~12–20 weeks and disappears about 1 week after birth
Left lateral displacement of the point of maximal impulse	Gravid uterus pressing upward on diaphragm and heart
Mammary souffle	Continuous murmur from mammary vessels, heard best in second intercostal space

Adapted from: Mohamad (2017); and Monga & Mastrobatista (2014).

blood flow (500–800 mL/min) and the 50% increase in blood flow to the kidneys (Monga & Mastrobatista, 2014). Blood flow is also increased to the breasts and the skin. These adaptations explain the flow murmurs and other changes in signs and symptoms listed in Table 3.3.

Vascular Changes

Collagen throughout the vascular system softens, resulting in increased compliance and decreased vascular resistance beginning around 5 weeks' gestation. Vasodilation occurs as the result of the relaxant effects of progesterone and prostaglandin (Monga & Mastrobatista, 2014). The low-resistance uteroplacental circulation acts like an arteriovenous connection, thereby contributing to lowered vascular resistance. In addition, there is an increased production of endothelial relaxant factors such as nitric oxide that contribute to lowered vascular resistance. All of these changes contribute to decreased venous resistance that will slow the speed of venous flow and contribute to stasis of the blood, thereby increasing the risk for deep vein thrombosis in pregnancy. These changes also contribute to an increased sensitivity to autonomic blockade, such as that produced by epidural anesthesia (Monga & Mastrobatista, 2014). When this anesthesia is administered to pregnant women, a sudden drop in blood pressure often occurs.

Blood Pressure Changes

Normally, arterial blood pressure decreases in pregnancy when the arteries relax and peripheral vascular resistance decreases. This decrease in blood pressure begins at about 7 weeks' gestation and persists until around 32 weeks' gestation, when it begins to rise to prepregnancy levels (Monga & Mastrobatista, 2014).

Maternal position affects blood pressure measurements. In fact, blood pressure decreases 5–10 mmHg systolic and 10–15 mmHg diastolic when a pregnant woman lies on her left side (Monga & Mastrobatista,

2014). Serial blood pressures taken with the pregnant woman sitting with her feet on the floor are the best for monitoring for any abnormal changes in blood pressure during pregnancy.

Supine Hypotensive Syndrome

Supine hypotensive syndrome occurs in approximately 8% of pregnant women in the second and third trimesters (Lanni, Tillinghast, & Silver, 2002). Lying flat on the back in the supine position after about 30 weeks' gestation can cause the weight of the gravid uterus to compress the vena cava. When the vena cava is compressed, it will limit the amount of blood that can return to the heart. This reduction in stroke volume causes a decrease in cardiac output and a decrease in blood pressure (Cunningham et al., 2014). The changes in the mother's cardiovascular system can cause her to feel faint and can lead to a drop in fetal heart rate. Rarely, loss of consciousness can occur. Women naturally tend to turn to the side when they feel this sensation and no harm is caused by this temporary state. It can be a problem during an office visit when a woman is lying on her back for an examination or during labor if she is immobile and supine. Side-lying positions will relieve the pressure of the gravid uterus and will restore blood flow and blood pressure.

Respiratory System Adaptations

Pregnancy puts less stress on the respiratory system than on the cardiovascular system; however, there are significant adaptations. Although some women may report shortness of breath, respiratory exchange is more efficient during pregnancy. The primary changes occur in lung volume and ventilation as the oxygen demands of maternal metabolism and the fetoplacental unit increase. These changes begin early in pregnancy.

Anatomical Changes

Estrogen and the increasing blood volume of pregnancy that causes capillary engorgement that leads to swelling and increased mucous production in the nose, sinuses, eustachian tubes, and middle ears. At the same time, progesterone causes a relaxation of veins and increased pooling that further contributes to mucous membrane swelling. The result is increased incidence of pregnancy rhinitis, epistaxis, serous otitis, and congested sinuses (Blackburn, 2013).

The hormone relaxin causes increased pliability of cartilage in the chest, allowing for an increase in chest circumference. As the gravid uterus increases in size, the diaphragm raises about 4 cm, the thoracic circumference increases about 6 cm, and the costal angle widens (Whitty & Dombrowski, 2014). There is also an increase in thoracic breathing and more diaphragmatic movement (Whitty & Dombrowski, 2014). Most of the chest wall changes persist after pregnancy.

Pulmonary Function Changes

Increased maternal progesterone affects respiratory rate, respiratory drive, and total pulmonary resistance. Progesterone reduces pulmonary airflow resistance and stimulates the respiratory center of the brainstem to increase the respiratory rate. It also lowers the threshold to carbon dioxide (CO_2) and increases the sensitivity of chemoreceptors to CO_2. An increased metabolic rate increases oxygen requirements and consumption (Monga & Mastrobatista, 2014). The combined effect is mild hyperventilation and mild respiratory alkalosis that occurs as the mother "blows off" CO_2 and decreases the carbon dioxide partial pressure in blood ($\mathbf{PCO_2}$). Progesterone has also been implicated in the increase in carbonic anhydrase in RBCs that helps in CO_2 transfer and a decrease in PCO_2 (Whitty & Dombrowski, 2014). A reduced maternal PCO_2 facilitates the movement of CO_2 waste from the fetus to the mother and enhances the release of oxygen from the mother to the fetus (Cunningham et al., 2014).

There are several pulmonary function parameters that are changed as adaptation to pregnancy occurs, listed in Table 3.4. It is important to note that increased oxygen requirements and adaptations in pulmonary function make respiratory diseases such asthma and pneumonia potentially much more serious in pregnancy (Whitty & Dombrowski, 2014).

Table 3.4 Changes in respiratory parameters in pregnancy

Total lung capacity	Decreased by 4%
Inspiratory capacity	Increased by ~300 mL
Expiratory reserve capacity	Decreased by ~200 mL
Residual volume	Decreased by 18%
Tidal volume	Increased by 50%
Minute ventilation	Increased by 40%
O_2 consumption	Increased by 20% (50% during labor)
Total pulmonary resistance	Reduced
Maternal pH	Mild respiratory alkalosis

Adapted from: Cunningham et al. (2014); Whitty & Dombrowski (2014).

Renal System Adaptations

The renal and urinary systems undergo dramatic change in response to pregnancy. The kidneys must adjust to increased blood and extracellular fluid volume, and increased maternal and fetal wastes. There are changes related to hormonal effects, pressure from the gravid uterus, and from cardiovascular adaptations.

Anatomical Changes

The kidneys grow in volume and length during pregnancy due to an increase in renal vascular and interstitial growth (Monga & Mastrobatista, 2014). The kidneys and ureters dilate when the gravid uterus grows enough to compress the ureters at the pelvic rim and slow urine flow. The right ureter is more greatly affected either because of the right-sided rotation of the uterus or because of the cushioning provided to the left ureter by the sigmoid colon (Cunningham et al., 2014). Ureter dilation may also be a consequence of progesterone, relaxin, and nitric oxide effects that relax smooth muscle; however, most studies support uterine compression as the most likely cause of these changes (Monga & Mastrobatista, 2014). Dilation of the kidneys and ureters increases the potential for urine stasis and infection. Hydroureter may persist for 3–4 months after child-birth.

The bladder begins adaptive changes at about 12 weeks of gestation (Cunningham et al., 2014). By then, **hyperemia** and **hyperplasia** of the muscle and connective tissue will cause elevation of the bladder **trigone** and increase the susceptibility to bladder infection. There is reduced bladder capacity and increased incidence of incontinence during the third trimester related to pressure on the bladder from the gravid uterus. In addition, pressure from the fetal presenting part may slow blood and lymph drainage, causing the base of the bladder to swell and become more prone to infection.

Renal Function Changes

Renal plasma flow increases 60–80% by midpregnancy then decreases to about 50% above prepregnancy rates by term (Monga & Mastrobatista, 2014, p. 98). Lateral lying positions increase venous return and renal plasma flow; the left lateral lying position is best for enhancing renal plasma flow. These position changes will lead to increased urine flow and nocturia.

Glomerular filtration rate (GFR) increases significantly within 2 weeks after conception and is 50% higher than prepregnancy levels by 12 weeks' gestation (Cunningham et al., 2014). This and the weight of the growing uterus on the bladder explain the urinary frequency experienced by women during the first weeks of pregnancy. The increase in GFR causes increased creatinine clearance and decreased serum creatinine, blood urea nitrogen, and serum osmolarity.

Renal tubular function also changes in pregnancy. The most impressive tubular function change is the reabsorption of sodium. Sodium retention is promoted by increased levels of estrogen, deoxycorticosterone, and the increased activity of the RAAS (Monga & Mastrobatista, 2014). Sodium retention is also enhanced by maternal sitting or standing. Interestingly, although sodium is retained during pregnancy, the serum levels of sodium decrease slightly due to hemodilution.

Two other important electrolytes are significantly affected by renal tubular function changes in pregnancy. Potassium is retained, but like sodium, serum levels slightly decrease due to increased plasma volume. Calcium excretion increases while total serum calcium decreases related to a decrease in plasma albumin (Monga & Mastrobatista, 2014). Further discussion of maternal and fetal calcium physiology is found in the musculoskeletal section of this chapter.

Glucose excretion increases, causing glycosuria in about 16% of normal pregnancies (Cunningham et al., 2014). Increased glycosuria will increase susceptibility to urinary tract infection.

Uric acid excretion is increased and serum uric acid levels decrease between 8 and 24 weeks of gestation. The serum levels begin to rise to near prepregnancy levels by term. Clinically, an increased plasma uric acid level has been used as a marker for preeclampsia, but lacks sensitivity and specificity as a diagnostic tool (Monga & Mastrobatista, 2014).

About two-thirds of the weight gain in pregnancy is retained fluid related to the changes in renal tubular function. About 6 L of body water is retained in extracellular areas and 2 L is gained in intracellular spaces. Plasma increases account for only about one-quarter of the increase in extracellular fluid (Monga & Mastrobatista, 2014). The allocation of fluid is described as about 3.5 L for amniotic fluid, fetus, and placenta; and about 3 L for maternal blood volume, breasts, and uterus (Cunningham et al., 2014). Clinically, fluid retention of more than 1.5 L is seen as dependent edema (Blackburn, 2013). Fluid seeps into interstitial spaces of the lower extremities because of increased venous hydrostatic pressure below the uterus when the gravid uterus places pressure on the inferior vena cava and pelvic vessels.

Gastrointestinal System Adaptations

Gastrointestinal (GI) changes related to pregnancy and pregnancy hormones cause discomforts that are experienced in most normal pregnancies. Occasionally, these changes mimic more serious conditions and require careful assessment.

Anatomical Adaptations

The stomach, liver, and intestines are displaced upward and back by the growing uterus. This change will move the appendix as high as the right upper quadrant, causing the pain of appendicitis to be much higher in the abdomen than expected. In most pregnancies, however, the change in location and the compression of the stomach and bowel is well tolerated.

Gastrointestinal Function Changes

The primary cause of changes in the function of the GI tract in pregnancy is progesterone. This hormone relaxes smooth muscle, thereby causing decreased lower esophageal sphincter tone and slowing of peristalsis and intestinal transit time. A relaxed lower esophageal sphincter will allow for reflux of stomach contents into the lower esophagus, resulting in heartburn, especially when pressure from the growing uterus is exerted against the stomach. The slowed transit time leads to increased absorption of water, vitamin B_{12}, some amino acids, iron, and calcium (Blackburn, 2013; Kelly & Savides, 2014). This also results in dryer, harder stool, an increased incidence of constipation and, straining at stool, and hemorrhoids.

In the mouth, the gums respond to increased estrogen by becoming hyperemic, friable, and softer. Some women will develop one or more **epulis**, a localized vascular swelling of the gums. These changes increase maternal risks for gingivitis and periodontal disease. There is no evidence that pregnancy increases tooth decay or tooth loss, although this belief is expressed in common folklore. See Chapter 14, Oral Health in the Childbearing Year.

Progesterone is an appetite stimulant leading to increased food intake to meet metabolic needs. This may be part of the reason for food cravings, including **pica**, the ingestion of substances such as clay, starch, or other matter with no nutritional value. However, sociocultural background is a strong influence on this eating behavior.

Ptyalism, or excess salivation, can occur in pregnancy. Most often, this is related to a reluctance to swallow saliva when a woman is troubled by nausea and vomiting of pregnancy. Nausea and vomiting of pregnancy, a common occurrence, has been linked to hCG, estrogen, elevated T4, prostaglandin E_2, altered motility related to progesterone, the emotional and psychological state of the mother, and reflux (Kelly & Savides, 2014). However, the exact cause is unknown; the phenomenon of nausea and vomiting has multiple determinants. The nausea likely increases some of the food aversions commonly observed in pregnancy.

Liver and Biliary Changes

Anatomically, the liver is displaced up and back as the uterus grows. The liver does not change in size and blood flow to the liver is unchanged. The production of proteins and enzymes by the liver does change. Plasma proteins, including albumin, decrease in pregnancy, in part, because of hemodilution. Newer studies indicate that the rise in alpha-fetoprotein may cause a drop in serum albumin levels (Williamson, Mackillop & Heneghan, 2014). The production of fibrinogen and coagulation factors VII, VIII, IX, and X is increased under the influence of estrogen. Progesterone stimulates an increase in cytochrome P450 isoenzymes, a group of enzymes that assist in the metabolism of organic substances and are important in the body's processing of many drugs. Thyroxine-binding and corticosteroid-binding globulins increase as estrogen levels increase (Nader, 2014a). Serum alkaline phosphatase (ALP) increases due to placental production, while other liver enzymes are slightly decreased or stay the same (Williamson, et al., 2014). Table 3.5 lists the changes in liver function tests during pregnancy.

Table 3.5 Liver Function Changes in Pregnancy

Albumin	Decreased
Alkaline phosphatase (ALP)	Increased (also produced in placenta)
Aspartate transaminase (AST)	Slight decrease due to hemodilution
Alanine transaminase (ALT)	Slight decrease due to hemodilution
Bilirubin (conjugated, unconjugated)	Unchanged
Gamma-glutamyl transpeptidase (GGT)	Slight decrease due to hemodilution
Total protein	Decreased

Adapted from: Creasy et al. (2013); Cunningham et al. (2014); Williamson, Mackillop, & Heneghan (2014).

The gallbladder is affected by progesterone-induced slowed peristalsis that will cause an increased in bile volume, bile stasis, and cholesterol saturation (Williamson et al., 2014). These changes create an environment ripe for gallstone formation. The two most common indications for nonobstetric surgery in pregnant women are acute appendicitis and acute biliary disease.

Metabolic System Adaptations

The maternal metabolism adjusts to ensure that glucose, protein, and fat are metabolized in a way that will meet the energy needs of the mother, the uteroplacental unit, and the fetus. To better understand this adaptation, several significant components involved in the process will be described.

Basal Metabolic Rate

By the end of a normal pregnancy, the maternal metabolic rate has increased eight times the nonpregnancy rates (Blackburn, 2013). This requires an average of an additional 300 kcal/day, generally starting in the second trimester. Most of this energy is needed for the growth of the fetus, placenta, uterus, and breasts. Some energy is set aside, stored as fat to be used during the last weeks of pregnancy when the fetus is growing more rapidly.

The first half of pregnancy is dominated by an **anabolic** state (Blackburn, 2013). The mother eats more, moves around less, and stores protein and fat substrates. Weight gain during this half of pregnancy is due to fat storage and the synthesis of protein into growing tissues. During this anabolic state, insulin is also increased and acts like a growth hormone, facilitating the processes of growth.

Catabolism occurs during the second half of pregnancy. **Lipolytic** activity is increased and pregnancy hormones lead to a relative insulin resistance. Human placental lactogen (hPL), produced by the placenta, has anti-insulin and lipolytic properties that help the mother change from glucose usage for energy to lipid usage for energy (Blackburn, 2013). This change leads to **accelerated starvation**. When a nonpregnant woman is deprived of food, it takes about 24–36 hours before she has used all the glucose-based energy and begins to burn fat. In pregnant women, lipolysis begins in about 12 hours.

Carbohydrate Metabolism

Serum glucose levels during fasting are lower in pregnancy than in the nonpregnant state. After eating, serum glucose and insulin levels are higher for a longer time in pregnancy. Higher levels of insulin cause a suppression of glucagon and maternal insulin resistance increases as the pregnancy advances. Insulin resistance in the maternal skeletal muscle and adipose tissue is mediated by progesterone, estrogen, hPL, and possibly by free fatty acids released by lipolysis (Cunningham et al., 2014).

Protein Metabolism

Protein is essential to tissue building in pregnancy. The placenta and fetus use amino acids and protein as they grow in mass and develop structure. These substances are also diverted to the liver for gluconeogenesis. Consequently, serum amino acid and serum protein levels are lower in pregnancy (Blackburn, 2013). At the same time, urinary excretion of protein byproducts does not change. This indicates that maternal muscle breakdown is not used to meet fetal needs (Cunningham et al., 2014).

Table 3.6 Lipid and lipoprotein levels in the third trimester

Cholesterol	Increased
VLDL	Increased
LDL-C	Increased
HDL-C	Increased
Triglycerides	Increased

Adapted from: Creasy et al. (2013); Cunningham et al. (2014), and Liu (2014).

Fat Metabolism

Lipids, lipoproteins, and apolipoproteins increase in maternal serum during pregnancy. These increases are due to lipolysis and decreased lipoprotein lipase action in fat tissue. Estradiol and progesterone effects on the liver also contribute to these changes (Cunningham et al., 2014). Interestingly, these increases are not associated with vascular endothelial dysfunction in healthy pregnant women. Table 3.6 lists the changes expected in cholesterol, triglycerides, and lipoproteins in late pregnancy.

Leptin and Ghrelin

Leptin is produced and secreted by maternal fat cells and the placenta. This peptide hormone helps regulate appetite and enhances energy use. It also contributes significantly to fetal growth and development. Maternal serum leptin is two to four times higher than in nonpregnant women (Cunningham et al., 2014). Leptin is increased even further in women with preeclampsia and gestational diabetes. It is well established that leptin levels are increased in women with obesity and the risk of both preeclampsia and gestational diabetes increases with body mass index. Leptin may mediate the relationship between body mass index and these pregnancy complications (Sommer et al., 2015; Taylor et al., 2016).

Ghrelin is a hormone secreted by stomach cells and the placenta that also has a role in fetal growth. Maternal serum levels of this hormone increase during the first half of pregnancy and decrease during the second half when insulin resistance increases. A similar decrease in ghrelin is seen in metabolic syndrome in nonpregnant individuals (Cunningham et al., 2014).

Insulin

Insulin is a polypeptide hormone produced and secreted by the beta cells of the islet of Langerhans of the pancreas. It is secreted in response to increased serum glucose, amino acids, free fatty acids, GI hormones, and the parasympathetic nervous system stimulation of the beta cells.

It functions to facilitate glucose entry into cells (Brashers, Jones & Huether, 2014).

Pregnant women with normal glucose tolerance will have an increase in insulin in response to estrogen-induced increased hepatic glucose production, and the increase in serum glucose produced after a meal. Insulin will facilitate the movement of glucose into maternal muscle and fat cells and will suppress further liver production of glucose. Late in pregnancy, insulin resistance increases and more insulin is produced. If a woman is obese or has an abnormal glucose tolerance before pregnancy, her pancreas may not be able to produce the amount of insulin needed to overcome the insulin resistance induced by pregnancy hormones, and gestational diabetes can result (Moore, Hauguel-DeMouzon, & Catalano, 2014).

Skin Changes

The skin is the body's largest organ. Skin functions as a barrier to infection and ultraviolet radiation; it retains body fluids, regulates body temperature, and produces vitamin D. Skin contains touch and pressure receptors and nociceptors that transmit pain sensation. Skin is part of the integumentary system, which also includes hair, nails, sebaceous glands, and sweat glands. The entire integumentary system is changed during pregnancy. Specifically, there are changes in pigment, vascular supply, and connective tissue of the skin; hair growth; nail structure; and in the sebaceous and sweat gland functions.

Pigmentation Changes

Estrogen and progesterone produced during pregnancy will stimulate the production of melanocyte-stimulating hormone (MSH). The most frequently seen manifestations of increased MSH are hyperpigmentation of the areolae, genital skin, axillae, inner thighs, and the **linea alba**, which becomes the **linea nigra** during pregnancy. Freckles and moles will also darken. These pigment changes can also be seen in women taking oral contraceptives. Pigment changes usually fade after pregnancy or when oral contraceptives are discontinued; however, women with darker skin are more likely to have persistent hyperpigmentation (Blackburn, 2013).

Melasma, or the "mask of pregnancy," occurs as a result of increased MSH in about 70% of pregnant women (Rapini, 2014). This patch of hyperpigmentation is distributed over the forehead, cheeks, and bridge of the nose in a symmetric pattern. About 30% of women affected will have persistent melasma months to years after delivery. Exposure to sunlight will exacerbate the hyperpigmentation. Sunscreen routinely used during pregnancy can decrease the degree of discoloration.

Vascular Changes

The hormones of pregnancy cause vasodilation and the proliferation of capillaries in the skin and can result in the development of **telangiectasias** (small dilated blood vessels near the skin surface) and palmar erythema. These changes help in thermoregulation by dissipating the heat generated by the fetus, increased maternal metabolic rate, and the thermogenic effects of progesterone (Blackburn, 2013).

Connective Tissue Changes

Estrogen, relaxin, and adrenocorticoids, along with stretching, contribute to *striae gravidarum*, commonly known as stretch marks. The hormones are thought to relax collagen adhesiveness and facilitate the formation of mucopolysaccharide substance that will cause a separation of collagen fibers. Increased cortisol during pregnancy causes the striae to be purplish in color. The usual locations for striae are over the abdomen, breasts, thighs, and buttocks where skin is stretched by the growing fetus, enlarged breast tissue, and weight gain. Striae become prominent by 6–7 months of gestation and are most prevalent in younger, white women (Blackburn, 2013). The more severe striae occur in teenagers, women with maternal family history of striae, women with obesity or who gain more than 30 lbs in the pregnancy, or women with large babies (Rapini, 2014). Interestingly, there is an increased incidence of pelvic relaxation and prolapse among women who have moderate to severe striae (Norton et al., 2015).

Skin tags are another connective tissue phenomenon seen in pregnant women. These tags are soft, **pedunculated** growths that are the same color of the surrounding skin or are hyperpigmented. They appear on the neck, face, axillae, groin, and between and under the breasts (Blackburn, 2013; Rapini, 2014). Skin tags will usually disappear after birth; however, sometimes they persist, particularly among obese women.

Sebaceous and Sweat Gland Changes

Sebaceous glands secrete more sebum during pregnancy secondary to increased ovarian and placental androgens (Blackburn, 2013). Apocrine sweat glands found in the axillae, scalp, face, abdomen, and genital area have decreased activity during pregnancy related to hormonal changes (McCann & Huether, 2014). Eccrine sweat glands that are distributed over the body have an increased activity during pregnancy. This activity increases under the influence of increased thyroid

activity, increased maternal metabolic rate, and increased fetal-produced heat. Their main function is to secrete sweat that will evaporate and help dissipate heat.

Hair and Nail Changes

During pregnancy, estrogen causes an increased number of hairs to remain in the **anagen** phase (growing phase), and a decreased number enter the **telogen** phase (resting phase). When pregnancy hormones are removed after the birth of the placenta, the number of hairs that enter the telogen phase increases, resulting in hair loss. This hair loss is called telogen effluvium and can also occur after surgery, illness, crash dieting, or other stressful life events. Hair loss after giving birth is expected and is easily distinguished from alopecia of other causes. This hair loss will generally resolve by 9 months postpartum without treatment.

Changes in the nails are uncommon in pregnancy; however, phenomena such as transverse grooves, increased brittleness, separation of the nail bed at the toe or fingertip, and whitish discoloration have been reported. These changes are benign and will disappear during the postpartum period (Blackburn, 2013; Rapini, 2014).

Immune System Adaptations

Pregnancy requires changes in the immune system of the woman. In order to accept and maintain a pregnancy to term, some innate, humoral, and cell-mediated immunologic functions must be altered. This section will outline those changes and explain how these alterations may increase risks for infection or provide remission for some autoimmune conditions for the mother.

Fetus as Allograft

The fetus is a **semiallograft** (an allograft is transplanted tissue; "semi" refers to the fact that fetal tissue carries half of mother's genetic material) that is not rejected by the mother's immune system. Even though half of the genetic material in the fetus is from the father, in most cases, the mother's immune system does not reject the foreign antigens on fetal cells. Several possible theories explain this phenomenon (Mor & Abrahams, 2014): The placenta is a selective barrier; the mother's immune system is suppressed; there is a cytokine shift; there is an absence of major histocompatibility complex (MHC) class I molecules on the conceptus; and there is a local immune suppression mediated by **Fas/FasL** (molecules involved with regulation of cell death). More recently, pregnancy protein 13 (PP13), produced solely by the syncyiotrophoblast and released into the maternal circulation during implantation, has been identified as an agent that diverts the mother's immune system so that the paternal antigen (placenta) will be well established and grow (Than, et al., 2014). Studies have shown that decreased placental production of PP13 contributes to the development of preeclampsia, a syndrome that begins due to impaired implantation and **placentation** (Meiri et al., 2014). A PP13 blood test for predicting preeclampsia is currently under investigation.

The placenta as barrier theory has been discounted; the placenta acts as only a partial barrier to selected substances. In fact, fetal cells can cross into maternal blood and have been found in maternal circulation or organs years after pregnancy (Body et al., 2015). Cell-free fetal DNA also enters the maternal system and new laboratory tests can isolate fetal DNA from a maternal venous blood sample and perform a limited number of genetic tests on the DNA.

Systemic immune suppression does not fully explain how the conceptus is accepted. How could mothers have lived to give birth through the millennia if they could not defend themselves against bacteria and viruses? Today, the best argument against this theory is that women with human immunodeficiency virus (HIV) infection do not progress into AIDS during pregnancy (Mor & Abrahams, 2014).

Another theory has been that pregnancy is anti-inflammatory in nature, which causes abnormal shifts in **cytokines**, the molecular messengers that regulate responses to inflammation. This can contribute to spontaneous pregnancy loss or preeclampsia. Newer information indicates that pregnancy actually occurs in three different phases with regard to maternal immune response: (1) a strong inflammatory response is required for the invasion of the trophoblast and placentation; (2) a quiet anti-inflammatory state follows when the fetus is growing; and (3) a renewed inflammatory response with an increase of immune cells migrating into the uterus to promote contractions, birth, and the rejection of the placenta (Mor & Abrahams, 2014).

Another theory is that there is no MHC class I antigen on the trophoblast, so the mother's immune system does not recognize it as foreign antigens. In fact, the placenta does express human leukocyte antigens (HLA-C, HLA-G, and HLA-E). These are subsets of MHC antigens. So, fetal tissues are capable of initiating a maternal T-cell response (Mor & Abrahams, 2014). Interestingly, women who have HLAs similar to those of the father of the baby will not produce the immune substances necessary to prevent rejection of the fetus (Cunningham et al., 2014). This can explain different pregnancy outcomes for the same woman with a new partner.

The theory of local immune suppression postulates that the maternal immune cells that would recognize the paternal antigens are removed from the mother's system

through **apoptosis** (Mor & Abrahams, 2014). In addition, a subset of T lymphocytes called T regulatory cells has been identified as being able to control other T cells that would attack paternal antigens. These are both possible explanations for the survival of the fetal allograft.

It is also important to recognize that several cells of the innate immune system have been identified at the site where the trophoblast implants, including uterine natural killer (uNK) cells, macrophages, and dendritic cells. Basically, this part of the mother's immune system does respond to the conceptus. These noncytotoxic uNK cells, which are specific to pregnancy, contribute to **angiogenesis** and implantation (Mor & Abrahams, 2014). Macrophages clean out dead cells and debris, while dendritic cells help with early implantation. These activities are crucial to placentation and the immune adjustments necessary for a successful pregnancy.

Disorders Related to Immunologic Changes in Pregnancy

During pregnancy, T-helper cells type 1 (Th1) and T-cytotoxic cells (Tc) are suppressed. This has been identified as a reason for remission of maternal autoimmune disorders such as rheumatoid arthritis, multiple sclerosis, and autoimmune thyroiditis (Blackburn, 2013). Suppression of Th1 has also been implicated in the increased susceptibility to viruses, *Candida albicans*, and other organisms. In fact, vulvovaginal candidiasis occurs more often in pregnant women due to increased estrogen and the changes in the cell-mediated immune response. This cell-mediated immune response, along with the changes in the lungs and heart, has also been identified as an explanation for the increase in influenza severity during pregnancy (CDC, 2016). Autoimmune disorders such as uncomplicated systemic lupus erythematosis (SLE) often remain stable during pregnancy due to the increase in Type 2 helper cells (Th2) that is normally seen in pregnancy (Blackburn, 2013). Unfortunately, these diseases often flare within 6–8 weeks after birth.

There are five inflammatory markers that are increased during pregnancy. These include leukocyte ALP, C-reactive protein, erythrocyte sedimentation rate (due to increased plasma globulins and fibrinogen), complement factors C_3 and C_4, and procalcitonin (Cunningham et al., 2014). This should be taken into consideration when interpreting laboratory measures of these markers during pregnancy.

Some spontaneous abortions are a result of immune system changes in pregnancy. Immunologic factors that have been implicated in spontaneous abortion include infection; increased Th1 activity against the trophoblast; an immune-related failure of the corpus luteum to produce progesterone; HLAs similar to those of the father; and, in women with SLE, antiphospholipid antibodies that prevent the development of the placenta (Blackburn, 2013; Cunningham et al., 2014). Recurrent (more than three) spontaneous abortions have been linked with the presence of uNK cells like those found in the periphery rather than the noncytotoxic uNK cells usually found in the decidua (Kuon et al., 2017).

Preterm labor and birth can result from infection that triggers the innate immune system to release inflammatory cytokines, interleukin, and tumor necrosis factors. These cytokines increase the production of prostaglandin that will stimulate contractions. At the same time, enzymes that cause a weakening of the fetal membranes are released and the membranes may rupture prematurely (Cunningham et al., 2014). It is estimated that up to 40% of preterm births occur because of intrauterine infection and inflammatory processes (Cunningham et al., 2014).

Preeclampsia is specific to pregnancy and is a complex chronic disorder that affects many maternal systems. Evidence suggests that preeclampsia has an immunologic component. In fact, preeclampsia has some of the same cellular changes seen in graft rejection including reduced HLA-G on the trophoblast, an increase in Th1 rather than suppression, more immune complexes, increased fibronectin, increased inflammatory cytokines, changes in complement, and the absence of PP13 (Blackburn, 2013, Than et al., 2014).

Unlike the cell-mediated and innate immune systems, the humoral system in pregnancy does not change significantly. However, maternal antibodies can have an effect on the fetus. Humoral immunity occurs when immunoglobulins (Ig) or antibodies are produced by B lymphocytes (plasma cells) in response to a specific antigen. There are five classes of Ig: IgG, IgM, IgE, IgA, and IgD. IgA and IgG are of particular interest during pregnancy. IgA normally protects body surfaces. Its primary benefit in pregnancy is that it is secreted in breast milk and serves to protect the newborn from GI infections (Rote & McCance, 2014; Blackburn, 2013). IgG is also present in breast milk; however, its primary function is due to its smaller size and ability to cross the placenta. IgG provides passive immunity to the fetus from infections for which the mother has manufactured specific antibodies (Rote & McCance, 2014).

There are potential problems for the newborn related to IgG crossing the placenta. Women with Graves' disease have thyroid-stimulating IgG that may cross the placenta and cause hyperthyroidism in about 1% of newborns of women with this disorder (Cunningham et al., 2014). Similarly, women with myasthenia gravis have antibodies against acetylcholine receptors that may cross the placenta and cause transient treatable muscular

weakness in the newborn that will last only a few weeks (Cunningham et al., 2014).

A more frequently encountered disorder related to the placental transfer of IgG is rhesus (Rh) incompatibility. This example of isoimmunization has the potential for causing severe hemolytic disease in the fetus. In order to develop IgG antibodies against Rh-positive RBCs, the maternal system must be exposed to the antigen. This means that Rh-positive RBCs must have entered the mother's system, either from an earlier pregnancy or from transfusion. Once the IgG to Rh antigen is established, it can cross the placenta to the fetus, recognize fetal Rh-positive RBCs as foreign, mount an attack, and destroy the fetal RBCs. The formation of this antibody occurs only among women with an Rh-negative blood type. The resulting IgG that passes to the fetus is harmful only to the fetus who has inherited Rh-positive RBCs from the father. The Rh antigen that is most associated with Rh incompatibility and fetal hemolytic disease is D. For this reason, passive immunization has been developed that prevents humoral production of antibodies in women who receive Rh-positive RBCs from the fetus.

Other RBC antigen incompatibilities exist including, but not limited to, anti-c, anti-Kell, Kidd, and Duffy. For this reason, RBC antibody titers are drawn from pregnant women during the first prenatal visit.

ABO incompatibility can also cause newborn hemolytic disease. However, this form of isoimmunization causes a very mild hemolysis and jaundice due to the increased bilirubin release when the RBC is destroyed. Unlike Rh isoimmunization, this incompatibility does not worsen with each pregnancy. The reason ABO incompatibility is less severe is that most of the anti-A and anti-B antibodies from women with O-type blood are IgM type and are too large to cross the placenta (Blackburn, 2013; Cunningham et al., 2014). If a woman has an O-negative blood type and her fetus is A positive, the Rh and ABO incompatibility can both occur. However, the mother's natural anti-A antibody will recognize and destroy fetal RBCs that may enter her system before these cells can cause an antibody response against the Rh positive factor.

Neurological System and Sensory Adaptations

Cognitive changes in pregnancy such as problems with memory, attention, and concentration, do not seem to have a basis in normal physiologic adaptations (Hampson et al., 2015; Logan et al., 2014). However, some evidence indicates that more women self-report difficulty with memory during pregnancy and early postpartum than nonpregnant women (Logan et al., 2014). One factor implicated in the cognitive changes of pregnancy reported by some women is the change in sleep patterns. During the first trimester, women tend to sleep longer at night and nap during the day if their schedules allow. This is in response to fatigue related to increased metabolism and the sedative effects of progesterone (Blackburn, 2013). As the pregnancy advances and placental progesterone and estrogen increase, sleep patterns are further altered. Approximately 76% of pregnant women report difficulty falling asleep, staying asleep, frequent nighttime wakening, and poor quality of sleep across all months of gestation (Mindell, Cook & Nikolovski, 2015). Studies have shown that the rise in the hormones of pregnancy change both rapid eye movement (REM) and nonrapid eye movement (NREM) sleep. Specifically, progesterone seems to enhance NREM, while estrogen and cortisol decrease REM sleep (Blackburn, 2013). An active fetus, increased discomforts of pregnancy, a growing uterus that limits position change, and decreased REM sleep combine to increase sleep disturbances during the last weeks of pregnancy.

Eye changes during pregnancy include corneal edema, decreased corneal sensitivity, decreased intraocular pressure, and transient loss in accommodation (Blackburn, 2013). Corneal edema and decreased sensitivity has been attributed to fluid retention. Decreased intraocular pressure is due to increased aqueous outflow and the effects of progesterone, relaxin, and hCG (Blackburn, 2013). Pregnancy is not an ideal time for a woman to be measured for new contact lenses or eyeglasses. The changes in the eyes will resolve after birth.

Estrogen-induced swollen membranes will affect the sense of smell, and in some women, the sense of hearing (Blackburn, 2013). The diminished sense of smell will affect taste and can lead to food aversions.

Musculoskeletal System Adaptations

The enlarging uterus changes the maternal center of gravity. The spine adjusts by increasing **lordosis**. At the same time, there is increased mobility of the sacroiliac, sacrococcygeal, and pubic joints related to changes in the cartilage brought about by relaxin and progesterone. Changes in the low back and pelvis can cause low-back discomfort, aching, numbness, and tingling in the legs as the pregnancy progresses. Changes in the cervical spine, along with slumping of the shoulders and upper back due to heavier breasts, can stretch the ulnar and median nerves, causing tingling discomfort in the arms and hands.

The growing fetus needs calcium for the formation and calcification of the skeleton and teeth. Calcium demands are the greatest in the third trimester of pregnancy. Much of the calcium needed is drawn from the maternal skeleton. At the same time, the absorption of

calcium from the maternal intestine doubles and urinary excretion is decreased. Changes in calcium concentration require changes in parathyroid hormone, magnesium, phosphate, vitamin D, and calcitonin physiology. Lowered calcium or magnesium levels have a negative-feedback effect that increases calcitonin and parathyroid hormone release (Monga & Mastrobatista, 2014). Parathyroid hormone acts on bone **resorption**, intestinal absorption, and kidney reabsorption of calcium and phosphate. Parathyroid hormone plasma levels increase steadily as the fetus draws more calcium for bone growth. At the same time, increased maternal glomerulofiltration rate (GFR) and increased plasma volume cause a lower serum calcium level.

Vitamin D is either ingested or obtained via synthesis in sun-exposed skin. During pregnancy, the kidney, decidua, and placenta change vitamin D to 1,25-dihydroxyvitamin D_3. This compound enhances calcium resorption and intestinal absorption of calcium during pregnancy (Cunningham et al., 2014).

Calcium serum levels begin to fall after fertilization regardless of maternal diet (Blackburn, 2013). Calcium levels may be compromised by increased ingestion of phosphate. Too much phosphate will limit calcium absorption in the intestine and increase calcium urinary excretion. Foods high in phosphorus include processed meats, chips and sodas that are commonly consumed as part of American diet.

Endocrine System Adaptations

Like other systems, the endocrine glands undergo changes during pregnancy that support fetal growth and pregnancy maintenance. This section is limited to an outline of the changes that occur in the pituitary, thyroid, and adrenal glands, and their hormones. The changes in the parathyroid and the endocrine pancreas have been described earlier in this chapter. Changes in the gonads are explained in Chapter 2.

Anatomical Changes

Physiological pituitary growth occurs in normal pregnancies. In fact, the pituitary will grow to 135% of its original size (Nader, 2014b). Very rarely, the enlargement will be big enough to increase intracranial pressure or put pressure on the optic chiasm. This may cause headaches or vision changes that will resolve after birth.

The thyroid gland will also increase in size during pregnancy as a result of increased vascularity and some hyperplasia of normal gland cells. Significant enlargement, however, may be a sign of iodine deficiency or other thyroid abnormalities (Nader, 2014a). The adrenal glands do not change in size.

Pituitary Function Changes

The pituitary has two lobes, anterior and posterior, and each lobe secretes hormones in response to the secretion of releasing hormones from the hypothalamus. Table 3.7 lists the hormones secreted by the anterior and posterior lobes of the pituitary.

In pregnancy, the most dramatic change in anterior pituitary function is that it secretes 10 times more prolactin (Nader, 2014b). The lactotrophs (cells that secrete prolactin) are stimulated by estrogen and account for most of the cellular growth of the pituitary. Prolactin prepares the breasts for breastfeeding and will maintain breast milk production for the duration of the lactation period.

Pituitary growth hormone secretion decreases beginning in the second trimester when placental growth hormone is produced (Nader, 2014b). Thyroid-stimulating hormone (TSH) secretion decreases slightly in the first 12 weeks under the influence of hCG. TSH levels then become static as the pregnancy progresses. Adrenocorticotropic hormone (ACTH) secretion increases, reaching its highest level during labor (Blackburn, 2013).

The posterior pituitary function also changes. The threshold for the release of antidiuretic hormone (ADH) is reset so that the decline in plasma osmolarity can occur. However, the amount of ADH released is not changed (Nader, 2014b). Also, thirst is stimulated by lower levels of osmolarity in pregnant women than in nonpregnant women.

The second posterior pituitary hormone, oxytocin, is increased during pregnancy and spikes during labor to

Table 3.7 Pituitary hormones

Anterior Pituitary	Target Organs
Growth hormone	Bone, muscle
Adrenocorticotropic hormone (ACTH)	Adrenal cortex
Thyroid-stimulating hormone (TSH)	Thyroid gland
Gonadotropic hormones (FSH, LH, and ICSH)	Testis, ovary
Melanocyte-stimulating hormone (MSH)	Skin
Prolactin	Mammary glands
Posterior Pituitary	**Target Organs**
[TBTX1]Antidiuretic hormone (ADH)	Kidney tubules
Oxytocin (OT)	Uterine smooth muscle, mammary glands

Adapted from: Brashers, Jones, & Huether (2014).

stimulate uterine contractions. Oxytocin does not start labor but is necessary to sustain the contractions needed for birth. Oxytocin continues to be elevated during lactation and is released when the suckling infant triggers a neural impulse. This surge of oxytocin causes contractions of the myoepithelial cells surrounding the mammary alveoli and the smooth muscle of the mammary ductal system, resulting in milk ejection (Nader, 2014b).

Oxytocin is also an important facilitator of the bonding process. Oxytocin is an evolutionary substance unique to mammals and has central nervous system effects, in addition to effects on the reproductive organs. The importance of oxytocin in regard to social recognition, pair bonding, and other social behaviors has been investigated. Oxytocin release appears to promote feelings of security in women, promotes bonding with the newborn, and leads to improved mental health and social outcomes (IsHak, Kahloon, Fakhry, 2011; Lee et al., 2009).

Thyroid Function Changes

The thyroid gland increases production of thyroid hormones in pregnancy. Increased estrogen causes the liver to produce more thyroxine-binding globulin (TBG) early in pregnancy. As thyroxine (T_4) is bound to TGB, there is a decrease in free T_4 that results in stimulation of the hypothalamus to release thyroxine-releasing hormone and, in response, the anterior pituitary is stimulated to release TSH (Nader, 2014a). This series of events is an example of a negative-feedback control loop.

At the same time, the thyroid is being stimulated by hCG, which acts like TSH. By 12 weeks of gestation, hCG has reached serum levels that inhibit pituitary production of TSH (Nader, 2014a). Free serum T_4 peaks at around the same time that hCG peaks (Cunningham et al., 2014). Thyroid clearance of iodine increases threefold. Free and total T_3 increase. All these changes in thyroid function lead to an increase in maternal basal metabolic rate.

There are significant changes in the thyroid laboratory testing parameters during pregnancy. The laboratory tests that provide the best clinical information for the evaluation of thyroid function in pregnancy are the third-generation TSH and free T_4 index using the product of T_4 and T_3 resin uptake (Nader, 2014a).

Adrenal Function Changes

The adrenal cortex, after stimulation by ACTH, releases glucocorticoids (primarily cortisol), mineralocorticoids (primarily aldosterone), and adrenal androgens and estrogens (Brashers, Jones, & Huether, 2014). Serum ACTH is lower in early pregnancy but begins to increase as pregnancy progresses. Serum cortisol is increased in pregnancy, and much of it is bound by cortisol-binding globulin that is three times higher during pregnancy. This causes the total cortisol levels to rise significantly. Aldosterone levels increase 20-fold during late pregnancy (Nader, 2014b). This increase is necessary because of the antagonistic effects of progesterone including increased sodium excretion (Cunningham et al., 2014). Adrenal testosterone increases in pregnancy because of increased sex hormone-binding globulin produced by the liver (Nader, 2014b).

Corticotropin-releasing hormone (CRH) and ACTH are produced by the placenta and increase significantly during the last weeks of pregnancy. Both hormones are considered very important to the initiation of labor (Cunningham et al., 2014). In addition, the fetal adrenal gland secretes high levels of cortisol and dehydroepiandrosterone sulfate (DHEA-S). These substances cause an increase in the production of maternal estriol that will enhance uterine muscle gap junctions and facilitate the development of oxytocin receptors within uterine tissue in preparation for rhythmic, uniform, and coordinated contractions.

Summary

Virtually all maternal body systems undergo changes during pregnancy that are necessary for maternal adaptation and fetal growth and development. Understanding the physiology foundational to these changes is imperative for healthcare professionals caring for pregnant women and their babies. Differentiating normal changes from potential or real abnormalities and being able to interpret laboratory findings accurately depend on knowledge of these miraculous, complex adaptations.

Resources for Women and Their Families

Pregnancy Week by Week: http://www.medicinenet.com/pregnancy/article.htm

Resources for Healthcare Providers

Physiology of Pregnancy: http://www.glowm.com/?p =glowm.cml/section_view&articleid = 103

Seasonal Flu Vaccine Safety and Pregnant Women: http://www.cdc.gov/flu/protect/vaccine/qa_vacpregnant.htm

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4

Physiological Alterations during the Postnatal Period

Kaitlin Wilson and Cindy L. Farley

Relevant Terms

Afterpains—uterine contractions that occur after childbirth that produce a range of discomfort perceived as mild to labor-like in intensity
Diastasis recti—a midline separation of the rectus abdominus muscles at the linea alba
Hyperplasia—enlargement of tissue by an increase in the number of cells
Hypertrophy—enlargement of tissue by the enlargement or growth of cells
Involution—the postpartum process by which the reproductive organs return to their prepregnant state
Lochia—vaginal discharge resulting from the sloughing of decidual tissue, debris from the products of conception, epithelial cells, red blood cells, white blood cells, and serum
Maternal reset hypothesis—a theory that lactation downregulates the metabolic hyperactivity of pregnancy, thus leading to the many short- and long-term maternal health benefits seen in women who breastfeed
Postpartum—period after birth beginning at the time of complete expulsion of the placenta and membranes, and ending in 6–8 weeks when the reproductive system is returned to nonpregnant status; also known as the puerperium or postnatal period
Telogen gravidarum—diffuse hair loss due to postpartum hormonal changes
Uterotonic—substance that induces uterine contractions

Introduction

The **postpartum** period begins with the expulsion of the placenta after the birth of the infant and continues for 6–8 weeks following birth. This period is characterized by the **involution** of the reproductive system to its prepregnant state as well as extensive physiological changes throughout the maternal organism. This chapter reviews the normal maternal physiological changes that occur in the maternal body systems during the postpartum period. Lactogenesis and the process of breastfeeding are described in Chapter 26. The return to fertility and the resumption of ovulation and menstruation are detailed in Chapter 27.

Uterus

In a nonpregnant state, the uterus is roughly the size and shape of an inverted pear and weighs only about 100 g. During pregnancy, uterine muscle fibers undergo extensive **hyperplasia** and **hypertrophy**, increasing uterine weight approximately 10-fold to an average weight of about 1000 g (Katz, 2012).

Immediately after the infant is born, the stretched-to-capacity smooth muscle fibers recoil and contract when the uterus is emptied, resulting in a smaller endometrial surface area. This change in the endometrial surface area leads to placental separation, and the placenta and membranes are usually born shortly thereafter. This site of placental separation is palm-sized. After the birth of the placenta, the uterus is usually located at about the level or slightly below the maternal umbilicus and remains there for the first two days after birth. The uterus should be firmly contracted and the consistency and size of a softball, approximately 15 cm in height, 12 cm in width, and 10 cm thick. In the immediate postpartum period, the uterus is retroverted (Diniz et al., 2014).

The uterus begins the process of involution at about 2 days after birth (Figure 4.1). During pregnancy, there is an increase in blood flow to the uterus with hypertrophy and adaptation of the pelvic vessels. In the puerperium, blood flow decreases and the vessels revert to their prepregnant state. Involution occurs by a dramatic reduction in the size of the myometrial cells

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