Reproduction

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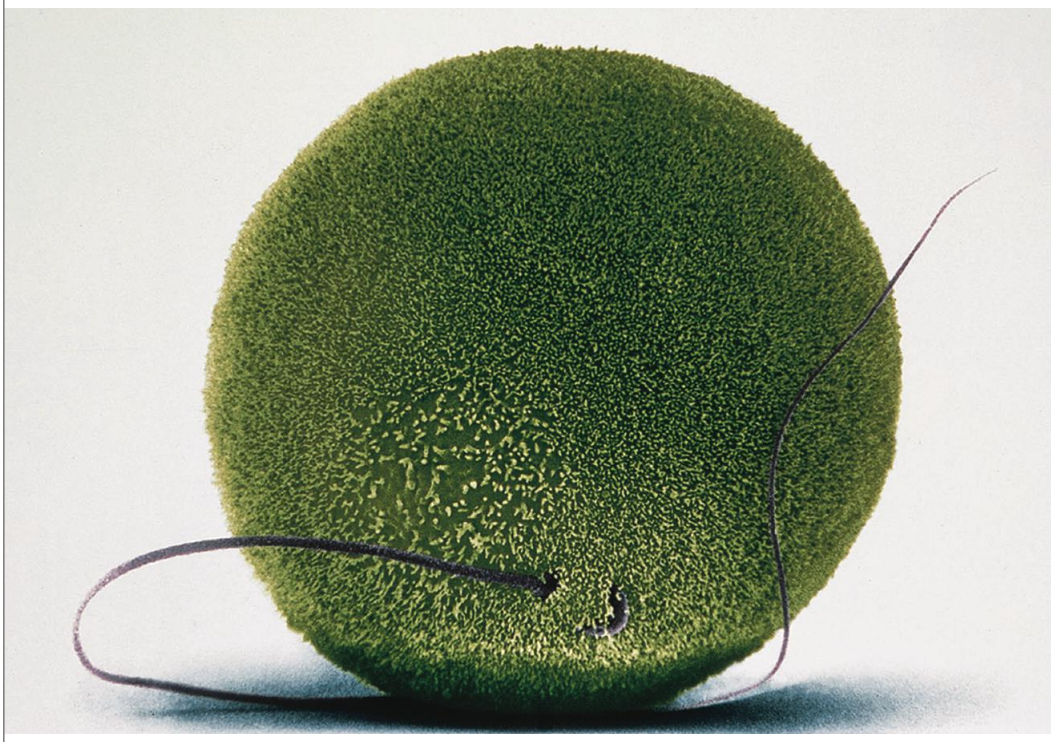

Scanning electron micrograph of a single sperm cell penetrating the surface of an egg.

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Reproduction is the process by which a species is perpetuated. As opposed to most of the physiological processes you have learned about in this book, reproduction is one of the few that is not necessary for the survival of an individual. However, normal reproductive function is essential for the production of healthy offspring and, therefore, for *survival of the species.* Sexual reproduction and the merging of parental chromosomes provide the biological variation of individuals that is necessary for adaptation of the species to our changing environment.

Reproduction includes the processes by which the male gamete (the sperm) and the female gamete (the ovum) develop, grow, and unite to produce a new and unique combination of genes in a new organism. This new entity, the zygote, develops into an embryo and then a fetus within the maternal uterus. The gametes are produced by gonads—the testes in the male and the ovaries in the female. Reproduction also includes the process by which a fetus is born. Over the course of a lifetime, reproductive functions also include sexual maturation (puberty), as well as pregnancy and lactation in women.

The gonads produce hormones that influence development of the offspring into male or female phenotypes. The gonadal hormones are controlled by and influence the secretion of hormones from the hypothalamus and the anterior pituitary gland. Together with the nervous system, these hormones regulate the cyclical activities of female reproduction, including the menstrual cycle, and provide a striking example of the general principle of physiology that most physiological processes are controlled by multiple regulatory systems, often working in opposition. The process of gamete maturation requires communication and feedback between the gonads, anterior pituitary gland, and brain, demonstrating the importance of two related general principles of physiology, namely, that information flow between cells, tissues, and organs is an essential feature of homeostasis and allows for integration of physiological processes; and that the functions of organ systems are coordinated with each other. ■

SECTION A

Gametogenesis, Sex Determination, and Sex Differentiation; General Principles of Reproductive Endocrinology

The primary reproductive organs are known as the **gonads:** the **testes** (singular, **testis**) in the male and the **ovaries** (singular, **ovary**) in the female. In both sexes, the gonads serve dual functions. The first of these is **gametogenesis,** which is the production of the reproductive cells, or **gametes.** These are **spermatozoa** (singular, **spermatozoan,** usually shortened to **sperm**) in males and **ova** (singular, **ovum**) in females. Secondly, the gonads secrete steroid hormones, often termed **sex hormones** or **gonadal steroids.** The major sex hormones are **androgens** (including **testosterone** and **dihydrotestosterone [DHT]**), **estrogens** (primarily **estradiol**), and **progesterone.** Both sexes have each of these hormones, but androgens predominate in males and estrogens and progesterone predominate in females.

17.1 Gametogenesis

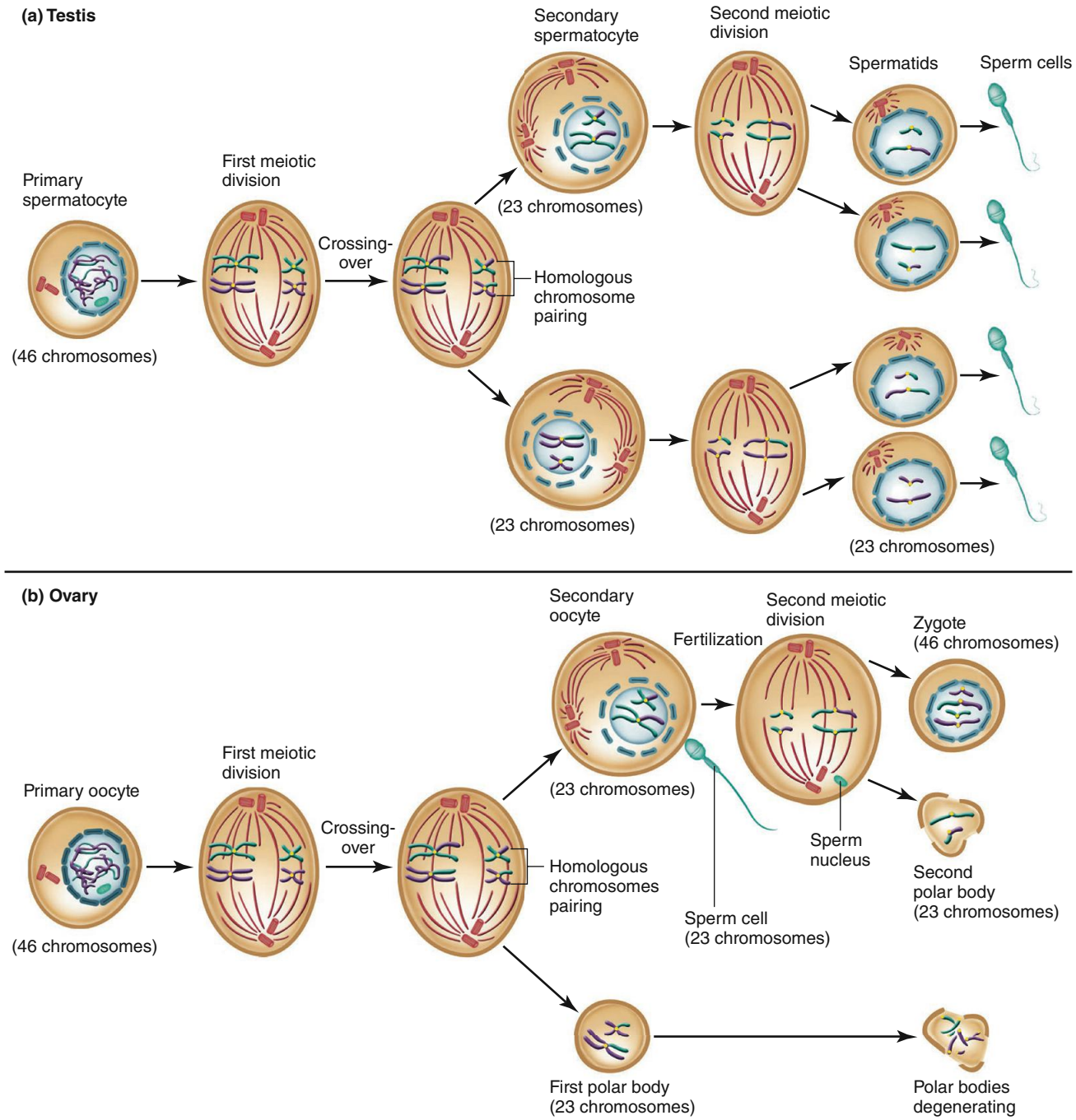
The process of gametogenesis is depicted in **Figure 17.1**. At any point in gametogenesis, the developing gametes are called **germ cells.** The first stage in gametogenesis is proliferation of the primordial (undifferentiated) germ cells by mitosis. With the exception of the gametes, the DNA of each nucleated human cell is contained in 23 pairs of chromosomes, giving a total of 46. The two corresponding chromosomes in each pair are said to be homologous to each other, with one coming from each parent. In **mitosis,** the 46 chromosomes of the dividing cell are replicated. The cell then divides into two new cells called daughter cells. Each of the two daughter cells resulting from the division receives a full set of 46 chromosomes identical to those of the original cell. Therefore, each daughter cell receives identical genetic information during mitosis.

In this manner, mitosis of primordial germ cells, each containing 46 chromosomes, provides a supply of identical germ cells for the next stages. The timing of mitosis in germ cells differs greatly in females and males. In the male, some mitosis occurs in the embryonic testes to generate the population of **primary spermatocytes** present at birth, but mitosis really begins in earnest in the male at puberty and usually continues throughout life. In the female, mitosis of germ cells in the ovary occurs primarily during fetal development, generating **primary oocytes.**

The second stage of gametogenesis is **meiosis,** in which each resulting gamete receives only 23 chromosomes from a 46-chromosome germ cell, one chromosome from each homologous pair. Meiosis consists of two cell divisions in succession (see Figure 17.1). The events preceding the first meiotic division are identical to those preceding a *mitotic* division. During the interphase period, which precedes a mitotic division, chromosomal DNA is replicated. Therefore, after DNA replication, an interphase cell has 46 chromosomes, but each chromosome consists of two identical strands of DNA, called sister chromatids, which are joined together by a centromere.

As the first meiotic division begins, homologous chromosomes, each consisting of two identical sister chromatids, come together and line up adjacent to each other. This results in the formation of 23 pairs of homologous chromosomes called **bivalents**. The sister chromatids of each chromosome condense into thick, rodlike structures. Then, within each homologous pair, corresponding segments of homologous chromosomes align closely. This allows two nonsister chromatids to undergo an exchange of sites of breakage in a process called **crossing-over** (see Figure 17.1). Crossing-over results in the recombination of genes on homologous chromosomes. As a result, the two sister chromatids are no longer identical. Recombination is one of the most significant features of sexual reproduction that creates genetic diversity.

Following crossing-over, the homologous chromosomes line up in the center of the cell. The orientation of each pair on the



AP|R **Figure 17.1** An overview of gametogenesis in (a) the testes and (b) the ovary. Only four chromosomes (two sets) are shown for clarity instead of the normal 46 in humans. Chromosomes from one parent are purple, and those from the other parent are green. The size of the cells can vary quite dramatically in ova development.

equator is random, meaning that sometimes the maternal portion points to a particular pole of the cell and sometimes the paternal portion does so. The cell then divides (the first meiotic division), with the maternal chromatids of any particular pair going to one of the two cells resulting from the division and the paternal chromatids going to the other. The results of the first meiotic division are the **secondary spermatocytes** in males and the **secondary oocyte** in females. Note in Figure 17.1 that, in females, one of the two cells arising from the first meiotic division is the **first polar body** that has no function and eventually degrades. Because of the random orientation of the homologous pairs at the equator, it is extremely unlikely that all 23 maternal chromatids will end up in one cell and all 23 paternal chromatids in the other. Over 8 million (2^{23}) different combinations of maternal and paternal chromosomes can result during this first meiotic division.

The second meiotic division occurs without any further replication of DNA. The sister chromatids—both of which were originally either maternal or paternal—of each chromosome separate and move apart into the new daughter cells. The daughter cells resulting from the second meiotic division, therefore, contain 23 one-chromatid chromosomes. Although the concept is the same, the timing of the second meiotic division is different in males and females. In males, this occurs continuously after puberty with the production of **spermatids** and ultimately mature

sperm cells described in detail in the next section. In females, the second meiotic division does not occur until after fertilization of a secondary oocyte by a sperm. This results in production of the **zygote,** which contains 46 chromosomes—23 from the oocyte (maternal) and 23 from the sperm (paternal)—and the **second polar body,** which, like the first polar body, has no function and will degrade.

To summarize, gametogenesis produces daughter cells having only 23 chromosomes, and two events during the first meiotic division contribute to the enormous genetic variability of the daughter cells: (1) crossing-over and (2) the random distribution of maternal and paternal chromatid pairs between the two daughter cells.

17.2 Sex Determination

The complete genetic composition of an individual is known as the **genotype.** Genetic inheritance sets the gender of the individual, or **sex determination,** which is established at the moment of fertilization. Gender is determined by genetic inheritance of two chromosomes called the **sex chromosomes.** The larger of the sex chromosomes is called the **X chromosome** and the smaller, the **Y chromosome.** Males possess one X and one Y, whereas females have two X chromosomes. Therefore, the key difference in genotype between males and females arises from this difference in one chromosome. As you will learn in the next section, the presence of the Y chromosome leads to the development of the male gonads—the testes; the absence of the Y chromosome leads to the development the female gonads—the ovaries.

The ovum can contribute only an X chromosome, whereas half of the sperm produced during meiosis are X and half are Y. When the sperm and the egg join, 50% should have XX and 50% XY. Interestingly, however, sex ratios at birth are not exactly 1:1; rather, there tends to be a slight preponderance of male births, possibly due to functional differences in sperm carrying the X versus Y chromosome.

When two X chromosomes are present, only one is functional; the nonfunctional X chromosome condenses to form a nuclear mass called the **sex chromatin,** or **Barr body,** which can be observed with a light microscope. Scrapings from the cheek mucosa or white blood cells are convenient sources of cells to be examined. The single X chromosome in male cells rarely condenses to form sex chromatin.

A more exacting technique for determining sex chromosome composition employs tissue culture visualization of all the chromosomes—a **karyotype.** This technique can be used to identify a group of genetic sex abnormalities characterized by such unusual chromosomal combinations such as XXX, XXY, and XO (the O denotes the absence of a second sex chromosome). The end result of such combinations is usually the failure of normal anatomical and functional sexual development. The karyotype is also used to evaluate many other chromosomal abnormalities such as the characteristic trisomy 21 of Down syndrome described later in this chapter.

17.3 Sex Differentiation

The multiple processes involved in the development of the reproductive system in the fetus are collectively called **sex differentiation.** It is not surprising that people with atypical chromosomal combinations can manifest atypical sex differentiation. However, there are individuals with chromosomal combinations that do not match their sexual appearance and function (**phenotype**). In these people, sex differentiation has been atypical, and their gender phenotype may not correspond with the presence of XX or XY chromosomes. The genes directly determine only whether the individual will have testes or ovaries. The rest of sex differentiation depends upon the presence or absence of substances produced by the genetically determined gonads, in particular, the testes.

Differentiation of the Gonads

The male and female gonads derive embryologically from the same site—an area called the urogenital (or gonadal) ridge. Until the sixth week of uterine life, primordial gonads are undifferentiated (see Figure 17.2). In the genetic male, the testes begin to develop during the seventh week. A gene on the Y chromosome (the ***SRY* gene,** for *s*ex-determining *r*egion of the *Y* chromosome) is expressed at this time in the urogenital ridge cells and triggers this development. In the absence of a Y chromosome and, consequently, the *SRY* gene, testes do not develop. Instead, ovaries begin to develop in the same area. The *SRY* gene codes for the SRY protein, which sets into motion a sequence of gene activations ultimately leading to the formation of testes from the various embryonic cells in the urogenital ridge.

Differentiation of Internal and External Genitalia

The internal duct system and external genitalia of the fetus are capable of developing into either sexual phenotype (**Figure 17.2** and **Figure 17.3**). Before the functioning of the fetal gonads, the undifferentiated reproductive tract includes a double genital duct system, comprised of the **Wolffian ducts** and **Müllerian ducts,** and a common opening to the outside for the genital ducts and urinary system. Usually, most of the reproductive tract develops from only one of these duct systems. In the male, the Wolffian ducts persist and the Müllerian ducts regress, whereas in the female, the opposite happens. The external genitalia in the two genders and the outer part of the vagina do not develop from these duct systems, however, but from other structures at the body surface.

Which of the two duct systems and types of external genitalia develops depends on the presence or absence of fetal testes. These testes secrete testosterone and a protein hormone called **Müllerian-inhibiting substance (MIS),** which is also known as *anti-Müllerian hormone* (*AMH*) (see Figure 17.2). SRY protein induces the expression of the gene for MIS; MIS then causes the degeneration of the Müllerian duct system. Simultaneously, testosterone causes the Wolffian ducts to differentiate into the epididymis, vas deferens, ejaculatory duct, and seminal vesicles. Externally and somewhat later, under the influence primarily of dihydrotestosterone (DHT) produced from testosterone in target tissue, a penis forms and the tissue near it fuses to form the scrotum (see Figure 17.3). The testes will ultimately descend into the scrotum, stimulated to do so by testosterone. Failure of the testes to descend is called ***cryptorchidism*** and is common in infants with decreased androgen secretion. Because sperm production requires about 2°C lower temperature than normal core body temperature, sperm production is usually decreased in cryptorchidism. Treatments include hormone therapy and surgical approaches to move the testes into the scrotum.

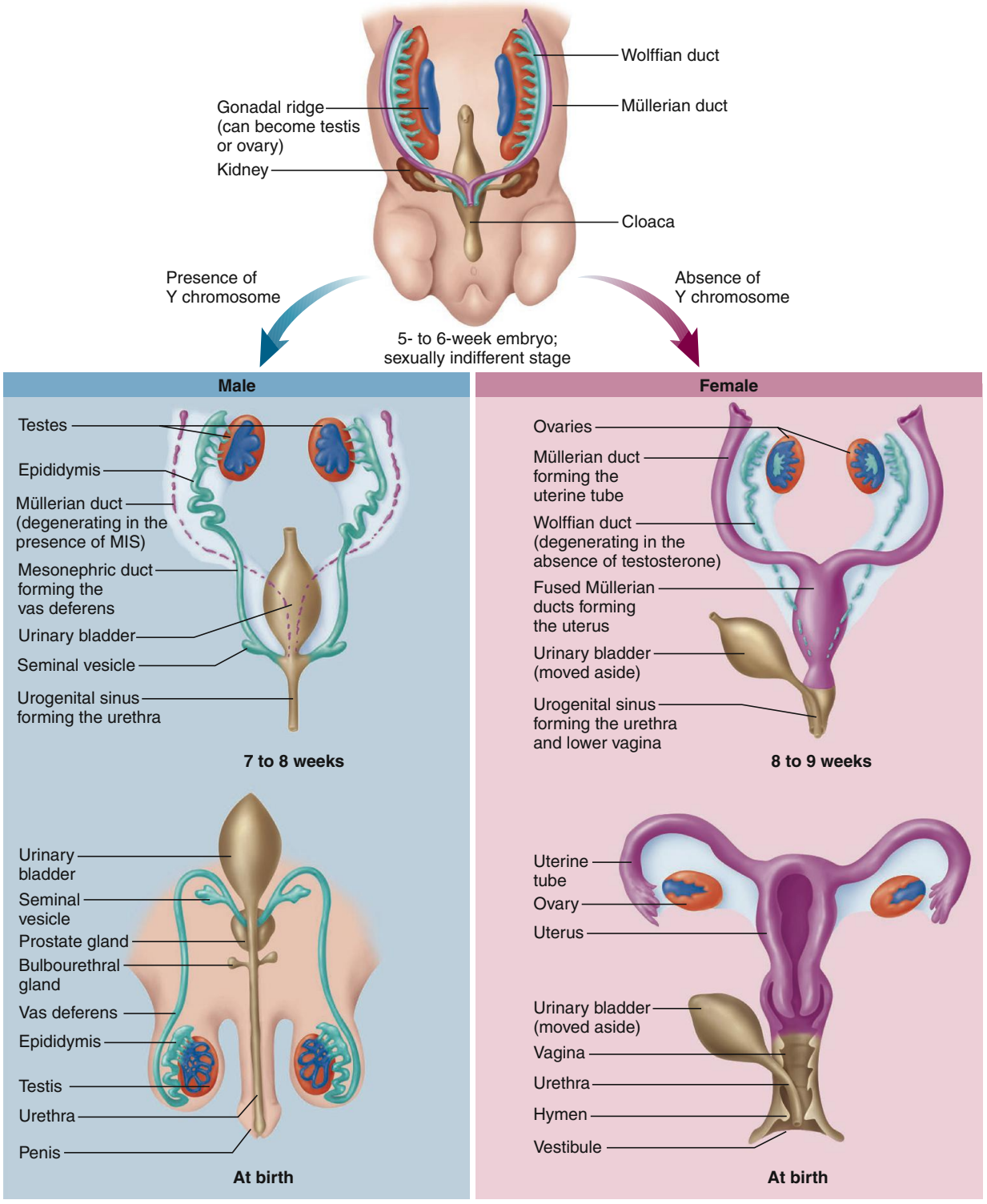


Figure 17.2 Embryonic sex differentiation of the male and female internal reproductive tracts. The testes develop in the presence of the Y chromosome (due to the expression of SRY protein), whereas the ovaries develop in the absence of the Y chromosome (due to the absence of SRY protein). In males, the testes secrete testosterone, which stimulates the maturation of the Wolffian duct into the vas deferens and associated structures, and Müllerian-inhibiting substance (MIS), which induces the degeneration of the Müllerian ducts and associated structures. MIS is also known as *anti-Müllerian hormone* (*AMH*). At birth, the testes have descended into the scrotum. In the female, the absence of testosterone allows the Wolffian ducts to degenerate and the absence of MIS allows the Müllerian ducts to develop into the uterine (fallopian) tubes and the uterus.

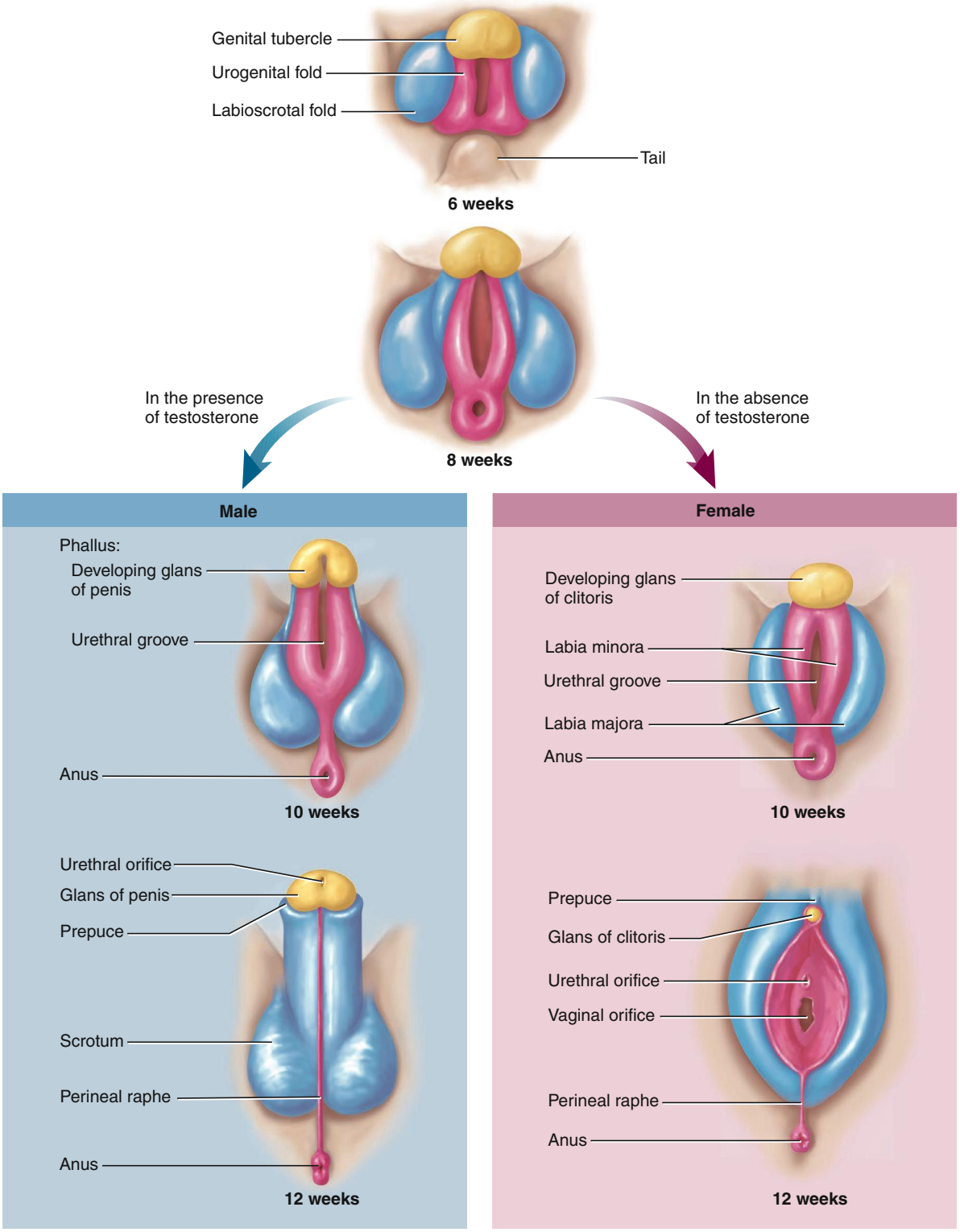


Figure 17.3 Development of the external genitalia in males and females. The major signal for sex differentiation of the external genitalia is the presence of testosterone in the male (produced by the testes shown in Figure 17.2) and its local conversion to dihydrotestosterone (DHT) in target tissue. By about 6 weeks of development, the three primordial structures of the embryo that will become the male or female external genitalia are the genital tubercle, the urogenital fold, and the labioscrotal fold. Sexual differentiation becomes apparent at 10 weeks of fetal life and is unmistakable by 12 weeks of fetal life. The female phenotype develops in the absence of testosterone and DHT. Matching colors identify homologous structures in the male and female.

In contrast, the female fetus, not having testes (because of the absence of the *SRY* gene), does not secrete testosterone and MIS. In the absence of MIS, the Müllerian system does not degenerate but rather develops into fallopian tubes and a uterus (see Figure 17.2). In the absence of testosterone, the Wolffian ducts degenerate and a vagina and female external genitalia develop from the structures at the body surface (see Figure 17.3). Ovaries, though present in the female fetus, do not influence these developmental processes. In other words, female fetal development will occur automatically unless stopped from doing so by the presence of factors released from functioning testes. The events in sex determination and sex differentiation in males and females are summarized in **Figure 17.4**.

There are various conditions in which normal sex differentiation does not occur. For example, in ***androgen insensitivity syndrome*** (also called ***testicular feminization***), the genotype is XY and testes are present but the phenotype (external genitalia and vagina) is female. It is caused by a mutation in the androgen-receptor gene that renders the receptor incapable of normal binding to testosterone. Under the influence of SRY protein, the fetal testes differentiate as usual and they secrete both MIS and testosterone. MIS causes the Müllerian ducts to regress, but the inability of the Wolffian ducts to respond to testosterone also causes them to regress, and so no duct system develops. The tissues that develop into external genitalia are also unresponsive to androgen, so female external genitalia and a vagina develop. The testes do not descend, and they are usually removed when the diagnosis is made. The syndrome is usually not detected until menstrual cycles fail to begin at puberty.

Whereas androgen insensitivity syndrome is caused by a failure of the developing fetus to respond to fetal androgens, ***congenital adrenal hyperplasia*** is caused by the production of too much androgen in the fetus. Rather than the androgen coming from the fetal testes, it is caused by adrenal androgen overproduction due to a partial defect in the ability of the fetal adrenal gland to synthesize cortisol. This is almost always due to a mutation in the gene for an enzyme in the cortisol synthetic pathway (**Figure 17.5**) leading to a partial decrease in the activity of the enzyme. The resultant decrease in cortisol in the fetal blood leads to an increase in the secretion of ACTH from the fetal pituitary gland due to a loss of glucocorticoid negative feedback. The increase in fetal plasma ACTH stimulates the fetal adrenal cortex to make more cortisol to overcome the partial enzyme dysfunction. Remember, however, that the adrenal cortex can synthesize androgens from the same precursor as cortisol (see Figure 11.5). ACTH stimulation results in an increase in androgen production because the precursors cannot be efficiently converted to cortisol. This increase in fetal androgen production results in ***virilization*** of an XX fetus (masculinized external genitalia). If untreated in the fetus, the XX baby can be born with ***ambiguous genitalia***—it is not obvious whether the baby is a phenotypic boy or girl. These babies require treatment with cortisol replacement.

Sexual Differentiation of the Brain

With regard to sexual behavior, differences in the brain may form during fetal and neonatal development. For example, genetic female monkeys treated with testosterone during their late fetal life manifest evidence of masculine sex behavior as adults, such as mounting. In this regard, a potentially important

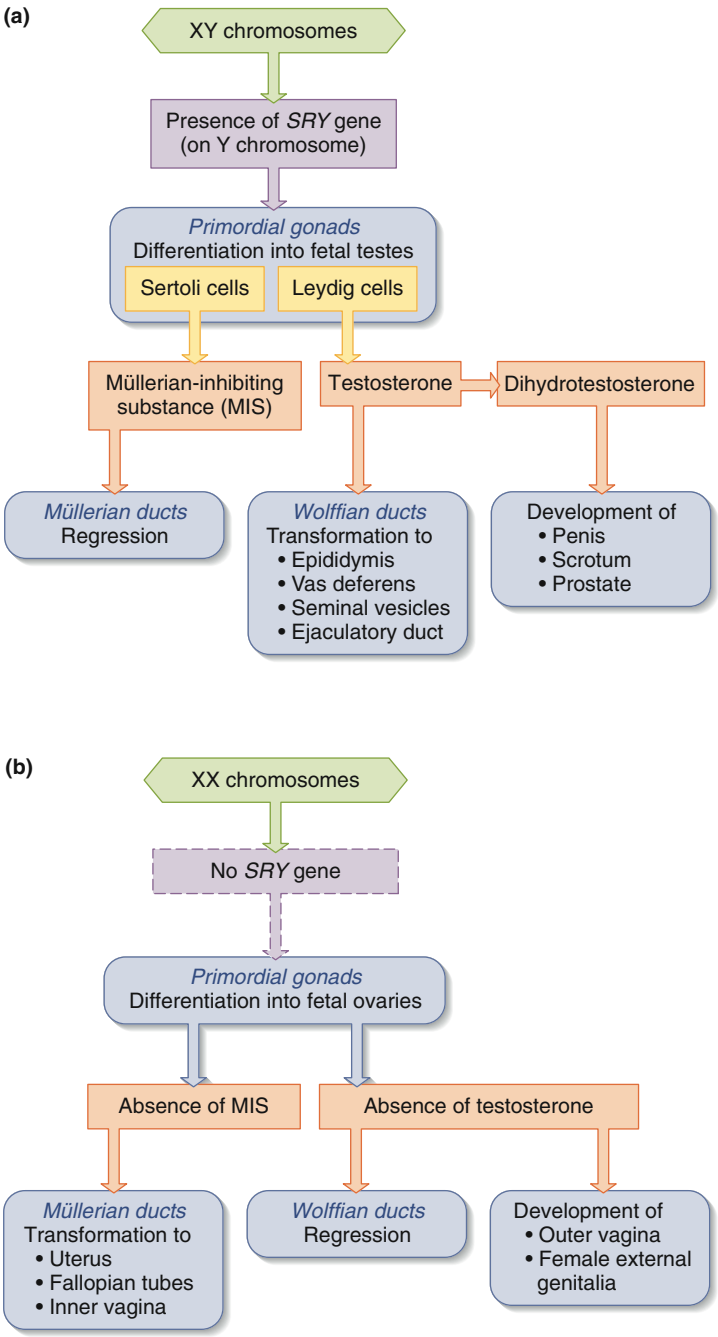


Figure 17.4 Summary of sex differentiation. (a) Male. (b) Female. The *SRY* gene codes for the SRY protein. Conversion of testosterone to dihydrotestosterone occurs primarily in target tissue. The Sertoli and Leydig cells in the testes will be described in Section B.

PHYSIOLOGICAL INQUIRY

- Referring to part (a), 5-α-reductase inhibitors, which block the conversion of testosterone to dihydrotestosterone (DHT) in target tissue, are used to treat some men with benign swelling of their prostate glands. (The prostate gland cells contain 5-α-reductase and are target tissues of locally produced DHT.) Examples of these drugs are finasteride and dutasteride. Why are pregnant women instructed not to take or even handle these drugs? (*Hint:* Some drugs can cross the placenta and enter the circulatory system of the fetus.)

Answer can be found at end of chapter.

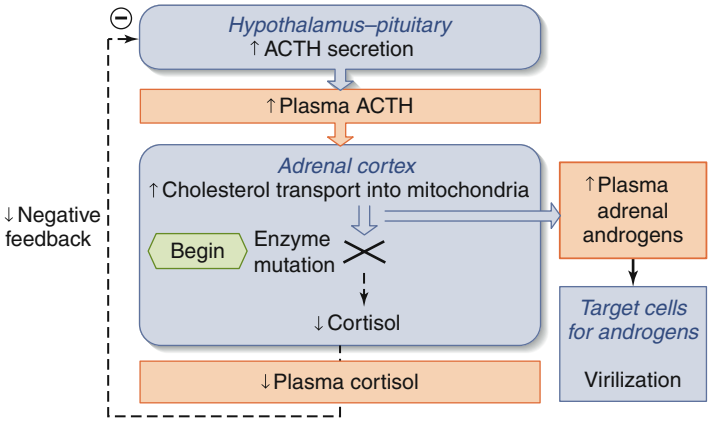


Figure 17.5 Mechanism of virilization in female fetuses with congenital adrenal hyperplasia. An enzyme defect (usually partial) in the steroidogenic pathway leads to decreased production of cortisol and a shift of precursors into the adrenal androgen pathway. Because cortisol negative feedback is decreased, ACTH release from the fetal pituitary gland increases. Although cortisol can eventually be normalized, it is at the expense of ACTH-stimulated adrenal hypertrophy and excess fetal adrenal androgen production.

PHYSIOLOGICAL INQUIRY

- Explain how this figure illustrates the general principle of physiology described in Chapter 1 that homeostasis is essential for health and survival. In what way can the figure also be considered an exception to this principle?

Answer can be found at end of chapter.

difference in human brain anatomy has been reported; the size of a particular nucleus (neuronal cluster) in the hypothalamus is significantly larger in men. There is also an increase in gonadal steroid secretion in the first year of postnatal life that contributes to the sexual differentiation of the brain. Sex-linked differences in appearance or form within a species are called sexual dimorphisms.

17.4 General Principles of Reproductive Endocrinology

This is a good place to review the synthesis of gonadal steroid hormones introduced in Chapter 11 (**Figure 17.6**). These steroidogenic pathways are excellent examples of how the understanding of physiological control is aided by an appreciation of fundamental chemical principles. Each step in this synthetic pathway is catalyzed by enzymes encoded by specific genes. Mutations in these enzymes can lead to atypical gonadal steroid synthesis and secretion and can have profound consequences on sexual development and function. As in the adrenal gland, steroid synthesis starts with cholesterol (see Figures 11.5 and 11.7).

Androgens

Testosterone belongs to a group of steroid hormones that have similar masculinizing actions and are collectively called androgens. In the male, most of the circulating testosterone is synthesized in the testes. Other circulating androgens are produced by the adrenal cortex, but they are much less potent than testosterone and are unable to maintain male reproductive function if testosterone

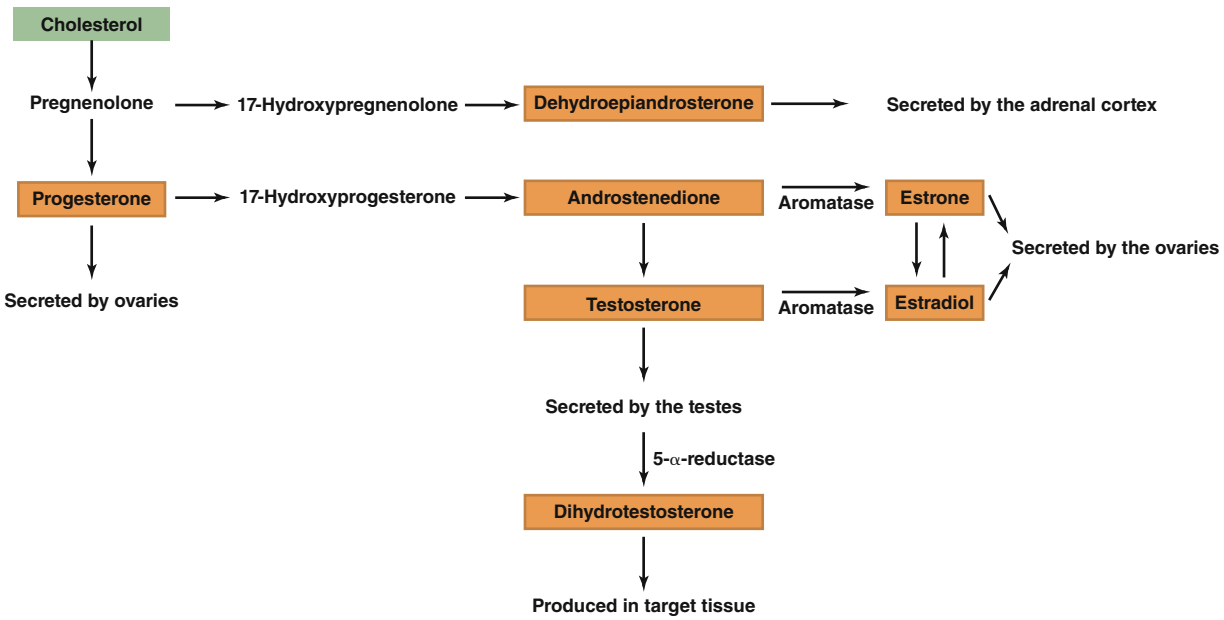


Figure 17.6 Synthesis of androgens in the testes and adrenal gland, and progesterone and estrogens in the ovaries. As in the adrenal cortex (see Figure 11.5), cholesterol is the precursor of steroid hormone synthesis. Progesterone and the estrogens (estrone and estradiol) are the main secretory products of the ovaries depending on the time in the menstrual cycle (look ahead to Figure 17.22). The adrenal cortex produces weak androgens in men and women. The primary gonadal steroid produced by the testes is testosterone, which can be activated to the more potent dihydrotestosterone (DHT) in target tissue. *Note:* Men can also produce some estrogen from testosterone by peripheral conversion due to the action of aromatase in some target tissue (particular adipocytes). For the basic chemical structure of some of these steroid hormones, see Figure 11.4.

secretion is inadequate. Furthermore, these adrenal androgens are also secreted by women. Some adrenal androgens, like dehydroepiandrosterone (DHEA) and androstenedione, are sold as dietary supplements and touted as miracle drugs with limited data showing effectiveness. Finally, some testosterone is converted to the more potent androgen dihydrotestosterone in target tissue by the action of the enzyme **5-α-reductase.**

Estrogens and Progesterone

Estrogens are a class of steroid hormones secreted in large amounts by the ovaries and placenta. There are three major estrogens in humans. As noted earlier, estradiol is the predominant estrogen in the plasma. It is produced by the ovary and placenta and is often used synonymously with the generic term estrogen. **Estrone** is also produced by the ovary and placenta. **Estriol** is found primarily in pregnant women in whom it is produced by the placenta. In all cases, estrogens are produced from androgens by the enzyme **aromatase** (see Figure 17.6). Because plasma concentrations of the different estrogens vary widely depending on the circumstances, and because they have similar actions in the female, we will refer to them throughout this chapter as *estrogen*.

As mentioned earlier, estrogens are not unique to females, nor are androgens to males. Estrogen in the blood in males is derived from the release of small amounts by the testes and from the conversion of androgens to estrogen by the aromatase enzyme in some nongonadal tissues (notably, adipose tissue). Conversely, in females, small amounts of androgens are secreted by the ovaries and larger amounts by the adrenal cortex. Some of these androgens are then converted to estrogen in nongonadal tissues, just as in men, and released into the blood.

Progesterone in females is a major secretory product of the ovary at specific times of the menstrual cycle, as well as of the placenta during pregnancy (see Figure 17.6). Progesterone is also an intermediate in the synthetic pathways for adrenal steroids, estrogens, and androgens.

Effects of Gonadal Steroids

As described in Chapters 5 and 11, all steroid hormones act in the same general way. They bind to intracellular receptors, and the hormone–receptor complex then binds to DNA in the nucleus to alter the rate of formation of particular mRNAs. The result is a change in the rates of synthesis of the proteins coded for by the genes being transcribed. The resulting change in the concentrations of these proteins in the target cells accounts for the responses to the hormone.

As described earlier, the development of the duct systems through which the sperm or eggs are transported and the glands lining or emptying into the ducts (the **accessory reproductive organs**) is controlled by the presence or absence of gonadal hormones. The breasts are also considered accessory reproductive organs; their development is under the influence of ovarian hormones. The development of the **secondary sexual characteristics,** comprising the many external differences between males and females, is also under the influence of gonadal steroids. Examples are hair distribution, body shape, and average adult height. The secondary sexual characteristics are not directly involved in reproduction.

Hypothalamo–Pituitary–Gonadal Control

Reproductive function is largely controlled by a chain of hormones (**Figure 17.7**). The first hormone in the chain is **gonadotropin-releasing hormone (GnRH).** As described in Chapter 11, GnRH is one of the hypophysiotropic hormones involved in the control of anterior pituitary gland function. It is secreted by neuroendocrine cells in the hypothalamus, and it reaches the anterior pituitary gland via the hypothalamo–pituitary portal blood vessels. In the anterior pituitary gland, GnRH stimulates the release of the pituitary **gonadotropins—follicle-stimulating hormone (FSH)** and **luteinizing hormone (LH)**, which in turn stimulate gonadal function. The brain is, therefore, the primary regulator of reproduction.

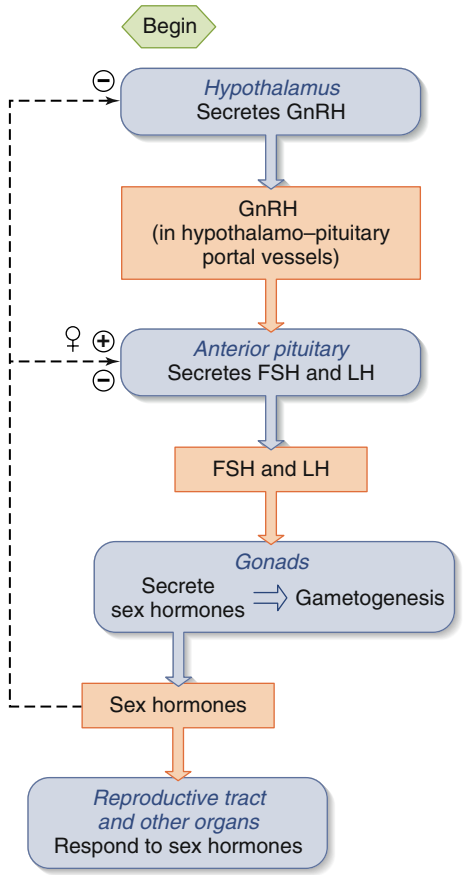


Figure 17.7 Pattern of reproduction control in both males and females. GnRH, like all hypothalamic–hypophysiotropic hormones, reaches the anterior pituitary gland via the hypothalamo–hypophyseal portal vessels. The arrow within the box marked "gonads" denotes the fact that the sex hormones act locally as paracrine agents to influence the gametes. ⊖ indicates negative feedback inhibition. ⊕ indicates estrogen stimulation of FSH and LH in the middle of the menstrual cycle in women (positive feedback).

PHYSIOLOGICAL INQUIRY

- What would be the short- and long-term effects of removal of one of the two gonads in an adult?

Answer can be found at end of chapter.

The cell bodies of the GnRH neurons receive input from throughout the brain as well as from hormones in the blood. This is why certain stressors, emotions, and trauma to the central nervous system can inhibit reproductive function. It has recently been discovered that neurons in discrete areas of the hypothalamus synapse on GnRH neurons and release a peptide called **kisspeptin** that is intimately involved in the activation of GnRH neurons. Secretion of GnRH is triggered by action potentials in GnRH-producing hypothalamic neuroendocrine cells. These action potentials occur periodically in brief bursts, with little secretion in between. The pulsatile pattern of GnRH secretion is important because the cells of the anterior pituitary gland that secrete the gonadotropins lose sensitivity to GnRH if the concentration of this hormone remains constantly elevated. This phenomenon is exploited by the administration of synthetic analogs of GnRH to men with androgen-sensitive prostate cancer and to women with estrogen-sensitive breast cancer. Although one may think that administration of a GnRH analog would stimulate FSH and LH, the constant nonpulsatile overstimulation actually decreases FSH and LH and results in a decrease in gonadal steroid secretion.

LH and FSH were named for their effects in the female, but their molecular structures are the same in both sexes. The two hormones act upon the gonads, the result being (1) the maturation of sperm or ova and (2) stimulation of sex hormone secretion. In turn, the sex hormones exert many effects on all portions of the reproductive system, including locally in the gonads from which they come as well as on other parts of the body. In addition, the gonadal steroids exert feedback effects on the secretion of GnRH, FSH, and LH. It is currently thought that gonadal steroids exert negative feedback effects on GnRH both directly and through inhibition of kisspeptin neuron cell bodies in the hypothalamus that have input to the GnRH neurons. Gonadal protein hormones such as **inhibin** also exert feedback effects on the anterior pituitary gland. Each link in this hormonal chain is essential. A decrease in function of the hypothalamus or the anterior pituitary gland can result in failure of gonadal steroid secretion and gametogenesis just as if the gonads themselves were diseased.

As a result of changes in the amount and pattern of hormone secretions, reproductive function changes markedly during a person's lifetime and may be divided into the stages summarized in **Table 17.1**.

TABLE 17.1 Stages in the Control of Reproductive Function

Fetal life to infancy: GnRH, the gonadotropins, and gonadal sex hormones are secreted at relatively high levels.
Infancy to puberty: GnRH, the gonadotropins, and gonadal sex hormones are very low and reproductive function is quiescent.
Puberty to adulthood: GnRH, the gonadotropins, and gonadal sex hormones increase markedly, showing large cyclical variations in women during the menstrual cycle. This ushers in the period of active reproduction.
Aging: Reproductive function diminishes largely because the gonads become less responsive to the gonadotropins. The ability to reproduce ceases entirely in women.

SECTION A SUMMARY

Gametogenesis

I. The first stage of gametogenesis is mitosis of primordial germ cells.
II. This is followed by meiosis, which is a sequence of two cell divisions resulting in each gamete receiving 23 chromosomes.
III. Crossing-over and random distribution of maternal and paternal chromatids to the daughter cells during meiosis cause genetic variability in the gametes.

Sex Determination

I. Gender is determined by the two sex chromosomes; males are XY, and females are XX.

Sex Differentiation

I. A gene on the Y chromosome is responsible for the development of testes. In the absence of a Y chromosome, testes do not develop and ovaries do instead.
II. When functioning male gonads are present, they secrete testosterone and MIS, so a male reproductive tract and external genitalia develop. In the absence of testes, the female system develops.
III. A sexually dimorphic brain region exists in humans and certain experimental animals that may be linked with male-type or female-type sexual behavior.

General Principles of Reproductive Endocrinology

I. The gonads have a dual function—gametogenesis and secretion of sex hormones.
II. The male gonads are the testes, which produce sperm and secrete the steroid hormone testosterone.
III. The female gonads are the ovaries, which produce ova and secrete the steroid hormones estrogen and progesterone.
IV. Gonadal function is controlled by the gonadotropins (FSH and LH) from the pituitary gland whose release is controlled by gonadotropin-releasing hormone (GnRH) from the hypothalamus.

SECTION A REVIEW QUESTIONS

1. Describe the stages of gametogenesis and how meiosis results in genetic variability.
2. State the genetic difference between males and females and a method for identifying genetic sex.
3. Describe the sequence of events, the timing, and the control of the development of the gonads and the internal and external genitalia.
4. Explain how administration of glucocorticoids to a pregnant woman would treat congenital adrenal hyperplasia in her fetus.

SECTION A KEY TERMS

androgens
dihydrotestosterone (DHT)
estradiol
estrogens
gametes
gametogenesis
gonadal steroids
gonads
ova (ovum)
ovaries (ovary)
progesterone
sex hormones
sperm
spermatozoa (spermatozoan)
testes (testis)
testosterone

17.1 Gametogenesis

bivalents
crossing-over
first polar body
germ cells
meiosis
mitosis
primary oocytes
primary spermatocytes

secondary oocyte
secondary spermatocytes
second polar body
spermatids
zygote

17.2 Sex Determination

Barr body
genotype
karyotype
sex chromatin
sex chromosomes
sex determination
X chromosome
Y chromosome

17.3 Sex Differentiation

Müllerian ducts
Müllerian-inhibiting substance (MIS)
phenotype
sex differentiation
SRY gene
Wolffian ducts

17.4 General Principles of Reproductive Endocrinology

accessory reproductive organs
aromatase
estriol
estrone
5-α-reductase
follicle-stimulating hormone (FSH)
gonadotropin-releasing hormone (GnRH)
gonadotropins
inhibin
kisspeptin
luteinizing hormone (LH)
secondary sexual characteristics

SECTION A CLINICAL TERMS

17.3 Sex Differentiation

ambiguous genitalia
androgen insensitivity syndrome
congenital adrenal hyperplasia
cryptorchidism
testicular feminization
virilization

SECTION B

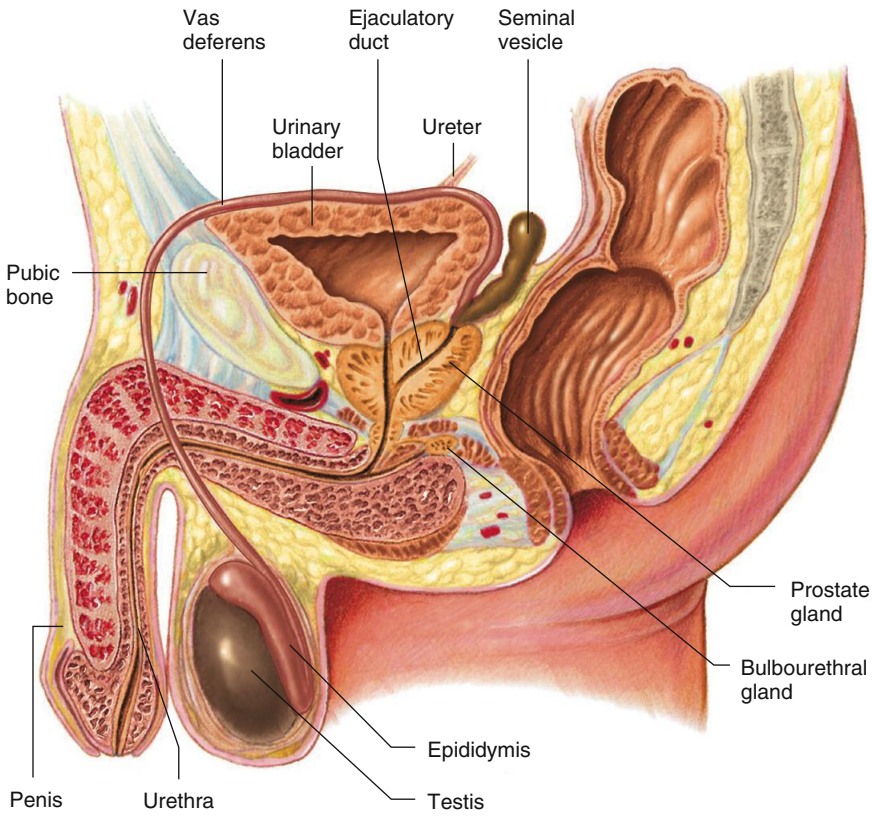
Male Reproductive Physiology

17.5 Anatomy

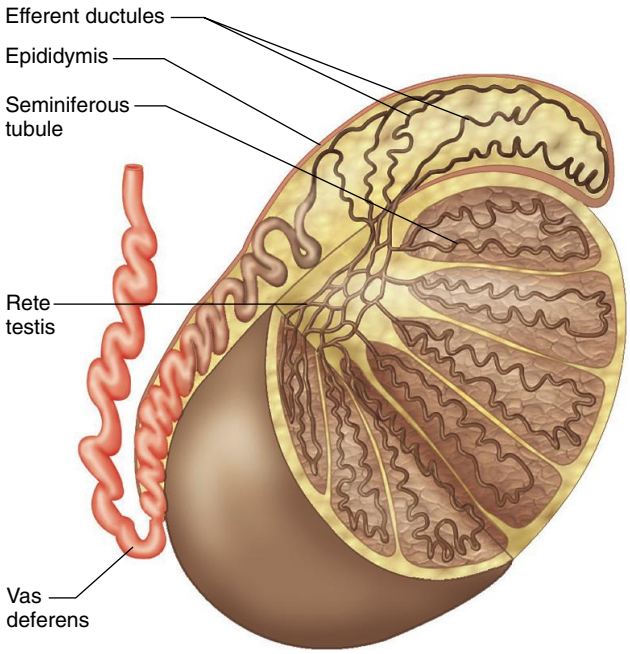
The male reproductive system includes the two testes, the system of ducts that store and transport sperm to the exterior, the glands that empty into these ducts, and the penis (**Figure 17.8**). The duct system, glands, and penis constitute the male accessory reproductive organs.

The testes are suspended outside the abdomen in the **scrotum,** which is an outpouching of the abdominal wall and is divided internally into two sacs, one for each testis. During early fetal development, the testes are located in the abdomen; but during later **gestation** (usually in the seventh month of pregnancy), they usually descend into the scrotum (see Figure 17.2). This descent is essential for normal sperm production during adulthood, because sperm formation requires a temperature approximately 2°C lower than normal internal body temperature. Cooling is achieved by air circulating around the scrotum and by a heat-exchange mechanism in the blood vessels supplying the testes. In contrast to spermatogenesis, testosterone secretion can usually occur normally at internal body temperature, so failure of testes descent usually does not impair testosterone secretion.

The sites of **spermatogenesis** (sperm formation) in the testes are the many tiny, convoluted **seminiferous tubules** (**Figure 17.9**). The combined length of these tubes is 250 m (the length of over 2.5 football fields). The seminiferous tubules from different areas of a testis converge to form a network of interconnected tubes, the **rete testis** (see Figure 17.9). Small ducts called efferent ductules leave the rete testis, pierce the fibrous covering of the testis, and empty into a single duct within a structure called the **epididymis** (plural, *epididymides*). The epididymis is loosely attached to the outside of the testis. The duct of the epididymis is so convoluted that, when straightened out at dissection, it measures 6 m. The epididymis draining each testis leads to a **vas deferens** (plural, *vasa deferentia*), a large, thick-walled tube lined with smooth muscle. Not shown in Figure 17.9 is that the vas deferens and the blood vessels and nerves supplying the testis are bound together in the **spermatic cord,** which passes to the testis through a slitlike passage, the inguinal canal, in the abdominal wall.



AP|R **Figure 17.8** Anatomical organization of the male reproductive tract. This figure shows the testis, epididymis, vas deferens, ejaculatory duct, seminal vesicle, and bulbourethral gland on only one side of the body, but they are all paired structures. The urinary bladder and a ureter are shown for orientation but are not part of the reproductive tract. Once the ejaculatory ducts join the urethra in the prostate, the urinary and reproductive tracts have merged.



AP|R **Figure 17.9** Section of a testis. The upper portion of the testis has been removed to show its interior.

After entering the abdomen, the two vasa deferentia—one from each testis—continue to behind the urinary bladder base (see Figure 17.8). The ducts from two large glands, the **seminal vesicles,** which lie behind the bladder, join the two vasa deferentia to form the two **ejaculatory ducts.** The ejaculatory ducts then enter the **prostate gland** and join the urethra, coming from the bladder. The prostate gland is a single walnut-sized structure below the bladder and surrounding the upper part of the urethra, into which it secretes fluid through hundreds of tiny openings in the side of the urethra. The urethra emerges from the prostate gland and enters the penis. The paired **bulbourethral glands,** lying below the prostate, drain into the urethra just after it leaves the prostate.

The prostate gland and seminal vesicles secrete most of the fluid in which ejaculated sperm are suspended. This fluid plus the sperm cells constitute **semen,** the sperm contributing a small percentage of the total volume. The glandular secretions contain a large number of different chemical substances, including (1) nutrients, (2) buffers for protecting the sperm against the acidic vaginal secretions and residual acidic urine in the male urethra, (3) chemicals (particularly from the seminal vesicles) that increase sperm motility, and (4) prostaglandins. The function of the prostaglandins, which are produced by the seminal vesicles, is still not clear. The bulbourethral glands contribute a small volume of lubricating mucoid secretions.

In addition to providing a route for sperm from the seminiferous tubules to the exterior, several of the duct system segments perform additional functions to be described in the section on sperm transport.

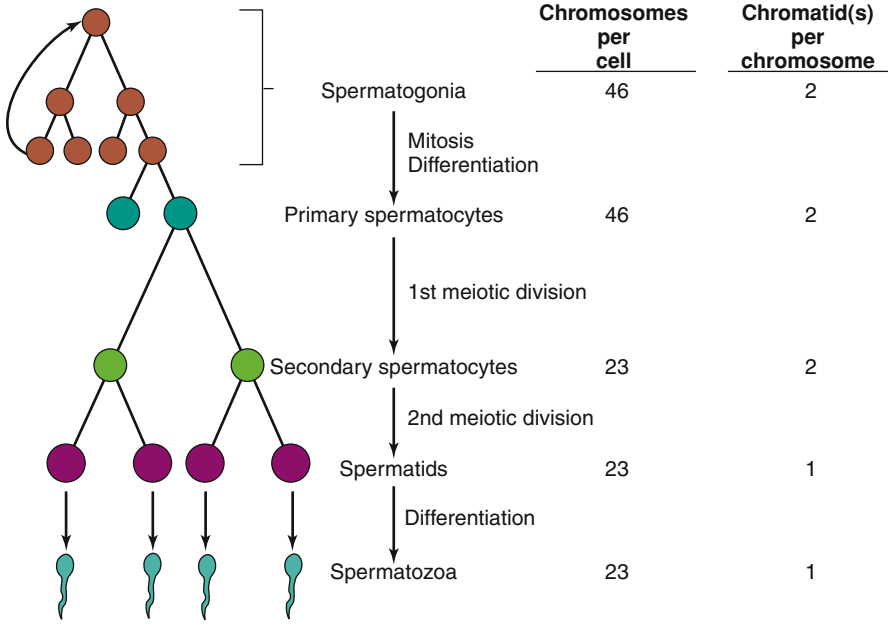
17.6 Spermatogenesis

The various stages of spermatogenesis were introduced in Figure 17.1 and are summarized in **Figure 17.10**. The undifferentiated germ cells, called spermatogonia (singular, **spermatogonium**), begin to divide mitotically at puberty. The daughter cells of this first division then divide again and again for a specified number of division cycles so that a clone of spermatogonia is produced from each stem cell spermatogonium. Some differentiation occurs in addition to cell division. The cells that result from the final mitotic division and differentiation in the series are called primary spermatocytes, and these are the cells that will undergo the first meiotic division of spermatogenesis.

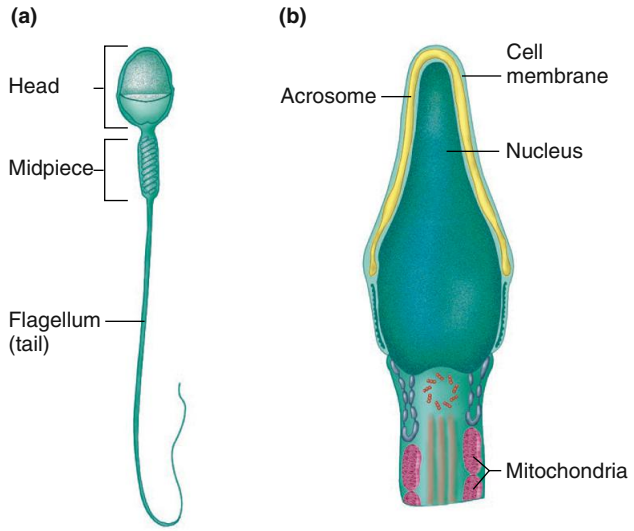
It should be emphasized that if all the cells in the clone produced by each stem cell spermatogonium followed this pathway, the spermatogonia would disappear—that is, they would all be converted to primary spermatocytes. This does not occur because, at an early point, one of the cells of each clone "drops out" of the mitosis–differentiation cycle to remain a stem cell spermatogonium that will later enter into its own full sequence of divisions. One cell of the clone it produces will do likewise, and so on. Therefore, the supply of undifferentiated spermatogonia is maintained.

Each primary spermatocyte increases markedly in size and undergoes the first meiotic division (see Figure 17.10) to form two secondary spermatocytes, each of which contains 23 two-chromatid chromosomes. Each secondary spermatocyte undergoes the second meiotic division (see Figure 17.1) to form spermatids. In this way, each primary spermatocyte, containing 46 two-chromatid chromosomes, produces four spermatids, each containing 23 one-chromatid chromosomes.

The final phase of spermatogenesis is the differentiation of the spermatids into spermatozoa (sperm). This process involves extensive cell remodeling, including elongation, but no further cell divisions.



AP|R **Figure 17.10** Summary of spermatogenesis, which begins at puberty. Each spermatogonium yields, by mitosis, a clone of spermatogonia; for simplicity, the figure shows only two such cycles, with a third mitotic cycle generating two primary spermatocytes. The arrow from one of the spermatogonia back to a stem cell spermatogonium denotes the fact that one cell of the clone does not go on to generate primary spermatocytes but reverts to an undifferentiated spermatogonium that gives rise to a new clone. Each primary spermatocyte produces four spermatozoa.



AP|R **Figure 17.11** (a) Diagram of a human mature sperm. (b) A close-up of the head drawn from a different angle. The acrosome contains enzymes required for fertilization of the ovum.

The head of a sperm cell (**Figure 17.11**) consists almost entirely of the nucleus, which contains the genetic information (DNA). The tip of the nucleus is covered by the **acrosome,** a protein-filled vesicle containing several enzymes that are important in fertilization. Most of the tail is a flagellum—a group of contractile filaments that produce whiplike movements capable of propelling the sperm at a velocity of 1 to 4 mm per min. Mitochondria form the midpiece of the sperm and provide the energy for movement.

The entire process of spermatogenesis, from primary spermatocyte to sperm, takes approximately 64 days. The typical human male manufactures approximately 30 million sperm per day.

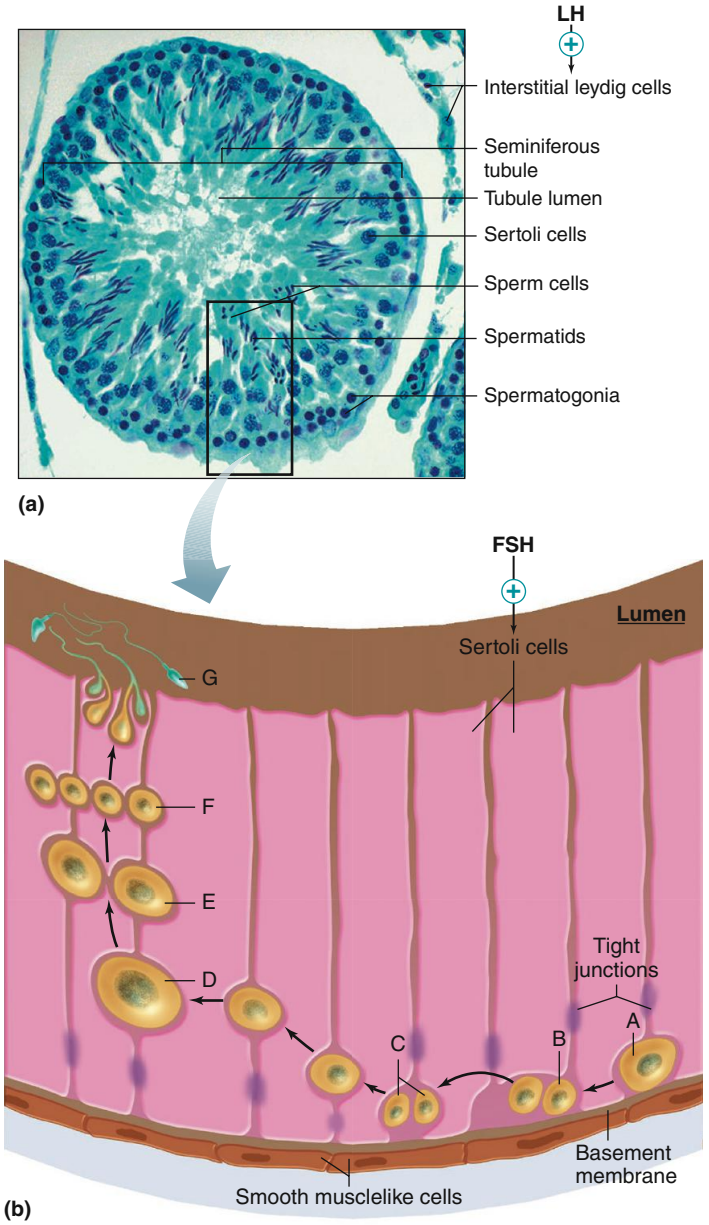
Sertoli Cells

Each seminiferous tubule is bounded by a basement membrane. In the center of each tubule is a fluid-filled lumen containing the mature sperm cells, called spermatozoa. The tubular wall is composed of developing germ cells and their supporting cells, called **Sertoli cells** (also known as sustentacular cells). Each Sertoli cell extends from the basement membrane all the way to the lumen in the center of the tubule and is joined to adjacent Sertoli cells by means of tight junctions (**Figure 17.12**). Thus, the Sertoli cells form an unbroken ring around the outer circumference of the seminiferous tubule. The tight junctions divide the tubule into two compartments—a basal compartment, between the basement membrane and the tight junctions, and a central compartment, beginning at the tight junctions and including the lumen.

The ring of interconnected Sertoli cells forms the **Sertoli cell barrier** (blood–testes barrier), which prevents the movement of many chemicals from the blood into the lumen of the seminiferous tubule and helps retain luminal fluid. This ensures proper conditions for germ cell development and differentiation in the tubules. The arrangement of Sertoli cells also permits different stages of spermatogenesis to take place in different compartments and, therefore, in different environments.

Leydig Cells

The **Leydig cells,** or interstitial cells, which lie in small, connective-tissue spaces between the tubules, synthesize and release testosterone. Therefore, the sperm-producing and testosterone-producing functions of the testes are carried out by different structures—the seminiferous tubules and Leydig cells, respectively.



AP|R **Figure 17.12** (a) Cross section of a seminiferous tubule and associated interstitial (Leydig) cells. (Light microscopic image [250x] stained blue for clarity.). The Sertoli cells (stimulated by FSH to increase spermatogenesis and produce inhibin) are in the seminiferous tubules, the sites of sperm production. The tubules are separated from each other by interstitial space (white) that contains Leydig cells (stimulated by LH to produce testosterone) (b) The Sertoli cells form a ring (barrier) around the entire tubule. For convenience of presentation, the various stages of spermatogenesis are shown as though the germ cells move up a line of adjacent Sertoli cells; in reality, all stages beginning with any given spermatogonium take place between the same two Sertoli cells. Spermatogonia (A and B) are found only in the basal compartment (between the tight junctions of the Sertoli cells and the basement membrane of the tubule). After several mitotic cycles (A to B), the spermatogonia (B) give rise to primary spermatocytes (C). Each of the latter crosses a tight junction, enlarges (D), and divides into two secondary spermatocytes (E), which divide into spermatids (F), which in turn differentiate into spermatozoa (G). This last step involves loss of cytoplasm by the spermatids.

Production of Mature Sperm

As shown in Figure 17.12, spermatogenesis is ultimately controlled by the gonadotropins that stimulate local testosterone secretion from Leydig cells and increase the activity of Sertoli cells. Mitotic cell divisions and differentiation of spermatogonia to yield primary spermatocytes take place entirely in the basal compartment. The primary spermatocytes then move through the tight junctions of the Sertoli cells (which open in front of them while at the same time forming new tight junctions behind them) to gain entry into the central compartment. In this central compartment, the meiotic divisions of spermatogenesis occur, and the spermatids differentiate into sperm while contained in recesses formed by invaginations of the Sertoli cell plasma membranes. When sperm formation is complete, the cytoplasm of the Sertoli cell around the sperm retracts and the sperm are released into the lumen to be bathed by the luminal fluid.

Sertoli cells serve as the route by which nutrients reach developing germ cells, and they also secrete most of the fluid found in the tubule lumen. This fluid contains **androgen-binding protein** (**ABP**), which binds the testosterone secreted by the Leydig cells and crosses the Sertoli cell barrier to enter the tubule. This protein maintains a high concentration of total testosterone in the lumen of the tubule. The dissociation of free testosterone from ABP continuously exposes the developing spermatocytes and Sertoli cells to testosterone.

Sertoli cells do more than influence the environment of the germ cells. In response to FSH from the anterior pituitary gland and to local testosterone produced in the Leydig cell, Sertoli cells secrete a variety of chemical messengers. These function as paracrine agents to stimulate proliferation and differentiation of the germ cells. In addition, the Sertoli cells secrete the protein hormone inhibin, which acts as a negative feedback controller of FSH, and paracrine agents that affect Leydig cell function. The many functions of Sertoli cells, several of which remain to be described later in this chapter, are summarized in **Table 17.2**.

TABLE 17.2 Functions of Sertoli Cells

Provide Sertoli cell barrier to chemicals in the plasma
Nourish developing sperm
Secrete luminal fluid, including androgen-binding protein
Respond to stimulation by testosterone and FSH to secrete paracrine agents that stimulate sperm proliferation and differentiation
Secrete the protein hormone inhibin, which inhibits FSH secretion from the pituitary gland
Secrete paracrine agents that influence the function of Leydig cells
Phagocytize defective sperm
Secrete Müllerian-inhibiting substance (MIS), also known as *anti-Mullerian hormone (AMH),* which causes the primordial female duct system to regress during embryonic life

17.7 Transport of Sperm

From the seminiferous tubules, the sperm pass through the rete testis and efferent ducts into the epididymis and from there to the vas deferens. The vas deferens and the portion of the epididymis closest to it serve as a storage reservoir for sperm until **ejaculation,** the discharge of semen from the penis.

Movement of the sperm as far as the epididymis results from the pressure that the Sertoli cells create by continuously secreting fluid into the seminiferous tubules. The sperm themselves are normally nonmotile at this time.

During passage through the epididymis, the concentration of the sperm increases dramatically due to fluid absorption from the lumen of the epididymis. Therefore, as the sperm pass from the end of the epididymis into the vas deferens, they are a densely packed mass whose transport is no longer facilitated by fluid movement. Instead, peristaltic contractions of the smooth muscle in the epididymis and vas deferens cause the sperm to move.

The absence of a large quantity of fluid accounts for the fact that ***vasectomy,*** the surgical tying off and removal of a segment of each vas deferens as a method of male contraception, does not cause the accumulation of much fluid behind the tie-off point. The sperm, which are still produced after vasectomy, do build up, however, and eventually break down, with their chemical components absorbed into the bloodstream. Vasectomy does not affect testosterone secretion because it does not alter the function of the Leydig cells.

Erection

The penis consists almost entirely of three cylindrical, vascular compartments running its entire length. Normally, the small arteries supplying the vascular compartments are constricted so that the compartments contain little blood and the penis is flaccid. During sexual excitation, the small arteries dilate, blood flow increases, the three vascular compartments become engorged with blood at high pressure, and the penis becomes rigid (**erection**). The vascular dilation is initiated by neural input to the small arteries of the penis. As the vascular compartments expand, the adjacent veins emptying them are passively compressed, further increasing the local pressure, thus contributing to the engorgement while blood flow remains elevated. This entire process occurs rapidly with complete erection sometimes taking only 5 to 10 seconds.

What are the neural inputs to the small arteries of the penis? At rest, the dominant input is from sympathetic neurons that release norepinephrine, which causes the arterial smooth muscle to contract. During erection, this sympathetic input is inhibited. Much more important is the activation of nonadrenergic, noncholinergic autonomic neurons to the arteries (**Figure 17.13**). These neurons and associated endothelial cells release **nitric oxide,** which relaxes the arterial smooth muscle. The primary stimulus for erection comes from mechanoreceptors in the genital region, particularly in the head of the penis. The afferent fibers carrying the impulses synapse in the lower spinal cord on interneurons that control the efferent outflow.

It must be stressed, however, that higher brain centers, via descending pathways, may also exert profound stimulatory or inhibitory effects upon the autonomic neurons to the small arteries of the penis. Thus, mechanical stimuli from areas other than the penis, as well as thoughts, emotions, sights, and odors, can

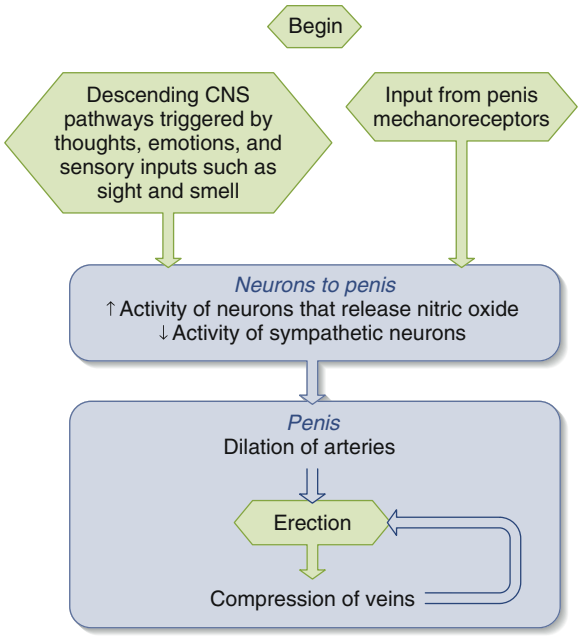


Figure 17.13 Reflex pathways for erection. Nitric oxide, a vasodilator, is the most important neurotransmitter to the arteries in this reflex.

PHYSIOLOGICAL INQUIRY

- How does this figure illustrate the general principle of physiology described in Chapter 1 that physiological processes are dictated by the laws of chemistry and physics?

Answer can be found at end of chapter.

induce erection in the complete absence of penile stimulation (or prevent erection even though stimulation is present).

Erectile dysfunction (also called *impotence*) is the consistent inability to achieve or sustain an erection of sufficient rigidity for sexual intercourse and is a common problem. Although it can be mild to moderate in degree, complete erectile dysfunction is present in as many as 10% of adult American males between the ages of 40 and 70. During this period of life, its rate almost doubles. The organic causes are multiple and include damage to or malfunction of the efferent nerves or descending pathways, endocrine disorders, various therapeutic and "recreational" drugs (e.g., alcohol), and certain diseases, particularly diabetes mellitus. Erectile dysfunction can also be due to psychological factors (such as depression), which are mediated by the brain and the descending pathways.

There are now a group of orally active ***cGMP-phosphodiesterase type 5*** (PDE5) ***inhibitors*** including sildenafil (*Viagra*), vardenafil (*Levitra*), and tadalafil (*Cialis*) that can improve the ability to achieve and maintain an erection. The most important event leading to erection is the dilation of penile arteries by nitric oxide, released from autonomic neurons. Nitric oxide stimulates the enzyme guanylyl cyclase, which catalyzes the formation of cyclic GMP (cGMP), as described in Chapter 5. This second messenger then continues the signal transduction pathway leading to the relaxation of the arterial smooth muscle. The sequence of events is terminated by an enzyme-dependent breakdown of cGMP. PDE5 inhibitors block the action of this enzyme and thereby permit a higher concentration of cGMP to exist.

Ejaculation

As stated earlier, ejaculation is the discharge of semen from the penis. Ejaculation is primarily a spinal reflex mediated by afferent pathways from penile mechanoreceptors. When the level of stimulation is high enough, a patterned sequence of discharge of the efferent neurons ensues. This sequence can be divided into two phases: (1) The smooth muscles of the epididymis, vas deferens, ejaculatory ducts, prostate, and seminal vesicles contract as a result of sympathetic nerve stimulation, emptying the sperm and glandular secretions into the urethra (emission); and (2) the semen, with an average volume of 3 mL and containing 300 million sperm, is then expelled from the urethra by a series of rapid contractions of the urethral smooth muscle as well as the skeletal muscle at the base of the penis. During ejaculation, the sphincter at the base of the urinary bladder is closed so that sperm cannot enter the bladder, nor can urine be expelled from it. Note that erection involves inhibition of sympathetic nerves (to the small arteries of the penis), whereas ejaculation involves stimulation of sympathetic nerves (to the smooth muscles of the duct system).

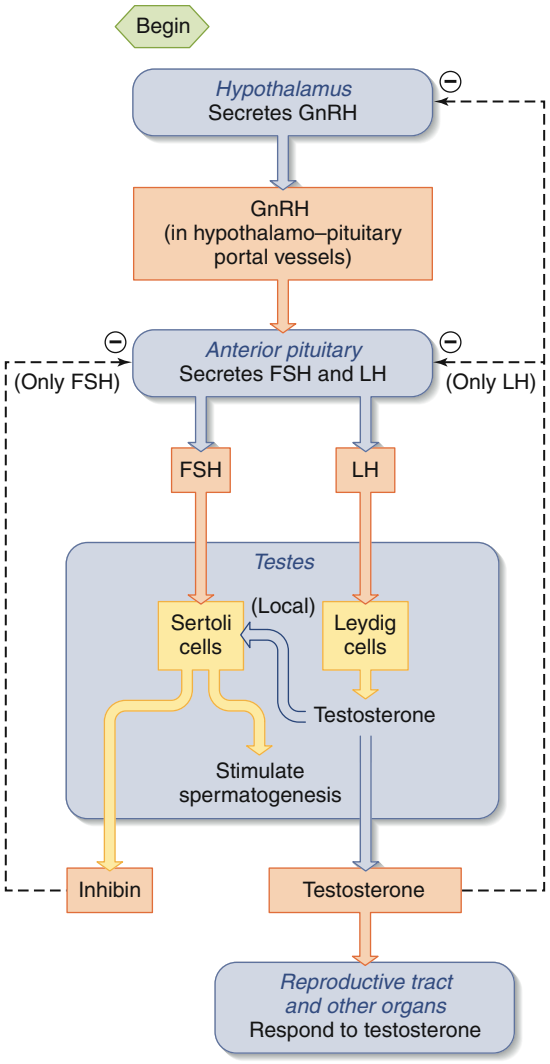
The rhythmic muscular contractions that occur during ejaculation are associated with intense pleasure and many systemic physiological changes, collectively termed an **orgasm.** Marked skeletal muscle contractions occur throughout the body, and there is a transient increase in heart rate and blood pressure. Once ejaculation has occurred, there is a latent period during which a second erection is not possible. The latent period is quite variable but may last from minutes to hours.

17.8 Hormonal Control of Male Reproductive Functions

Control of the Testes

Figure 17.14 summarizes the control of testicular function. In a normal adult man, the GnRH-secreting neuroendocrine cells in the hypothalamus fire a brief burst of action potentials approximately every 90 min, secreting GnRH at these times. The GnRH reaching the anterior pituitary gland via the hypothalamo–hypophyseal portal vessels during each periodic pulse triggers the release of both LH and FSH from the same cell type, although not necessarily in equal amounts. Therefore, plasma concentrations of FSH and LH also show pulsatility—rapid increases followed by slow decreases over the next 90 min or so as the hormones are slowly removed from the plasma.

There is a separation of the actions of FSH and LH within the testes (see Figure 17.14). FSH acts primarily on the Sertoli cells to stimulate the secretion of paracrine agents required for spermatogenesis. LH, by contrast, acts primarily on the Leydig cells to stimulate testosterone secretion. In addition to its many important systemic effects, the testosterone secreted by the Leydig cells also acts locally, in a paracrine manner, by diffusing from the interstitial spaces into the seminiferous tubules. Testosterone enters Sertoli cells, where it facilitates spermatogenesis. Despite the absence of a *direct* effect on cells in the seminiferous tubules, LH exerts an essential *indirect* effect because the testosterone secretion stimulated by LH is required for spermatogenesis.



AP|R **Figure 17.14** Summary of hormonal control of male reproductive function. Note that FSH acts only on the Sertoli cells, whereas LH acts primarily on the Leydig cells. The secretion of FSH is inhibited mainly by inhibin, a protein hormone secreted by the Sertoli cells, and the secretion of LH is inhibited mainly by testosterone, the steroid hormone secreted by the Leydig cells. Testosterone, acting locally on Sertoli cells, stimulates spermatogenesis, whereas FSH stimulates inhibin release from Sertoli cells.

PHYSIOLOGICAL INQUIRY

- Men with decreased anterior pituitary gland function often have decreased sperm production as well as low testosterone concentrations. Would you expect the administration of testosterone alone to restore sperm production to normal?

Answer can be found at end of chapter.

The last components of the hypothalamo–hypophyseal control of male reproduction that remain to be discussed are the negative feedback effects exerted by testicular hormones. Even though FSH and LH are produced by the same cell type, their secretion rates can be altered to different degrees by negative feedback inputs.

Testosterone inhibits LH secretion in two ways (see Figure 17.14): (1) It acts on the hypothalamus to decrease the amplitude of GnRH bursts, which results in a decrease in the secretion of gonadotropins; and (2) it acts directly on the anterior pituitary gland to decrease the LH response to any given amount of GnRH.

How do the testes reduce FSH secretion? The major inhibitory signal, exerted directly on the anterior pituitary gland, is the protein hormone inhibin secreted by the Sertoli cells (see Figure 17.14). This is a logical completion of a negative feedback loop such that FSH stimulates Sertoli cells to increase both spermatogenesis and inhibin production, and inhibin decreases FSH release.

Despite all these complexities, the total amounts of GnRH, LH, FSH, testosterone, and inhibin secreted and of sperm produced do not change dramatically from day to day in the adult male. This is different from the cyclical variations of reproductive function characteristic of the adult woman.

Testosterone

In addition to its essential paracrine action within the testes on spermatogenesis and its negative feedback effects on the hypothalamus and anterior pituitary gland, testosterone exerts many other effects, as summarized in **Table 17.3**.

In Chapter 11, we mentioned that some hormones undergo transformation in their target cells in order to be more effective. This is true of testosterone in some of its target cells. In some cells, like in the adult prostate, after its entry into the cytoplasm, testosterone is converted to dihydrotestosterone (DHT), which is more potent than testosterone (see Figure 17.6). This conversion is catalyzed by the enzyme 5-α-reductase, which is expressed in several androgen target tissues. In certain other target cells (e.g., the brain), testosterone is transformed to estradiol, which is the active hormone in these cells. The enzyme aromatase catalyzes this conversion. In the latter case, the "male" sex hormone is converted to the "female" sex hormone to be active in the male. The fact that, depending on the target cells, testosterone may act as testosterone or be converted to dihydrotestosterone or estradiol has important pathophysiological implications because some genetic (XY) males lack 5-α-reductase or aromatase in some

TABLE 17.3 Effects of Testosterone in the Male

Required for initiation and maintenance of spermatogenesis (acts via Sertoli cells)
Decreases GnRH secretion via an action on the hypothalamus
Inhibits LH secretion via a direct action on the anterior pituitary gland
Induces differentiation of male accessory reproductive organs and maintains their function
Induces male secondary sex characteristics; opposes action of estrogen on breast growth
Stimulates protein anabolism, bone growth, and cessation of bone growth
Required for sex drive and may enhance aggressive behavior
Stimulates erythropoietin secretion by the kidneys

tissues. Therefore, they will exhibit certain signs of testosterone deficiency but not others. For example, an XY fetus with 5-α-reductase deficiency will have normal differentiation of male reproductive duct structures (an effect of testosterone) but will not have normal development of external male genitalia, which requires DHT.

Therapy for ***prostate cancer*** makes use of these facts: Prostate cancer cells are stimulated by dihydrotestosterone, so the cancer can be treated with inhibitors of 5-α-reductase. Furthermore, ***male pattern baldness*** may also be treated with 5-α-reductase inhibitors because DHT tends to promote hair loss from the scalp.

Accessory Reproductive Organs The fetal differentiation and later growth and function of the entire male duct system, glands, and penis all depend upon testosterone (see Figures 17.2 and 17.3). If there is a decrease in testicular function and testosterone synthesis for any reason, the accessory reproductive organs decrease in size, the glands significantly reduce their secretion rates, and the smooth muscle activity of the ducts is diminished. Sex drive (**libido**), erection, and ejaculation are usually impaired. These defects lessen with the administration of testosterone. This would also occur with ***castration*** (removal of the gonads), or with drugs that suppress testosterone secretion or action.

17.9 Puberty

Puberty is the period during which the reproductive organs mature and reproduction becomes possible. In males, this usually occurs between 12 and 16 years of age. Some of the first signs of puberty are due not to gonadal steroids but to increased secretion of adrenal androgens, probably under the stimulation of adrenocorticotropic hormone (ACTH). These androgens cause the very early development of pubic and axillary (armpit) hair, as well as the early stages of the pubertal growth spurt in concert with growth hormone and insulin-like growth factor I (see Chapter 11). The other developments in puberty, however, reflect increased activity of the hypothalamo–pituitary–gonadal axis.

The amplitude and pulse frequency of GnRH secretion increase at puberty, probably stimulated by input from kisspeptin neurons in the hypothalamus. This causes increased secretion of pituitary gonadotropins, which stimulate the seminiferous tubules and testosterone secretion. Testosterone, in addition to its critical role in spermatogenesis, induces the pubertal changes that occur in the accessory reproductive organs, secondary sex characteristics, and sex drive. The mechanism of the brain change that results in increased GnRH secretion at puberty remains unknown. One important event is that the brain becomes less sensitive to the negative feedback effects of gonadal hormones at the time of puberty.

Secondary Sex Characteristics and Growth

Virtually all the male secondary sex characteristics are dependent on testosterone and its metabolite, DHT. For example, a male lacking normal testicular secretion of testosterone before puberty has minimal facial, axillary, or pubic hair. Other androgen-dependent secondary sexual characteristics are deepening of the voice resulting from the growth of the larynx, thick secretion of the skin oil glands (that can cause acne), and the masculine pattern of fat distribution. Androgens also stimulate bone growth, mostly through the stimulation of growth hormone secretion. Ultimately, however, androgens terminate bone growth by causing closure of the bones' epiphyseal plates. Androgens are "anabolic steroids" in that they exert a direct stimulatory effect on protein synthesis in muscle. Finally, androgens stimulate the secretion of the hormone erythropoietin by the kidneys; this is a major reason why men have a higher hematocrit than women.

Behavior

Androgens are essential in males for the development of sex drive at puberty, and they are important in maintaining sex drive (libido) in the adult male. Whether endogenous androgens influence other human behaviors in addition to sexual behavior is not certain. However, androgen-dependent behavioral differences based on gender do exist in other mammals. For example, aggression is greater in males and is androgen-dependent.

Anabolic Steroid Use

The abuse of synthetic androgens (anabolic steroids) is a major public health problem, particularly in younger athletes. Although there are positive effects on muscle mass and athletic performance, the negative effects—such as overstimulation of prostate tissue and increase in aggressiveness—are of significant concern. Ironically, the increase in muscle mass and other masculine characteristics in men belies the fact that negative feedback has decreased GnRH, LH, and FSH secretion. This results in a decrease in both endogenous testosterone and spermatogenesis in Sertoli cells. This actually induces a decrease in testicular size and low sperm count (infertility) as described in the next section. In fact, administration of low doses of anabolic steroids is being tested as a potential male birth control pill.

17.10 Hypogonadism

A decrease in testosterone release from the testes—***hypogonadism***—can be caused by a wide variety of disorders. They can be classified into testicular failure (primary hypogonadism) or a failure to supply the testes with appropriate gonadotrophic stimulus (secondary hypogonadism). The loss of normal testicular androgen production before puberty can lead to a failure to develop secondary sex characteristics such as deepening of the voice, pubic and axillary hair, and increased libido, as well as a failure to develop normal sperm production.

A relatively common genetic cause of primary hypogonadism is ***Klinefelter's syndrome.*** The most common form, occurring in 1 in 500 male births, is an extra X chromosome (XXY) caused by meiotic nondisjunction. Nondisjunction is the failure of a pair of chromosomes to separate during meiosis, such that two chromosome pairs go to one daughter cell and the other daughter cell fails to receive either chromosome. The classic form of Klinefelter's syndrome is caused by the failure of the two sex chromosomes to separate during the first meiotic division in gametogenesis (see Figure 17.1). The extra X chromosome can come from either the egg or the sperm. That is, if nondisjunction occurs in the ovary leading to an XX ovum, an XXY genotype will result if fertilized by a Y sperm. If nondisjunction occurs in the testis leading to an XY sperm, an XXY genotype will result if that sperm fertilizes a normal (single X) ovum.

Male children with the XXY genotype appear normal before puberty. However, after puberty, the testes remain small and poorly developed, with insufficient Leydig and Sertoli cell function. The abnormal Leydig cell function results in decreased concentrations of plasma and testicular testosterone; this, in turn, leads to abnormal development of the seminiferous tubules and therefore decreased sperm production. Normal secondary sex characteristics do not appear, and breast size increases (***gynecomastia***) (**Figure 17.15**). Men with this set of characteristics have relatively high gonadotropin concentrations (LH and FSH) due to loss of androgen and inhibin negative feedback. Men with Klinefelter's syndrome can be treated with androgen-replacement therapy to increase libido and decrease breast size.

Hypogonadism in men can also be caused by a decrease in LH and FSH secretion (secondary hypogonadism). Although there are many causes of the loss of function of pituitary gland cells that secrete LH and FSH, ***hyperprolactinemia*** (increased prolactin in the blood) is one of the most common. Although prolactin probably has only minor physiological effects in men under normal conditions, the pituitary gland still has cells (lactotrophs) that secrete prolactin. Pituitary gland tumors arising from prolactin-secreting cells can develop and secrete too much prolactin. One of the effects of increased prolactin concentrations in the blood is to inhibit LH and FSH secretion from the anterior pituitary gland. (This occurs in men and women.) Hyperprolactinemia is discussed in more detail at the end of this chapter. Another cause of secondary hypogonadism is the total loss of anterior pituitary gland function, called ***hypopituitarism*** or panhypopituitarism. There are many causes of hypopituitarism, including head trauma, infection, and inflammation of the pituitary gland. When all anterior pituitary gland function is decreased or absent, male patients need to be treated with testosterone. In addition, male and female patients are treated with cortisol because of low ACTH, and with thyroid hormone because of low TSH. Children and some adults are also treated with growth hormone injections. In most circumstances, posterior pituitary gland function remains intact so that vasopressin analogs do not need to be administered to avoid diabetes insipidus (see Chapter 14, Section B).

Figure 17.15 Klinefelter's syndrome in a 20-year-old man. Note relatively increased lower/upper body segment ratio, gynecomastia, small penis, and sparse body hair with a female pubic hair pattern.
Courtesy of Glenn D. Braunstein, M.D.

17.11 Andropause

Changes in the male reproductive system with aging are less drastic than those in women (described later in this chapter). Once testosterone and pituitary gland gonadotropin secretions are initiated at puberty, they continue, at least to some extent, throughout adult life. There is a steady decrease, however, in testosterone secretion, beginning at about 40 years of age, which apparently reflects slow deterioration of testicular function and failure of the gonads to respond to the pituitary gland gonadotropins. Along with the decreasing testosterone concentrations in the blood, libido decreases and sperm become less motile. Despite these events, many elderly men continue to be fertile. With aging, some men manifest increased emotional problems, such as depression, and this is sometimes referred to as the ***andropause*** (***male climacteric***). It is not clear, however, what function hormonal changes have in this phenomenon.

SECTION B SUMMARY

Anatomy

I. The male gonads, the testes, produce sperm in the seminiferous tubules and secrete testosterone from the Leydig cells.

Spermatogenesis

I. The meiotic divisions of spermatogenesis result in sperm containing 23 chromosomes, compared to the original 46 of the spermatogonia.
II. The developing germ cells are intimately associated with the Sertoli cells, which perform many functions, as summarized in Table 17.2.

Transport of Sperm

I. From the seminiferous tubules, the sperm pass into the epididymis, where they are concentrated and become mature.
II. The epididymis and vas deferens store the sperm, and the seminal vesicles and prostate secrete most of the semen.
III. Erection of the penis occurs because of vascular engorgement accomplished by relaxation of the small arteries and passive occlusion of the veins.
IV. Ejaculation includes emission—emptying of semen into the urethra—followed by expulsion of the semen from the urethra.

Hormonal Control of Male Reproductive Functions

I. Pulses of hypothalamic GnRH stimulate the anterior pituitary gland to secrete FSH and LH, which then act on the testes: FSH on the Sertoli cells to stimulate spermatogenesis and inhibin secretion, and LH on the Leydig cells to stimulate testosterone secretion.

II. Testosterone, acting locally on the Sertoli cells, is essential for maintaining spermatogenesis.
III. Testosterone exerts a negative feedback inhibition on both the hypothalamus and the anterior pituitary gland to reduce mainly LH secretion. Inhibin exerts a negative feedback inhibition on FSH secretion.
IV. Testosterone maintains the accessory reproductive organs and male secondary sex characteristics and stimulates the growth of muscle and bone. In many of its target cells, it must first undergo transformation to dihydrotestosterone or to estrogen.

Puberty

I. A change in brain function at the onset of puberty results in increases in the hypothalamo–pituitary–gonadal axis (because of increases in GnRH).
II. The first sign of puberty is the appearance of pubic and axillary hair.

Hypogonadism

I. Male hypogonadism is a decrease in testicular function. Klinefelter's syndrome (usually XXY genotype) is a common cause of male hypogonadism.
II. Hypogonadism can be caused by testicular failure (primary hypogonadism) or a loss of gonadotrophic stimuli to the testes (secondary hypogonadism).

Andropause

I. The andropause is a decrease in testosterone with aging (but usually not a complete cessation of androgen production).

SECTION B REVIEW QUESTIONS

1. Describe the sequence of events leading from spermatogonia to sperm.
2. List the functions of the Sertoli cells.
3. Describe the path sperm take from the seminiferous tubules to the urethra.
4. Describe the roles of the prostate gland, seminal vesicles, and bulbourethral glands in the formation of semen.
5. Describe the neural control of erection and ejaculation.
6. Diagram the hormonal chain controlling the testes. Contrast the effects of FSH and LH.
7. What are the feedback controls from the testes to the hypothalamus and pituitary gland?
8. Define *puberty* in the male. When does it usually occur?
9. List the effects of androgens on accessory reproductive organs, secondary sex characteristics, growth, protein metabolism, and behavior.
10. Describe the conversion of testosterone to DHT and estrogen.
11. How does hyperprolactinemia cause hypogonadism?

SECTION B KEY TERMS

17.5 Anatomy

bulbourethral glands
ejaculatory ducts
epididymis
gestation
prostate gland
rete testis
scrotum
semen
seminal vesicles
seminiferous tubules
spermatic cord
spermatogenesis
vas deferens

17.6 Spermatogenesis

acrosome
androgen-binding protein (ABP)
Leydig cells
Sertoli cell barrier
Sertoli cells
spermatogonium

17.7 Transport of Sperm

ejaculation
erection
nitric oxide
orgasm

17.8 Hormonal Control of Male Reproductive Functions

libido

17.9 Puberty

puberty

SECTION B CLINICAL TERMS

17.7 Transport of Sperm

cGMP-phosphodiesterase type 5 inhibitors
erectile dysfunction
vasectomy

17.8 Hormonal Control of Male Reproductive Functions

castration
male pattern baldness
prostate cancer

17.10 Hypogonadism

gynecomastia
hyperprolactinemia
hypogonadism
hypopituitarism
Klinefelter's syndrome

17.11 Andropause

andropause (male climacteric)

SECTION C
Female Reproductive Physiology

Unlike the continuous sperm production of the male, the maturation of the female gamete (the ovum) followed by its release from the ovary—**ovulation**—is cyclical. The female germ cells, like those of the male, have different names at different stages of development. However, the term **egg** is often used to refer to the female germ cells; we will use the two terms — egg and ovum — interchangeably hereafter. The structure and function of certain components of the female reproductive system (e.g., the uterus) are synchronized with these ovarian cycles. In human beings, these cycles are called **menstrual cycles.** The length of a menstrual cycle varies from woman to woman, and even in any particular woman, but averages about 28 days. The first day of menstrual flow (**menstruation**) is designated as day 1.

Menstruation is the result of events occurring in the uterus. However, the uterine events of the menstrual cycle are due to cyclical changes in hormone secretion by the ovaries. The ovaries are also the sites for the maturation of gametes. One oocyte usually becomes fully mature and is ovulated around the middle of each menstrual cycle.

The interactions among the ovaries, hypothalamus, and anterior pituitary gland produce the cyclical changes in the ovaries that result in (1) maturation of a gamete each cycle and

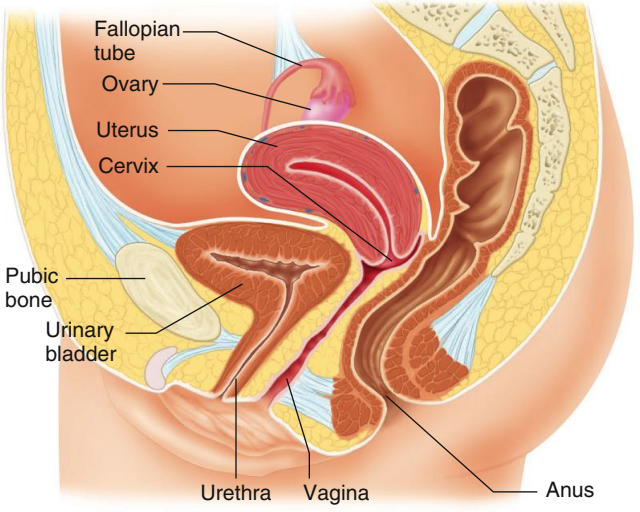
(2) hormone secretions that cause cyclical changes in all of the female reproductive organs (particularly the uterus). The interaction of these different structures in the adult female reproductive cycle is an excellent example of the general principle of physiology that the functions of organ systems are coordinated with each other. These changes prepare the uterus to receive and nourish the developing embryo; only when there is no pregnancy does menstruation occur.

17.12 Anatomy

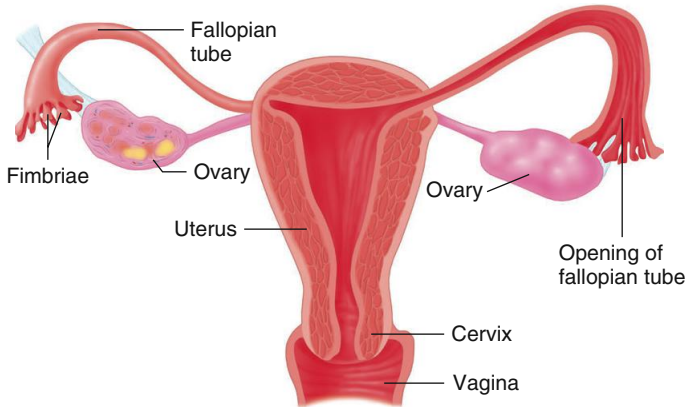
The female reproductive system includes the two ovaries and the female reproductive tract—two **fallopian tubes** (or oviducts), the uterus, the cervix, and the vagina. These structures are termed the **female internal genitalia** (Figures 17.16 and 17.17). Unlike in the male, the urinary and reproductive duct systems of the female are separate from each other. Before proceeding with this section, the reader should review Figures 17.2 and 17.3 concerning the development of the internal and external female genitalia.

The ovaries are almond-sized organs in the upper pelvic cavity, one on each side of the uterus. The ends of the fallopian tubes are not directly attached to the ovaries but open into the abdominal cavity close to them. The opening of each fallopian tube is funnel-shaped and surrounded by long, fingerlike projections (the **fimbriae**) lined with ciliated epithelium. The other ends of the fallopian tubes are attached to the uterus and empty directly into its cavity. The **uterus** is a hollow, thick-walled, muscular organ lying between the urinary bladder and rectum. The uterus is the source of menstrual flow and is where the fetus develops during pregnancy. The lower portion of the uterus is the **cervix.** A small opening in the cervix leads to the **vagina,** the canal leading from the uterus to the outside.

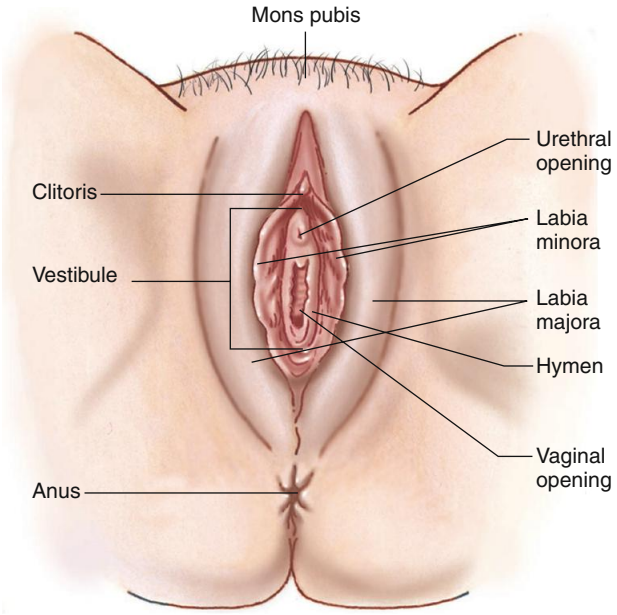
The **female external genitalia** (Figure 17.18) include the mons pubis, labia majora, labia minora, clitoris, vestibule of the vagina, and vestibular glands. The term **vulva** is another name for all these structures. The mons pubis is the rounded fatty prominence over the junction of the pubic bones. The labia majora, the female homologue of the scrotum, are two prominent skin folds



AP|R **Figure 17.16** Side view of a section through a female pelvis.



AP|R **Figure 17.17** Frontal view cut away on the right (left side of the body) to show the continuity between the organs of the female reproductive duct system—fallopian tubes, uterus, and vagina.



AP|R **Figure 17.18** Female external genitalia.

that form the outer lips of the vulva. (The terms *homologous* and *analogous* mean that the two structures are derived embryologically from the same source [see Figures 17.2 and 17.3] and/or have similar functions.) The labia minora are small skin folds lying between the labia majora. They surround the urethral and vaginal openings, and the area thus enclosed is the vestibule, into which secretory glands empty. The vaginal opening lies behind the opening of the urethra. Partially overlying the vaginal opening is a thin fold of mucous membrane, the **hymen.** The **clitoris,** the female homologue of the penis, is an erectile structure located at the top of the vulva.

17.13 Ovarian Functions

The ovary, like the testis, serves several functions: (1) **oogenesis,** the production of gametes during the fetal period; (2) maturation of the oocyte; (3) expulsion of the mature oocyte (ovulation); and (4) secretion of the female sex steroid hormones (estrogen and

progesterone), as well as the protein hormone inhibin. Before ovulation, the maturation of the oocyte and endocrine functions of the ovaries take place in a single structure, the follicle. After ovulation, the follicle, now without an egg, differentiates into a corpus luteum, the functions of which are described later.

Oogenesis

At birth, the ovaries contain an estimated 2 to 4 million eggs, and no new ones appear after birth. Only a few, perhaps 400, will be ovulated during a woman's lifetime. All the others degenerate at some point in their development so that few, if any, remain by the time a woman reaches approximately 50 years of age. One result of this developmental pattern is that the eggs ovulated near age 50 are 35 to 40 years older than those ovulated just after puberty. It is possible that certain chromosomal defects more common among children born to older women are the result of aging changes in the egg.

During early fetal development, the primitive germ cells, or **oogonia** (singular, **oogonium**) undergo numerous mitotic divisions (**Figure 17.19**). Oogonia are analogous to spermatogonia in the male (see Figure 17.1). Around the seventh month of gestation, the fetal oogonia cease dividing. Current thinking is that from this point on, no new germ cells are generated.

During fetal life, all the oogonia develop into primary oocytes (analogous to primary spermatocytes), which then begin a first meiotic division by replicating their DNA. They do not, however, complete the division in the fetus. Accordingly, all the eggs present at birth are primary oocytes containing 46 chromosomes, each with two sister chromatids. The cells are said to be in a state of meiotic arrest.

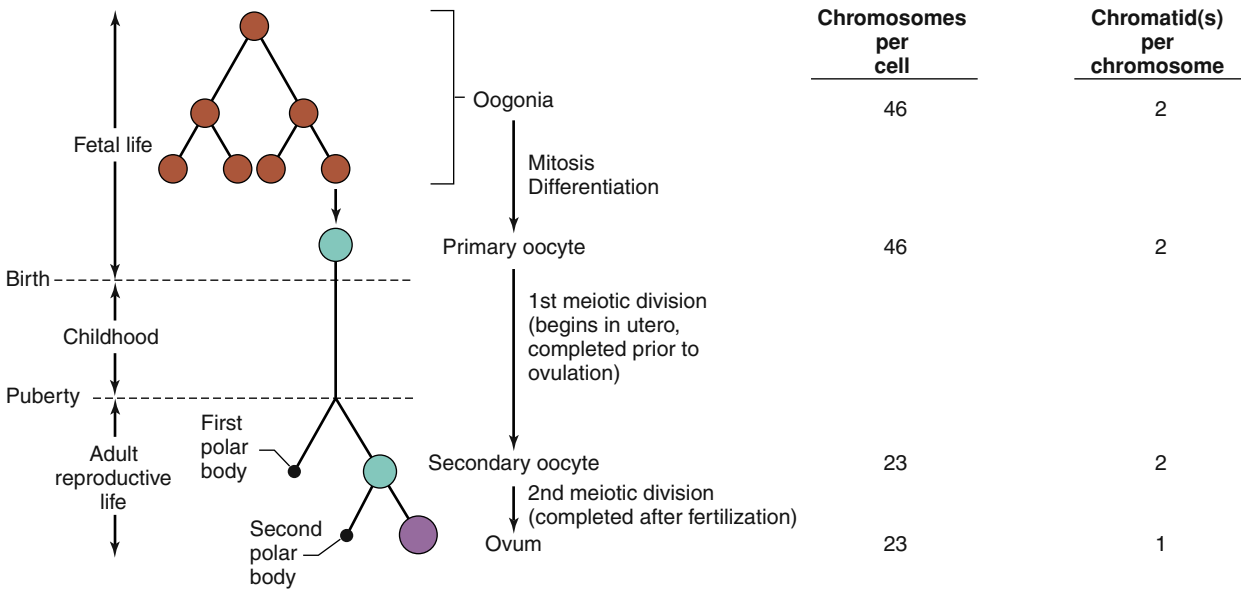
This state continues until puberty and the onset of renewed activity in the ovaries. Indeed, only those primary oocytes destined for ovulation will complete the first meiotic division, for it occurs just before the egg is ovulated. This division is analogous to the division of the primary spermatocyte, and each daughter cell receives 23 chromosomes, each with two chromatids. In this division, however, one of the two daughter cells, the secondary oocyte, retains virtually all the cytoplasm. The other, the first polar body, is very small and nonfunctional. The primary oocyte, which is already as large as the egg will be, passes on to the secondary oocyte just half of its chromosomes but almost all of its nutrient-rich cytoplasm.

The second meiotic division occurs in a fallopian tube *after ovulation,* but only if the secondary oocyte is fertilized—that is, penetrated by a sperm (see Figure 17.1). As a result of this second meiotic division, the daughter cells each receive 23 chromosomes, each with a single chromatid. Once again, one daughter cell retains nearly all the cytoplasm. The other daughter cell, the second polar body, is very small and nonfunctional. The net result of oogenesis is that each primary oocyte can produce only one ovum (see Figure 17.19). In contrast, each primary spermatocyte produces four viable spermatozoa.

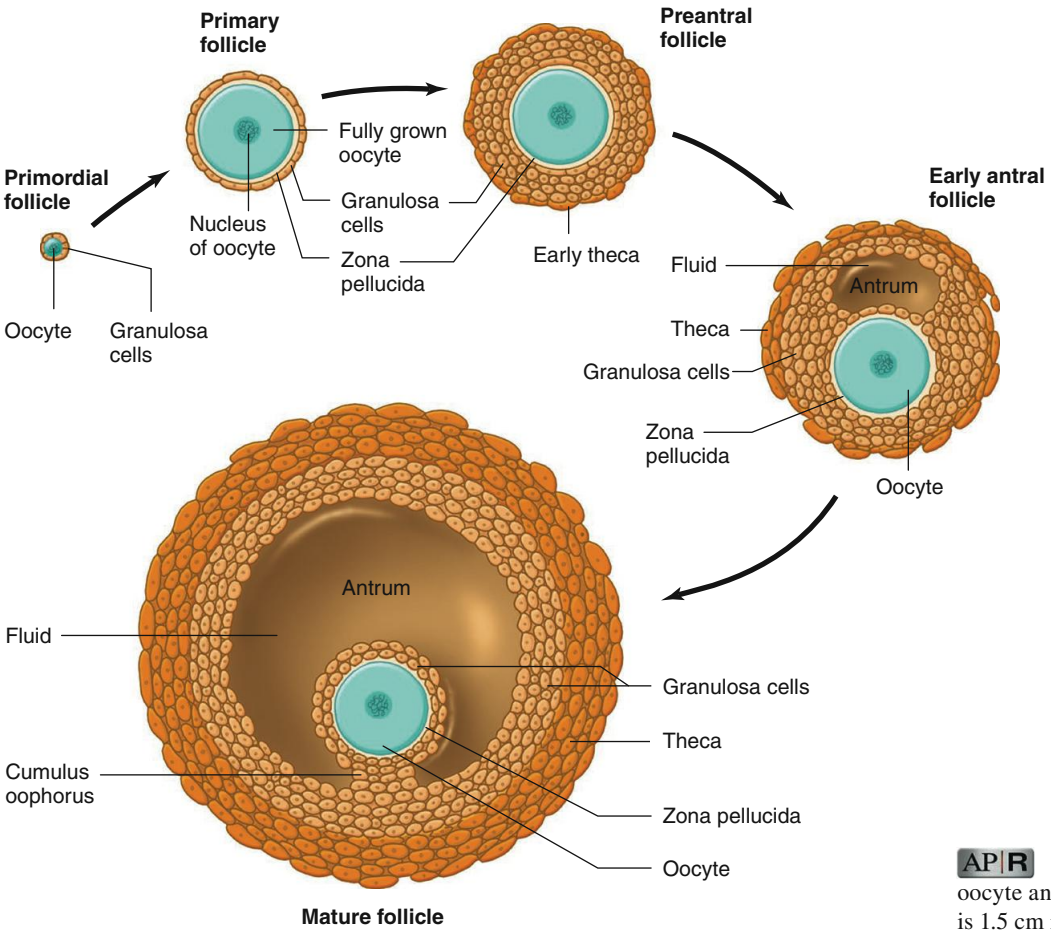
Follicle Growth

Throughout their life in the ovaries, the eggs exist in structures known as **follicles.** Follicles begin as **primordial follicles,** which consist of one primary oocyte surrounded by a single layer of cells called **granulosa cells.** The granulosa cells secrete estrogen, small amounts of progesterone (just before ovulation), and inhibin. Further development from the primordial follicle stage (**Figure 17.20**) is characterized by an increase in the size of the oocyte; a proliferation of the granulosa cells into multiple layers; and the separation of the oocyte from the inner granulosa cells by a thick layer of material, the **zona pellucida,** secreted by the surrounding follicular cells. The zona pellucida contains glycoproteins that have a function in the binding of a sperm cell to the surface of an egg after ovulation.

Despite the presence of a zona pellucida, the inner layer of granulosa cells remains closely associated with the oocyte by means of cytoplasmic processes that traverse the zona pellucida and form gap junctions with the oocyte. Through these gap junctions, nutrients and chemical messengers are passed to the oocyte.



AP|R **Figure 17.19** Summary of oogenesis. Compare with the male pattern in Figure 17.10. The secondary oocyte is ovulated and does not complete its meiotic division unless it is penetrated (fertilized) by a sperm. Once the nuclei of the ovum and sperm merge to form a diploid cell, the structure is called a fertilized ovum or zygote. Note that each primary oocyte yields only one secondary oocyte, which can yield only one ovum.



AP|R **Figure 17.20** Development of a human oocyte and ovarian follicle. The fully mature follicle is 1.5 cm in diameter. Blood vessels are not shown.

As the follicle grows by proliferation of granulosa cells, connective-tissue cells surrounding the granulosa cells differentiate and form layers of cells known as the **theca,** which function together with the granulosa cells in the synthesis of estrogen. Shortly after this, the primary oocyte reaches full size (~115 μm in diameter), and a fluid-filled space, the **antrum,** begins to form in the midst of the granulosa cells as a result of fluid they secrete.

The progression of some primordial follicles to the preantral and early antral stages (see Figure 17.20) occurs throughout infancy and childhood and then during the entire menstrual cycle. Therefore, although most of the follicles in the ovaries are still primordial, a nearly constant number of preantral and early antral follicles are also always present. At the beginning of each menstrual cycle, 10 to 25 of these preantral and early antral follicles begin to develop into larger antral follicles. About one week into the cycle, a further selection process occurs: Only one of the larger antral follicles, the **dominant follicle,** continues to develop. The exact process by which a follicle is selected for dominance is not known, but it is likely related to the amount of estrogen produced locally within the follicle. (This is probably why hyperstimulation of infertile women with gonadotropin injections can result in the maturation of many follicles.) The nondominant follicles (in both ovaries) that had begun to enlarge undergo a degenerative process called **atresia,** which is an example of programmed cell death, or apoptosis. The eggs in the degenerating follicles also die.

Atresia is not limited to just antral follicles, however, for follicles can undergo atresia at any stage of development. Indeed, this process is already occurring in the female fetus, so that the 2 to 4 million follicles and eggs present at birth represent only a small fraction of those present earlier in gestation. Atresia then continues all through prepubertal life so that only 200,000 to 400,000 follicles remain when active reproductive life begins. Of these, all but about 400 will undergo atresia during a woman's reproductive life. Therefore, 99.99% of the ovarian follicles present at birth will undergo atresia.

The dominant follicle enlarges as a result of an increase in fluid, causing the antrum to expand. As this occurs, the granulosa cell layers surrounding the egg form a mound that projects into the antrum and is called the **cumulus oophorus** (see Figure 17.20). As the time of ovulation approaches, the egg (a primary oocyte) emerges from meiotic arrest and completes its first meiotic division to become a secondary oocyte. The cumulus separates from the follicle wall so that it and the oocyte float free in the antral fluid. The mature follicle (also called a **graafian follicle**) becomes so large (diameter about 1.5 cm) that it balloons out on the surface of the ovary.

Ovulation occurs when the thin walls of the follicle and ovary rupture at the site where they are joined because of enzymatic digestion. The secondary oocyte, surrounded by its tightly adhering zona pellucida and granulosa cells, as well as the cumulus, is carried out of the ovary and onto the ovarian surface by the antral fluid. All this happens on approximately day 14 of the menstrual cycle.

Occasionally, two or more follicles reach maturity, and more than one egg may be ovulated. This is the more common cause of multiple births. In such cases, the siblings are **fraternal**

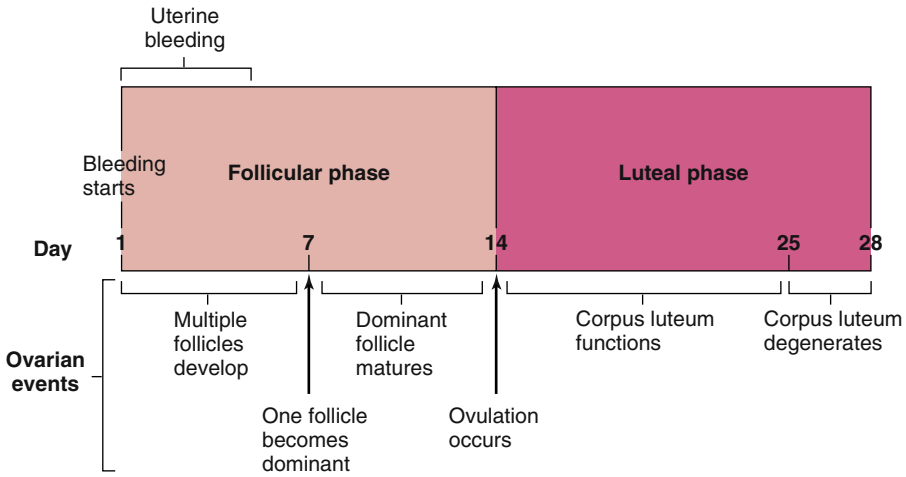


Figure 17.21 Summary of ovarian events during a menstrual cycle (if fertilization does not occur). The first day of the cycle is named for a uterine event—the onset of bleeding—even though ovarian events are used to denote the cycle phases.

(**dizygotic**) **twins,** not identical, because the eggs carry different sets of genes and are fertilized by different sperm. We will describe later how identical twins form.

Formation of the Corpus Luteum

After the mature follicle discharges its antral fluid and egg, it collapses around the antrum and undergoes a rapid transformation. The granulosa cells enlarge greatly, and the entire glandlike structure formed is called the **corpus luteum,** which secretes estrogen, progesterone, and inhibin. If the discharged egg, now in a fallopian tube, is not fertilized by fusing with a sperm cell, the corpus luteum reaches its maximum development within approximately 10 days. It then rapidly degenerates by apoptosis. As we will see, it is the loss of corpus luteum function that leads to menstruation and the beginning of a new menstrual cycle.

In terms of ovarian function, therefore, the menstrual cycle may be divided into two phases approximately equal in length and separated by ovulation (Figure 17.21): (1) the **follicular phase,** during which a mature follicle and secondary oocyte develop; and (2) the **luteal phase,** beginning after ovulation and lasting until the death of the corpus luteum. As you will see, these ovarian phases correlate with and control the changes in the appearance of the uterine lining (to be described subsequently).

Sites of Synthesis of Ovarian Hormones

The synthesis of gonadal steroids was introduced in Figure 17.6 and can be summarized as follows. Estrogen (primarily estradiol and estrone) is synthesized and released into the blood during the follicular phase mainly by the granulosa cells. After ovulation, estrogen is synthesized and released by the corpus luteum. Progesterone, the other major ovarian steroid hormone, is synthesized and released in very small amounts by the granulosa and theca cells just before ovulation, but its major source is the corpus luteum. Inhibin is secreted by both the granulosa cells and the corpus luteum.

17.14 Control of Ovarian Function

The major factors controlling ovarian function are analogous to the controls described for testicular function. They constitute a hormonal system made up of GnRH, the anterior pituitary gland gonadotropins FSH and LH, and gonadal sex hormones—estrogen and progesterone.

As in the male, the entire sequence of controls depends upon the pulsatile secretion of GnRH from hypothalamic neuroendocrine cells. In the female, however, the frequency and amplitude of these pulses change over the course of the menstrual cycle. Also, the responsiveness both of the anterior pituitary gland to GnRH and of the ovaries to FSH and LH changes during the cycle.

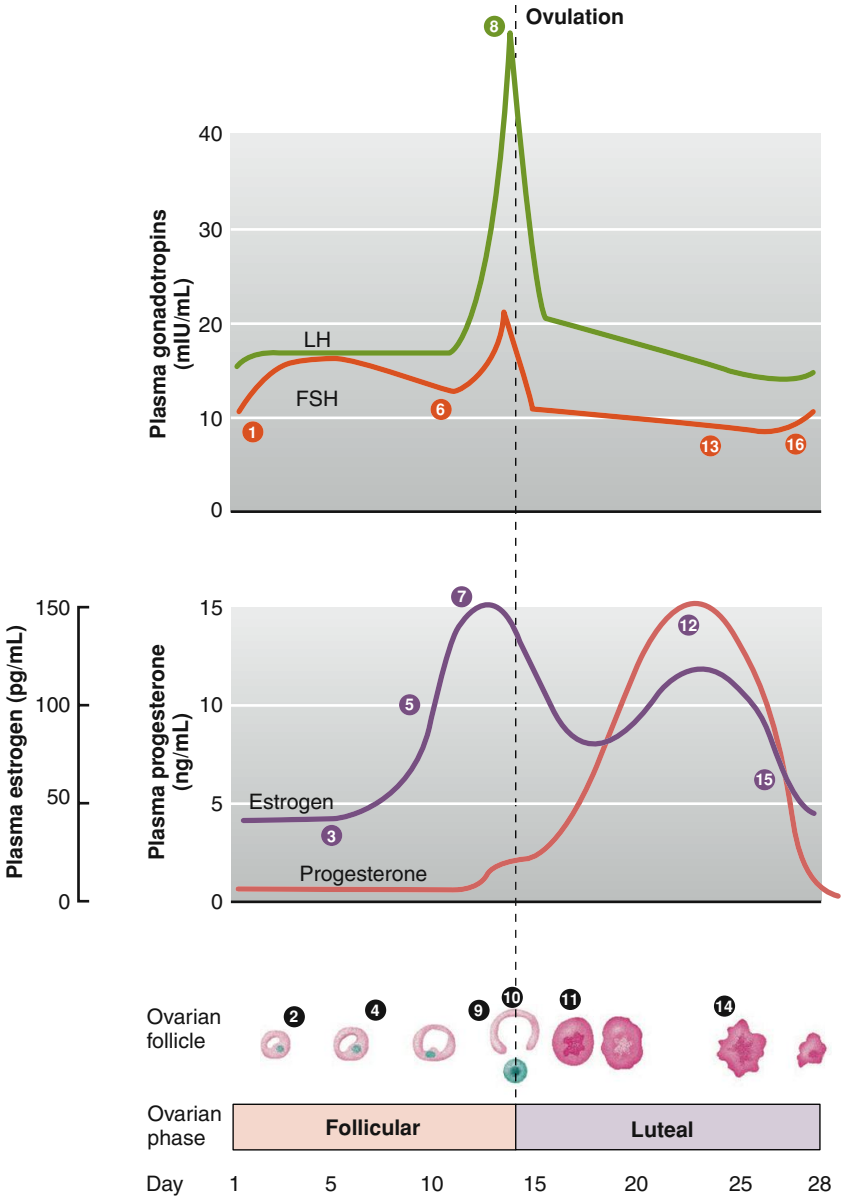
Let us look first at the patterns of hormone concentrations in systemic plasma during a normal menstrual cycle (Figure 17.22). (GnRH is not shown because its concentration in systemic plasma does not reflect GnRH secretion from the hypothalamus into the hypothalamo–hypophyseal portal blood vessels.) In Figure 17.22, the lines are plots of average daily concentrations; that is, the increases and decreases during a single day stemming from episodic secretion have been averaged. For now, ignore both the legend and circled numbers in this figure because we are concerned here only with hormonal patterns and not the explanations of these patterns.

FSH increases in the early part of the follicular phase and then steadily decreases throughout the remainder of the cycle except for a small midcycle peak. LH is constant during most of the follicular phase but then shows a very large midcycle increase—the **LH surge**—peaking approximately 18 h *before* ovulation. This is followed by a rapid decrease and then a further slow decline during the luteal phase.

After remaining fairly low and stable for the first week, the plasma concentration of estrogen increases rapidly during the second week as the dominant ovarian follicle grows and secretes more estrogen. Estrogen then starts decreasing shortly before LH has peaked. This is followed by a second increase due to secretion by the corpus luteum and, finally, a rapid decrease during the last days of the cycle. Very small amounts of progesterone are released by the ovaries during the follicular phase until just before ovulation. Very soon after ovulation, the developing corpus luteum begins to release large amounts of progesterone; from this point, the progesterone pattern is similar to that for estrogen.

Not shown in Figure 17.22 is the plasma concentration of inhibin. Its pattern is similar to that of estrogen: It increases during the late follicular phase, remains high during the luteal phase, and then decreases as the corpus luteum degenerates.

The following discussion will explain how these hormonal changes are interrelated to produce a self-cycling pattern. The numbers in Figure 17.22 are keyed to the text. The feedback effects of the ovarian hormones to be described in the text are summarized for reference in Table 17.4.



AP|R Figure 17.22 Summary of systemic plasma hormone concentrations and ovarian events during the menstrual cycle. The events marked by the circled numbers are described later in the text and are listed here to provide a summary. The arrows in this legend denote causality. ❶ FSH and LH secretion increase (because plasma estrogen concentration is low and exerting little negative feedback). → ❷ Multiple antral follicles begin to enlarge and secrete estrogen. → ❸ Plasma estrogen concentration begins to rise. ❹ One follicle becomes dominant and secretes very large amounts of estrogen. → ❺ Plasma estrogen concentration increases markedly. → ❻ FSH secretion and plasma FSH concentration decrease, causing atresia of nondominant follicles, but then ❼ increasing plasma estrogen exerts a "positive" feedback on gonadotropin secretion. → ❽ An LH surge is triggered. → ❾ The egg completes its first meiotic division and cytoplasmic maturation while the follicle secretes less estrogen accompanied by some progesterone, ❿ ovulation occurs, and ⓫ the corpus luteum forms and begins to secrete large amounts of both estrogen and progesterone. → ⓬ Plasma estrogen and progesterone increase. → ⓭ FSH and LH secretion are inhibited and their plasma concentrations decrease. ⓮ The corpus luteum begins to degenerate and decrease its hormone secretion. → ⓯ Plasma estrogen and progesterone concentrations decrease. → ⓰ FSH and LH secretions begin to increase, and a new cycle begins (back to ❶).

PHYSIOLOGICAL INQUIRY

- (1) Why do plasma FSH concentrations increase at the end of the luteal phase? (2) What naturally occurring event could rescue the corpus luteum and prevent its degeneration starting in the middle of the luteal phase?

Answer can be found at end of chapter.

Follicle Development and Estrogen Synthesis During the Early and Middle Follicular Phases

Before reading this section, the reader should review Figure 17.20 to appreciate the structure of the developing follicles. There are always a number of preantral and early antral follicles in the ovary between puberty and menopause. Further development of the follicle beyond these stages requires stimulation by FSH. Prior to puberty, the plasma concentration of FSH is too low to induce such development. This changes during puberty, and menstrual cycles commence. The increase in FSH secretion that occurs as one cycle ends and the next begins (numbers ⓰ to ❶ in Figure 17.22) provides this stimulation, and a group of preantral and early antral follicles enlarge ❷. The increase in FSH at the end of the cycle (⓰ to ❶) is due to release from negative feedback inhibition because of decreased progesterone, estrogen, and inhibin from the dying corpus luteum.

During the next week or so, there is a division of labor between the actions of FSH and LH on the follicles: FSH acts on the granulosa cells, and LH acts on the theca cells. The reasons are that, at this point in the cycle, granulosa cells have FSH receptors but no LH receptors and theca cells have just the reverse. FSH stimulates the granulosa cells to multiply and produce estrogen, and it also stimulates enlargement of the antrum. Some of the estrogen produced diffuses into the blood and maintains a relatively stable plasma concentration ❸. Estrogen also functions as a paracrine or autocrine agent within the follicle, where, along with FSH and growth factors, it stimulates the proliferation of granulosa cells, which further increases estrogen production.

The granulosa cells, however, require help to produce estrogen because they are deficient in the enzymes required to produce the androgen precursors of estrogen (see Figure 17.6). The granulosa cells are aided by the theca cells. As shown in **Figure 17.23**, LH acts upon the theca cells, stimulating them not only to proliferate but also to synthesize androgens. The androgens diffuse into the granulosa cells and are converted to estrogen by aromatase. Therefore, the secretion of estrogen by the granulosa cells requires the interplay of both types of follicle cells and both pituitary gland gonadotropins.

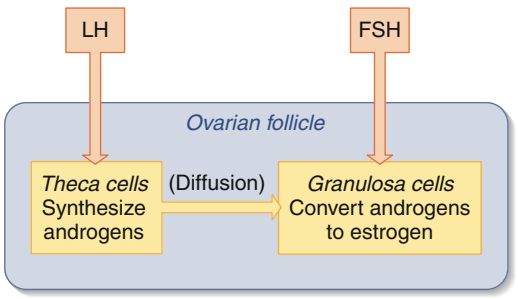
At this point, it is worthwhile to emphasize the similarities that the two types of follicle cells bear to cells of the testes during this period of the cycle. The granulosa cell is similar to the Sertoli cell in that it controls the microenvironment in which the germ cell

TABLE 17.4 Summary of Major Feedback Effects of Estrogen, Progesterone, and Inhibin

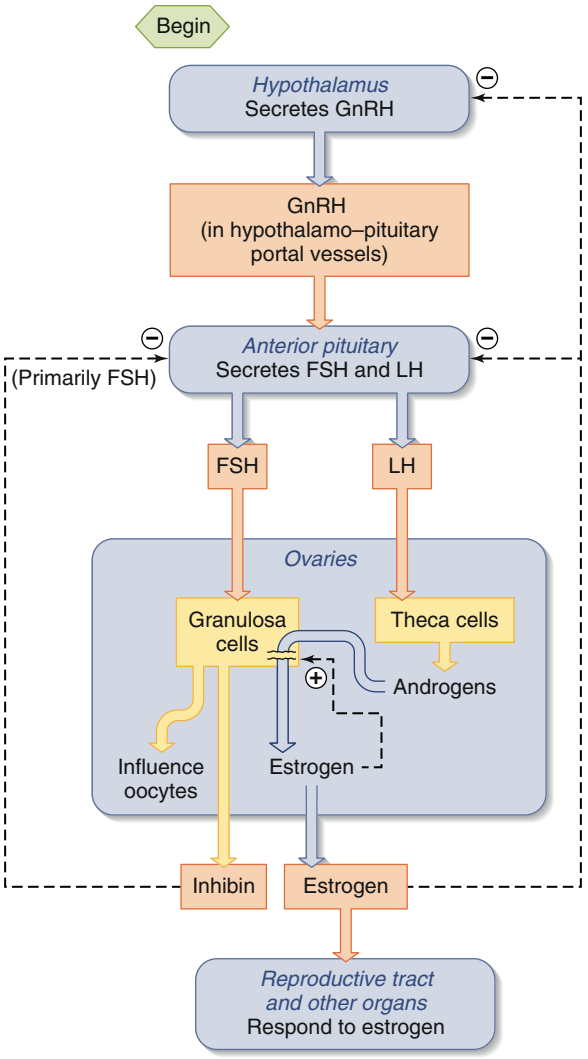
Estrogen, in low plasma concentrations, causes the anterior pituitary gland to secrete less FSH and LH in response to GnRH and also inhibit the hypothalamic neurons that secrete GnRH. *Result:* Negative feedback inhibition of FSH and LH secretion during the early and middle follicular phase.
Inhibin acts on the pituitary gland to inhibit the secretion of FSH. *Result:* Negative feedback inhibition of FSH secretion.
Estrogen, when increasing dramatically, causes anterior pituitary gland cells to secrete more LH and FSH in response to GnRH. Estrogen also stimulates the hypothalamic neurons that secrete GnRH. *Result:* Positive feedback stimulation of the LH surge, which triggers ovulation.
High plasma concentrations of progesterone, in the presence of estrogen, inhibit the hypothalamic neurons that secrete GnRH. *Result:* Negative feedback inhibition of FSH and LH secretion and prevention of LH surges during the luteal phase and pregnancy.

develops and matures, and it is stimulated by both FSH and the major gonadal sex hormone. The theca cell is similar to the Leydig cell in that it produces mainly androgens and is stimulated to do so by LH. This makes sense when one considers that the testes and ovaries arise from the same embryonic structure (see Figure 17.2).

By the beginning of the second week, one follicle has become dominant (number ❹ in Figure 17.22) and the other developing follicles degenerate. The reason for this is that, as shown in Figure 17.22, the plasma concentration of FSH, a crucial factor necessary for the survival of the follicle cells, begins to decrease and there is no longer enough FSH to prevent atresia. Although it is not known precisely how a specific follicle is selected to become dominant, there are several reasons why this follicle, having gained a head start, is able to continue maturation. First, its granulosa cells have achieved a greater sensitivity to FSH because of increased numbers of FSH receptors. Second, its granulosa cells now begin to be stimulated not only by FSH but by LH as well. We emphasized in the previous section that, during the first week or so of the follicular phase, LH acts only on the theca cells. As the dominant follicle matures, this situation changes, and LH receptors, induced by FSH, also begin to appear in large numbers on the granulosa cells. The increase in local estrogen within the follicle results from these factors.



AP|R **Figure 17.23** Control of estrogen synthesis during the early and middle follicular phases. (The major androgen secreted by the theca cells is androstenedione.) Androgen diffusing from theca to granulosa cell passes through the basement membrane (not shown).



AP|R **Figure 17.24** Summary of hormonal control of ovarian function during the early and middle follicular phases. Compare with the analogous pattern of the male (see Figure 17.14). Inhibin is a protein hormone that inhibits FSH secretion. The wavy broken lines in the granulosa cells denote the conversion of androgens to estrogen in these cells, as shown in Figure 17.23. The dashed line with an arrow within the ovaries indicates that estrogen increases granulosa cell function (local positive feedback).

PHYSIOLOGICAL INQUIRY

- A 30-year-old woman has failed to have menstrual cycles for the past few months; her pregnancy test is negative. Her plasma FSH and LH concentrations are increased, whereas her plasma estrogen concentrations are low. What is the likely cause of her failure to menstruate?

Answer can be found at end of chapter.

The dominant follicle now starts to secrete enough estrogen that the plasma concentration of this steroid begins to increase ❺. We can now also explain why plasma FSH starts to decrease at this time. Estrogen, at these still relatively low concentrations, is exerting a *negative feedback* inhibition on the secretion of gonadotropins (Table 17.4 and **Figure 17.24**). A major site of estrogen action is the anterior pituitary gland, where it decreases the amount of FSH

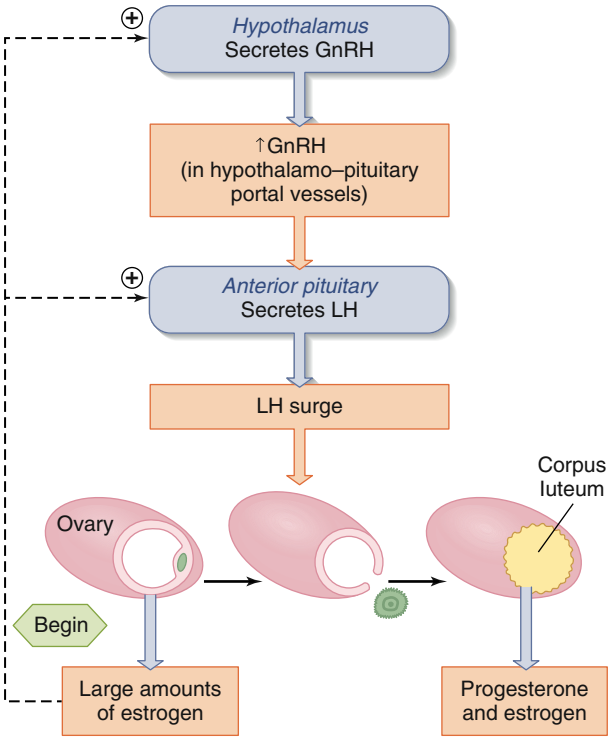
and LH secreted in response to any given amount of GnRH. Estrogen also acts on the hypothalamus to decrease the amplitude of GnRH pulses and, therefore, the total amount of GnRH secreted over any time period.

As expected from this negative feedback, the plasma concentration of FSH (and LH, to a lesser extent) begins to decrease as a result of the increasing concentration of estrogen as the follicular phase continues (❻ in Figure 17.22). One reason that FSH decreases more than LH is that the granulosa cells also secrete inhibin, which, as in the male, primarily inhibits the secretion of FSH (see Figure 17.24).

LH Surge and Ovulation

The inhibitory effect of estrogen on gonadotropin secretion occurs when plasma estrogen concentration is relatively low, as during the early and middle follicular phases. In contrast, increasing plasma concentrations of estrogen for 1 to 2 days, as occurs during the estrogen peak of the late follicular phase (❼ in Figure 17.22), acts upon the anterior pituitary gland to enhance the sensitivity of gonadotropin-releasing cells to GnRH (Table 17.4 and **Figure 17.25**) and also stimulates GnRH release from the hypothalamus. The estrogen-induced increase in GnRH release may be mediated by activation of kisspeptin neurons in the hypothalamus described earlier in this chapter. The stimulation of gonadotropin release by estrogen is a particularly important example of *positive feedback* in physiological control systems, and normal menstrual cycles and ovulation would not occur without it.

The net result is that rapidly increasing estrogen leads to the LH surge (❺ ❽ in Figure 17.22). As shown in Figure 17.22 ❾, an increase in FSH and progesterone also occurs at the time of the LH surge.



AP|R **Figure 17.25** In the late follicular phase, the dominant follicle secretes large amounts of estrogen, which act on the anterior pituitary gland and the hypothalamus to cause an LH surge. The increased plasma LH then triggers both ovulation and formation of the corpus luteum. These actions of LH are mediated via the granulosa cells.

The midcycle surge of LH is the primary event that induces ovulation. The high plasma concentration of LH acts upon the granulosa cells to cause the events, presented in **Table 17.5**, that culminate in ovulation ❿, as indicated by the dashed vertical line in Figure 17.22.

The function of the granulosa cells in mediating the effects of the LH surge is the last in the series of these cells' functions described in this chapter. They are all summarized in **Table 17.6**. The LH surge peaks and starts to decline just as ovulation occurs. Although the precise signal to terminate the LH surge is not known, it may be due to negative feedback from the small increase in progesterone described earlier (see Figure 17.22) as well as down-regulation of LH receptors in the dominant follicle of the ovary, thereby reducing estrogen-induced positive feedback.

TABLE 17.5 Sequence of Effects of the LH Surge on Ovarian Function

1. The primary oocyte completes its first meiotic division and undergoes cytoplasmic changes that prepare the ovum for implantation should fertilization occur. These LH effects on the oocyte are mediated by messengers released from the granulosa cells in response to LH.
2. Antrum size (fluid volume) and blood flow to the follicle increase markedly.
3. The granulosa cells begin releasing progesterone and decreasing the release of estrogen, which accounts for the midcycle decrease in plasma estrogen concentration and the small rise in plasma progesterone concentration just before ovulation.
4. Enzymes and prostaglandins, synthesized by the granulosa cells, break down the follicular–ovarian membranes. These weakened membranes rupture, allowing the oocyte and its surrounding granulosa cells to be carried out onto the surface of the ovary.
5. The remaining granulosa cells of the ruptured follicle (along with the theca cells of that follicle) are transformed into the corpus luteum, which begins to release progesterone and estrogen.

TABLE 17.6 Functions of Granulosa Cells

Nourish oocyte
Secrete chemical messengers that influence the oocyte and the theca cells
Secrete antral fluid
The site of action for estrogen and FSH in the control of follicle development during early and middle follicular phases
Express aromatase, which converts androgen (from theca cells) to estrogen
Secrete inhibin, which inhibits FSH secretion via an action on the pituitary gland
The site of action for LH induction of changes in the oocyte and follicle culminating in ovulation and formation of the corpus luteum

The Luteal Phase

The LH surge not only induces ovulation by the mature follicle but also stimulates the reactions that transform the remaining granulosa and theca cells of that follicle into a corpus luteum (⓫ in Figure 17.22). A low but adequate LH concentration maintains the function of the corpus luteum for about 14 days.

During its short life in the nonpregnant woman, the corpus luteum secretes large quantities of progesterone and estrogen ⓬, as well as inhibin. In the presence of estrogen, the high plasma concentration of progesterone causes a decrease in the secretion of the gonadotropins by the pituitary gland. It probably does this by acting on the hypothalamus to *suppress* the pulsatile secretion of GnRH. Progesterone also prevents any LH surges during the first half of the luteal phase despite the high concentrations of estrogen at this time. The increase in plasma inhibin concentration in the luteal phase also contributes to the suppression of FSH secretion. Consequently, during the luteal phase of the cycle, plasma concentrations of the gonadotropins are very low ⓭. The feedback suppression of gonadotropins in the luteal phase is summarized in **Figure 17.26**.

The corpus luteum has a finite life in the absence of an increase in gonadotropin secretion. If pregnancy does not occur, the corpus luteum degrades within 2 weeks ⓮. With degeneration of the corpus luteum, plasma progesterone and estrogen concentrations decrease ⓯. The secretion of FSH and LH (and probably GnRH, as well) increases (⓰ and ❶) as a result of being freed from the inhibiting effects of high concentrations of ovarian hormones. The cycle then begins anew.

This completes the description of the control of ovarian function during a typical menstrual cycle. It should be emphasized that, although the hypothalamus and anterior pituitary gland are essential components, events within the *ovary* are the real sources of timing for the cycle. When the ovary secretes enough estrogen, the LH surge is induced, which in turn causes ovulation. When the corpus luteum degenerates, the decrease in hormone secretion allows the gonadotropin concentrations to increase enough to promote the growth of another group of follicles. This illustrates that ovarian events, via hormonal feedback, control the hypothalamus and anterior pituitary gland.

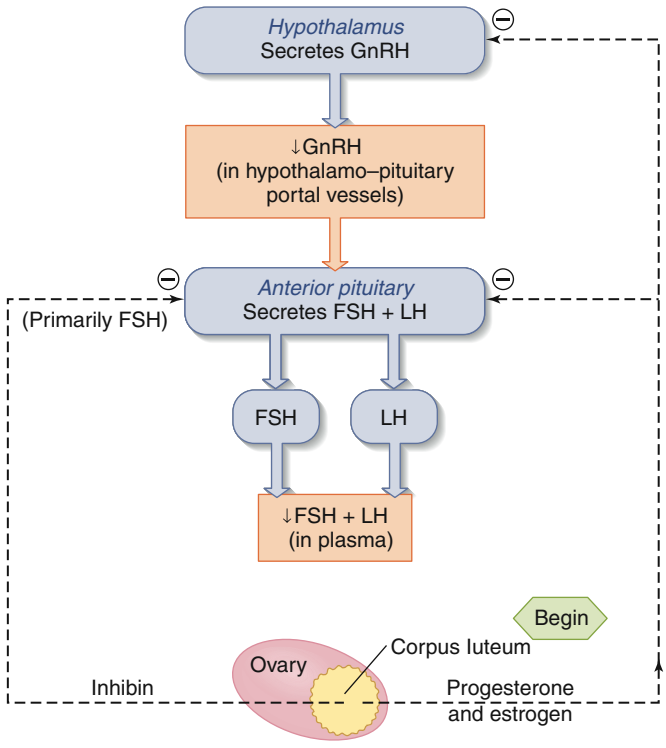


Figure 17.26 Suppression of FSH and LH during luteal phase. If implantation of a developing conceptus does not occur and hCG does not appear in the blood, the corpus luteum dies, progesterone and estrogen decrease, menstruation occurs, and the next menstrual cycle begins.

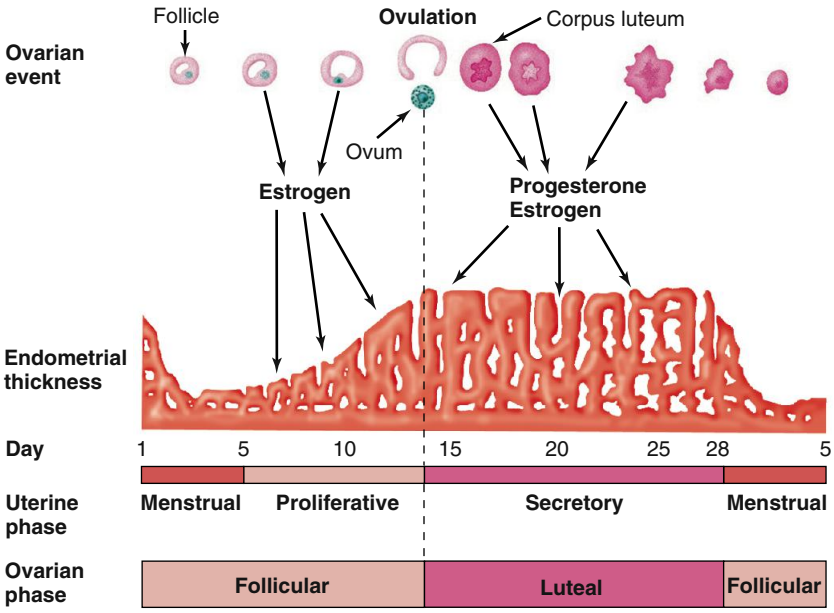
17.15 Uterine Changes in the Menstrual Cycle

The phases of the menstrual cycle can also be described in terms of uterine events (**Figure 17.27**). Day 1 is the first day of menstrual flow, and the entire duration of menstruation is known as the **menstrual phase** (generally about 3 to 5 days in a typical 28-day cycle). During this time, the epithelial lining of the uterus—the **endometrium**—degenerates, resulting in the menstrual flow. The menstrual flow then ceases, and the endometrium begins to thicken as it regenerates under the influence of estrogen. This period of growth, the **proliferative phase,** lasts for the 10 days or so between cessation of menstruation and the occurrence of ovulation. Soon after ovulation, under the influence of progesterone and estrogen from the corpus luteum, the endometrium begins to secrete glycogen in the glandular epithelium, followed by glycoproteins and mucopolysaccharides. The part of the menstrual cycle between ovulation and the onset of the next menstruation is called the **secretory phase.** As shown in Figure 17.27, the ovarian follicular phase includes the uterine menstrual and proliferative phases, whereas the ovarian luteal phase is the same as the uterine secretory phase.

The uterine changes during a menstrual cycle are caused by changes in the plasma concentrations of estrogen and progesterone secreted by the ovaries (see Figure 17.22). During the proliferative phase, an increasing plasma estrogen concentration stimulates growth of both the endometrium and the underlying uterine smooth muscle (called the **myometrium**). In addition, it induces the synthesis of receptors for progesterone in endometrial cells. Then, following ovulation and formation of the corpus luteum (during the secretory phase), progesterone acts upon this estrogen-primed endometrium to convert it to an actively secreting tissue. The endometrial glands become coiled and filled with glycogen, the blood vessels become more numerous, and enzymes accumulate in the glands and connective tissue. These changes are essential to make the endometrium a hospitable environment for implantation and nourishment of the developing embryo.

Progesterone also inhibits myometrial contractions, in large part by opposing the stimulatory actions of estrogen and locally generated prostaglandins. This is very important to ensure that a fertilized egg can safely implant once it arrives in the uterus. Uterine quiescence is maintained by progesterone throughout pregnancy and is essential to prevent premature delivery.

Estrogen and progesterone also have important effects on the secretion of mucus by the cervix. Under the influence of estrogen alone, this mucus is abundant, clear, and watery. All of these characteristics are most pronounced at the time of ovulation and allow sperm deposited in the vagina to move easily through



AP|R **Figure 17.27** Relationships between ovarian and uterine changes during the menstrual cycle. Refer to Figure 17.22 for specific hormonal changes.

the mucus on their way to the uterus and fallopian tubes. In contrast, progesterone, present in significant concentrations only after ovulation, causes the mucus to become thick and sticky—in essence, a "plug" that prevents bacteria from entering the uterus from the vagina. The antibacterial blockage protects the uterus and the embryo if fertilization has occurred.

The decrease in plasma progesterone and estrogen concentrations that results from degeneration of the corpus luteum deprives the highly developed endometrium of its hormonal support and causes menstruation. The first event is constriction of the uterine blood vessels, which leads to a diminished supply of oxygen and nutrients to the endometrial cells. Disintegration starts in the entire lining, except for a thin, underlying layer that will regenerate the endometrium in the next cycle. Also, the uterine smooth muscle begins to undergo rhythmic contractions.

Both the vasoconstriction and uterine contractions are mediated by prostaglandins produced by the endometrium in response to the decrease in plasma estrogen and progesterone concentrations. The major cause of menstrual cramps, ***dysmenorrhea,*** is overproduction of these prostaglandins, leading to excessive uterine contractions. The prostaglandins also affect smooth muscle elsewhere in the body, which accounts for some of the systemic symptoms that sometimes accompany the cramps, such as nausea, vomiting, and headache.

After the initial period of vascular constriction, the endometrial arterioles dilate, resulting in hemorrhage through the weakened capillary walls. The menstrual flow consists of this blood mixed with endometrial debris. Typical blood loss per menstrual period is about 50 to 150 mL.

The major events of the menstrual cycle are summarized in **Table 17.7**. This table, in essence, combines the information in Figures 17.22 and 17.27.

TABLE 17.7 Summary of the Menstrual Cycle

Day(s)	Major Events
1–5	Estrogen and progesterone are low because the previous corpus luteum is regressing. *Therefore:* a. Endometrial lining sloughs. b. Secretion of FSH and LH is released from inhibition, and their plasma concentrations increase. *Therefore:* Several growing follicles are stimulated to mature.
7	A single follicle (usually) becomes dominant.
7–12	Plasma estrogen increases because of secretion by the dominant follicle. *Therefore:* Endometrium is stimulated to proliferate.
7–12	LH and FSH decrease due to estrogen and inhibin negative feedback. *Therefore:* Degeneration (atresia) of nondominant follicles occurs.
12–13	LH surge is induced by increasing plasma estrogen secreted by the dominant follicle. *Therefore:* a. Oocyte is induced to complete its first meiotic division and undergo cytoplasmic maturation. b. Follicle is stimulated to secrete digestive enzymes and prostaglandins.
14	Ovulation is mediated by follicular enzymes and prostaglandins.
15–25	Corpus luteum forms and, under the influence of low but adequate levels of LH, secretes estrogen and progesterone, increasing plasma concentrations of these hormones. *Therefore:* a. Secretory endometrium develops. b. Secretion of FSH and LH from the anterior pituitary gland is inhibited, lowering their plasma concentrations. *Therefore:* No new follicles develop.
25–28	Corpus luteum degenerates (if implantation of the conceptus does not occur). *Therefore:* Plasma estrogen and progesterone concentrations decrease. *Therefore:* Endometrium begins to slough at conclusion of day 28, and a new cycle begins.

17.16 Additional Effects of Gonadal Steroids

Estrogen has other effects in addition to its paracrine function within the ovaries, its effects on the anterior pituitary gland and the hypothalamus, and its uterine actions. They are summarized in **Table 17.8**.

Progesterone also exerts a variety of effects (also shown in Table 17.8). Because the plasma progesterone concentration is markedly increased only after ovulation has occurred, several of these effects can be used to indicate whether ovulation has taken place. First, progesterone inhibits proliferation of the cells lining the vagina. Second, there is a small increase (approximately 0.5°C) in body temperature that usually occurs after ovulation and persists throughout the luteal phase; this change is probably due to an action of progesterone on temperature regulatory centers in the brain.

Note that in its myometrial and vaginal effects, as well as several others listed in Table 17.8, progesterone exerts an "anti-estrogen effect," probably by decreasing the number of estrogen receptors. In contrast, the synthesis of progesterone receptors is stimulated by estrogen in many tissues (for example, the endometrium), and so responsiveness to progesterone usually requires the presence of estrogen (**estrogen priming**).

Transient physical and emotional symptoms that appear in many women prior to the onset of menstrual flow and disappear within a few days after the start of menstruation. The symptoms—which may include painful or swollen breasts; headache; backache; depression; anxiety; irritability; and other physical, emotional, and behavioral changes—are often attributed to estrogen or progesterone excess. The plasma concentrations of these hormones, however, are usually normal in women having these symptoms, and the cause of the symptoms is not actually known. In order of increasing severity of symptoms, the overall problem is categorized as ***premenstrual tension***, ***premenstrual syndrome*** (***PMS***), or ***premenstrual dysphoric disorder*** (***PMDD***), the last-named being so severe as to be temporarily disabling. These symptoms appear to result from a complex interplay between the sex steroids and brain neurotransmitters.

Androgens are present in the blood of women as a result of production by the adrenal glands and ovaries (see Figure 17.6). These androgens have several important functions in the female, including stimulation of the growth of pubic hair, axillary hair, and, possibly, skeletal muscle, and maintenance of sex drive. Excess androgens may cause ***virilization:*** The female fat distribution lessens, a beard appears along with the male body hair distribution, the voice lowers in pitch, the skeletal muscle mass increases, the clitoris enlarges, and the breasts diminish in size.

17.17 Puberty

Puberty in females is a process similar to that in males (described earlier in this chapter). It usually starts earlier in girls (10 to 12 years old) than in boys. In the female, GnRH, the gonadotropins, and estrogen are all secreted at very low rates during

TABLE 17.8 Some Effects of Female Sex Steroids

I. Estrogen
- A. Stimulates growth of ovary and follicles (local effects)
- B. Stimulates growth of smooth muscle and proliferation of epithelial linings of reproductive tract; in addition:
  1. Fallopian tubes: increases contractions and ciliary activity
  2. Uterus: increases myometrial contractions and responsiveness to oxytocin; stimulates secretion of abundant, watery cervical mucus; prepares endometrium for progesterone's actions by inducing progesterone receptors
  3. Vagina: increases layering of epithelial cells
- C. Stimulates external genitalia growth, particularly during puberty
- D. Stimulates breast growth, particularly ducts and fat deposition during puberty
- E. Stimulates female body configuration development during puberty: narrow shoulders, broad hips, female fat distribution (deposition on hips and breasts)
- F. Stimulates fluid secretion from lipid (sebum)-producing skin glands (sebaceous glands); (This "anti-acne" effect opposes the acne-producing effects of androgen.)
- G. Stimulates bone growth and ultimate cessation of bone growth (closure of epiphyseal plates); protects against osteoporosis; does not have an anabolic effect on skeletal muscle
- H. Vascular effects (deficiency produces "hot flashes")
- I. Has feedback effects on hypothalamus and anterior pituitary gland (see Table 17.4)
- J. Stimulates prolactin secretion but inhibits prolactin's milk-inducing action on the breasts
- K. Protects against atherosclerosis by effects on plasma cholesterol (Chapter 16), blood vessels, and blood clotting (Chapter 12)

II. Progesterone
- A. Converts the estrogen-primed endometrium to an actively secreting tissue suitable for implantation of an embryo
- B. Induces thick, sticky cervical mucus
- C. Decreases contractions of fallopian tubes and myometrium
- D. Decreases proliferation of vaginal epithelial cells
- E. Stimulates breast growth, particularly glandular tissue
- F. Inhibits milk-inducing effects of prolactin
- G. Has feedback effects on hypothalamus and anterior pituitary gland (see Table 17.4)
- H. Increases body temperature

childhood. For this reason, there is no follicle maturation beyond the early antral stage and menstrual cycles do not occur. The female accessory sex organs remain small and nonfunctional, and there are minimal secondary sex characteristics. The onset of puberty is caused, in large part, by an alteration in brain function that increases the secretion of GnRH. It is currently thought that activation of kisspeptin neurons in the hypothalamus is involved in the increase in GnRH that occurs early in puberty. GnRH in turn stimulates the secretion of pituitary gland gonadotropins, which stimulate follicle development and estrogen secretion. Estrogen, in addition to its critical role in follicle development, induces the changes in the accessory sex organs and secondary sex characteristics associated with puberty. **Menarche,** the first menstruation, is a late event of puberty (averaging about 12.5 years of age in the United States).

As in males, the mechanism of the brain change that results in increased GnRH secretion in girls at puberty is not certain. The brain may become less sensitive to the negative feedback effects of gonadal hormones at the time of puberty. Also, the adipose-tissue hormone leptin (see Chapter 16) is known to stimulate the secretion of GnRH and may contribute to the onset of puberty. This may explain why the onset of puberty tends to correlate with the attainment of a certain level of energy stores (fat) in the girl's body.

The failure to have menstrual flow (menses) is called ***amenorrhea.*** Primary amenorrhea is the failure to begin normal menstrual cycles at puberty (menarche), whereas secondary amenorrhea is defined as the loss of previously normal menstrual cycles. As we will see, the most common causes of secondary amenorrhea are pregnancy and menopause. Excessive exercise and ***anorexia nervosa*** (self-imposed starvation) can cause primary or secondary amenorrhea. There are a variety of theories for why this is so. One unifying theory is that the brain can sense a loss of body fat, possibly via decreased concentrations of the hormone leptin, and that this leads the hypothalamus to cease GnRH pulses. From a teleological view, this makes sense because pregnant women must supply a large caloric input to the developing fetus and a lack of body fat would indicate inadequate energy stores. The prepubertal appearance of adolescent female athletes with minimal body fat may indicate hypogonadism and probably amenorrhea, which can persist for many years after menarche would normally take place.

The onset of puberty in both sexes is not abrupt but develops over several years, as evidenced by slowly increasing plasma concentrations of the gonadotropins and testosterone or estrogen. The age of the normal onset of puberty is controversial, although it is generally thought that pubertal onset before the age of 6 to 7 in girls and 8 to 9 in boys warrants clinical investigation. ***Precocious puberty*** is defined as the very premature appearance of secondary sex characteristics and is usually caused by an early increase in gonadal steroid production. This leads to an early onset of the puberty growth spurt, maturation of the skeleton, breast development (in girls), and enlargement of the genitalia (in boys). Therefore, these children are usually taller at an early age. However, because gonadal steroids also stop the pubertal growth spurt by inducing epiphyseal closure, final adult height is usually less than predicted. Although there are a variety of causes for the premature increase in gonadal steroids, *true* (or complete) precocious puberty is caused by the premature activation of GnRH and LH and FSH secretion. This is often caused by tumors or infections in the area of the central nervous system that controls GnRH release. Treatments that decrease LH and FSH release are important to allow normal development.

17.18 Female Sexual Response

The female response to sexual intercourse is characterized by marked increases in blood flow and muscular contraction in many areas of the body. For example, increasing sexual excitement is associated with vascular engorgement of the breasts and erection of the nipples, resulting from contraction of smooth muscle fibers in them. The clitoris, which has a rich supply of sensory nerve endings, increases in diameter and length as a result of increased blood flow. During intercourse, the blood flow to the vagina increases and the vaginal epithelium is lubricated by mucus.

Orgasm in the female, as in the male, is accompanied by pleasurable feelings and many physical events. There is a sudden increase in skeletal muscle activity involving almost all parts of the body; the heart rate and blood pressure increase, and there is a transient rhythmic contraction of the vagina and uterus. Orgasm seems to have a minimal function in ensuring fertilization because fertilization can occur in the absence of an orgasm. Sexual desire in women is probably more dependent upon androgens, secreted by the adrenal glands and ovaries, than estrogen.

17.19 Pregnancy

For pregnancy to occur, the introduction of sperm must occur between 5 days before and 1 day after ovulation. This is because the sperm, following their ejaculation into the vagina, remain capable of fertilizing an egg for up to 4 to 6 days, and the ovulated egg remains viable for only 24 to 48 h.

Egg Transport

At ovulation, the egg is extruded onto the surface of the ovary. Recall that the fimbriae at the ends of the fallopian tubes are lined with ciliated epithelium. At ovulation, the smooth muscle of the fimbriae causes them to pass over the ovary while the cilia beat in waves toward the interior of the duct. These ciliary motions sweep the egg into the fallopian tube as it emerges onto the ovarian surface.

Within the fallopian tube, egg movement, driven almost entirely by fallopian-tube cilia, is so slow that the egg takes about 4 days to reach the uterus. If fertilization is to occur, it does so in the fallopian tube because of the short viability of the unfertilized egg.

Intercourse, Sperm Transport, and Capacitation

Ejaculation, described earlier in this chapter, results in deposition of semen into the vagina during intercourse. The act of intercourse itself provides some impetus for the transport of sperm out of the vagina to the cervix because of the fluid pressure of the ejaculate. Passage into the cervical mucus by the swimming sperm is dependent on the estrogen-induced changes in consistency of the mucus described earlier. Sperm can enter the uterus within minutes of ejaculation. Furthermore, the sperm can usually survive for up to a day or two within the cervical mucus, from which they can be released to enter the uterus. Transport of the sperm through the length of the uterus and into the fallopian tubes occurs via the sperm's own propulsions and uterine contractions.

The mortality rate of sperm during the trip is huge. One reason for this is that the vaginal environment is acidic, a protection against yeast and bacterial infections. Two more reasons are the length and energy requirements of the trip. Of the several hundred million sperm deposited in the vagina in an ejaculation, only about 100 to 200 usually reach the fallopian tube. This is the major reason there must be so many sperm in the ejaculate for fertilization to occur.

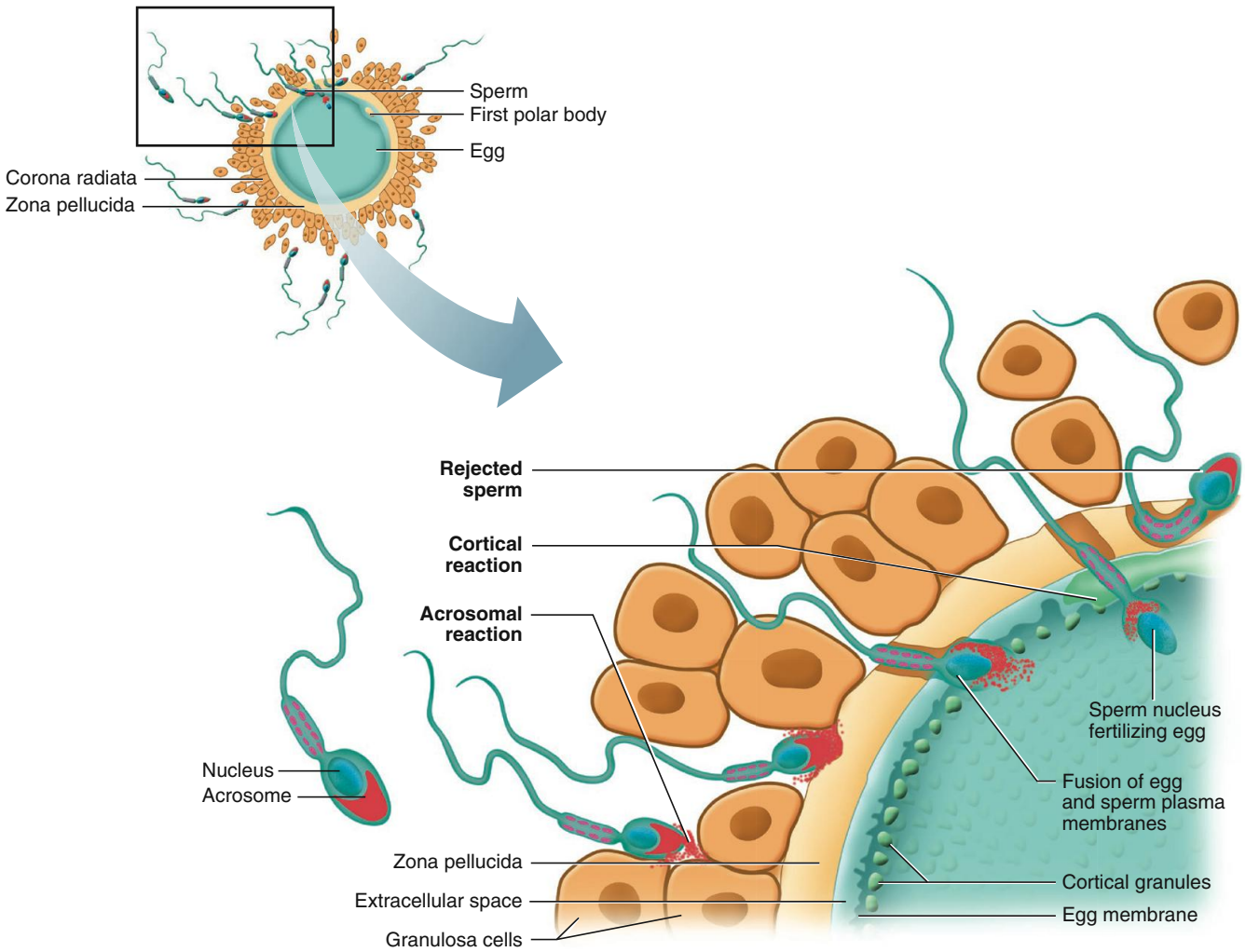
Sperm are not able to fertilize the egg until they have resided in the female tract for several hours and been acted upon by secretions of the tract. This process, called **capacitation,** causes (1) the previously regular wavelike beats of the sperm's tail to be replaced by a more whiplike action that propels the sperm forward in strong surges and (2) the sperm's plasma membrane to become altered so that it will be capable of fusing with the surface membrane of the egg.

Fertilization

Fertilization begins with the fusion of a sperm and egg in the fallopian tube, usually within a few hours after ovulation. The egg usually must be fertilized within 24 to 48 hours of ovulation. Many sperm, after moving between the granulosa cells (composing the corona radiata) still surrounding the egg, bind to the zona pellucida (**Figure 17.28**). The zona pellucida glycoproteins function as receptors for sperm surface proteins. The sperm head has many of these proteins and so becomes bound simultaneously to many sperm receptors on the zona pellucida.

This binding triggers what is termed the **acrosome reaction** in the bound sperm: The plasma membrane of the sperm head is altered so that the underlying membrane-bound acrosomal enzymes are now exposed to the outside—that is, to the zona pellucida. The enzymes digest a path through the zona pellucida as the sperm, using its tail, advances through this coating. The first sperm to penetrate the entire zona pellucida and reach the egg's plasma membrane fuses with this membrane. The head of the sperm then slowly passes into the cytosol of the egg.

Viability of the newly fertilized egg, now called a zygote**,** depends upon preventing the entry of additional sperm. A specific mechanism mediates this **block to polyspermy.** The initial fusion of the sperm and egg plasma membranes triggers a reaction that changes membrane potential, preventing additional sperm from binding. Subsequently, during the **cortical reaction,** cytosolic secretory vesicles located around the egg's periphery release their contents, by exocytosis, into the narrow space between the egg plasma membrane and the zona pellucida. Some of these molecules are enzymes that enter the zona pellucida and cause both



AP|R **Figure 17.28** Fertilization and the block to polyspermy. Rectangle on top image indicates area of enlargement below. The size of the sperm is exaggerated for clarity. The photograph on the first page of this chapter shows the actual size relationship between the sperm and the egg.

inactivation of its sperm-binding sites and hardening of the entire zona pellucida. This prevents additional sperm from binding to the zona pellucida and those sperm already advancing through it from continuing.

The fertilized egg completes its second meiotic division over the next few hours, and the one daughter cell with practically no cytoplasm—the second polar body—is extruded and disintegrates (see Figure 17.1b). The two sets of chromosomes—23 from the egg and 23 from the sperm, which are surrounded by distinct membranes and are known as pronuclei—migrate to the center of the cell. During this period of a few hours, the DNA of the chromosomes in both pronuclei is replicated, the pronuclear membranes break down, the cell is ready to undergo a mitotic division, and fertilization is complete. Fertilization also triggers activation of enzymes required for the ensuing cell divisions and embryogenesis. The major events of fertilization are summarized in **Figure 17.29**. If fertilization had not occurred, the egg would have slowly disintegrated and been phagocytized by cells lining the uterus.

Rarely, a fertilized egg remains in a fallopian tube and embeds itself in the tube wall. Even more rarely, a fertilized egg may move backward out of the fallopian tube into the abdominal cavity, where implantation can occur. Both kinds of ***ectopic pregnancies*** cannot succeed, and surgery is necessary to end the pregnancy (unless there is a spontaneous abortion) because of the risk of maternal hemorrhage.

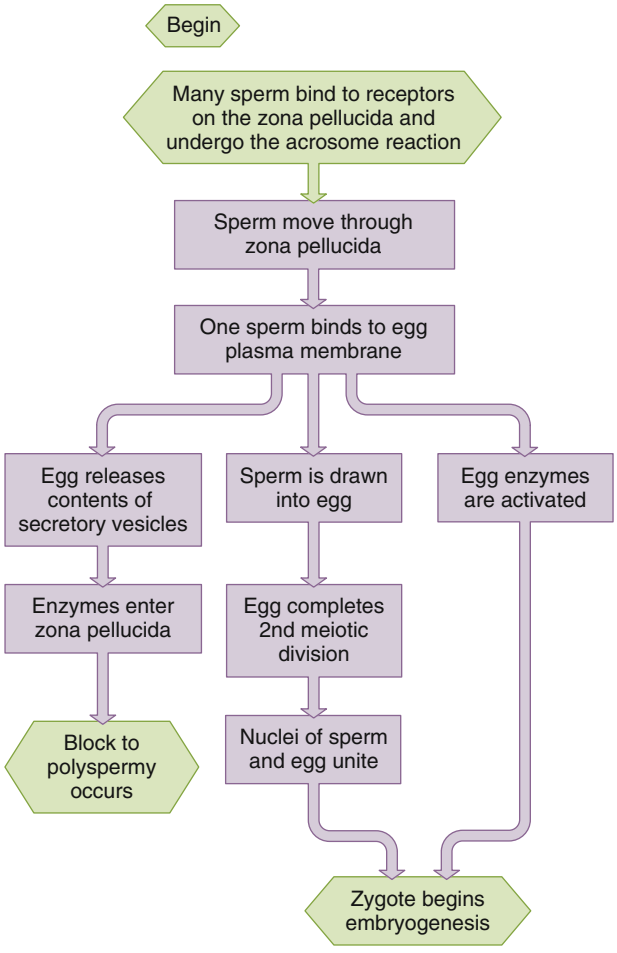


Figure 17.29 Events leading to fertilization, block to polyspermy, and the beginning of embryogenesis.

Early Development, Implantation, and Placentation

The previously described events from ovulation and fertilization to implantation of the blastocyst are summarized in **Figure 17.30**. The **conceptus**—a collective term for everything ultimately derived from the original zygote (fertilized egg) throughout the pregnancy—remains in the fallopian tube for 3 to 4 days. The major reason is that estrogen maintains the contraction of the smooth muscle near where the fallopian tube enters the wall of the uterus. As plasma progesterone concentrations increase, this smooth muscle relaxes and allows the conceptus to pass. During its stay in the fallopian tube, the conceptus undergoes a number of mitotic cell divisions, a process known as **cleavage.** These divisions, however, are unusual in that no cell growth occurs before each division; the 16- to 32-cell conceptus that reaches the uterus is essentially the same size as the original fertilized egg.

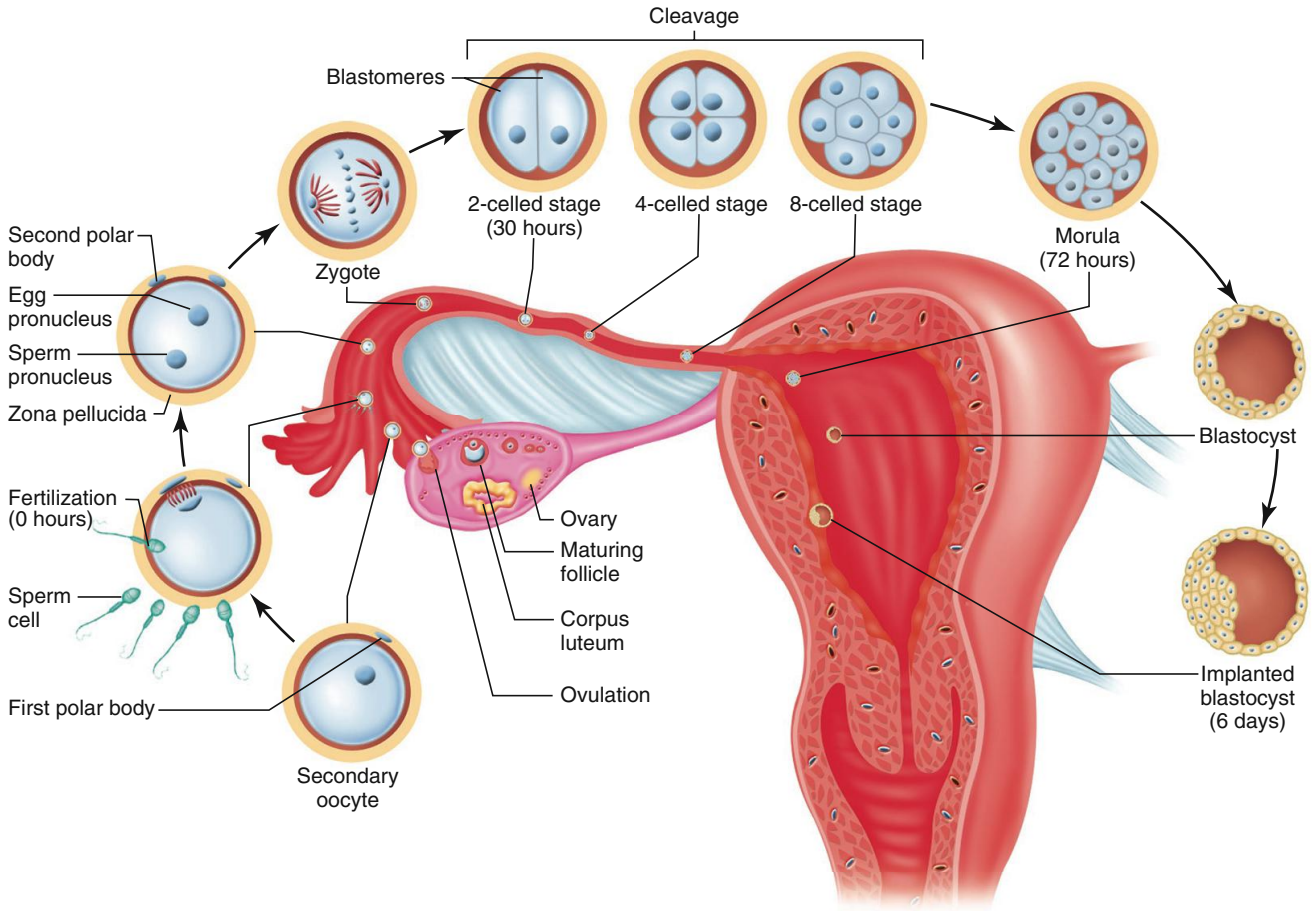
Each of these cells is **totipotent**—that is, they are **stem cells** that have the capacity to develop into an entire individual. Therefore, identical (monozygotic) twins result when, at some point during cleavage, the dividing cells become completely separated into two independently growing cell masses. In contrast, as described earlier, dizygotic twins result when two eggs are ovulated and fertilized.

After reaching the uterus, the conceptus floats free in the intrauterine fluid, from which it receives nutrients, for approximately 3 days, all the while undergoing further cell divisions to approximately 100 cells. Soon the conceptus reaches the stage known as a **blastocyst,** by which point the cells have lost their totipotentiality and have begun to differentiate. The blastocyst consists of an outer layer of cells called the **trophoblast,** an **inner cell mass,** and a central fluid-filled cavity (**Figure 17.31**). During subsequent development, the inner cell mass will give rise to the developing human—called an **embryo** during the first 2 months and a **fetus** after that—and some of the membranes associated with it. The trophoblast will surround the embryo and fetus throughout development and be involved in its nutrition as well as in the secretion of several important hormones.

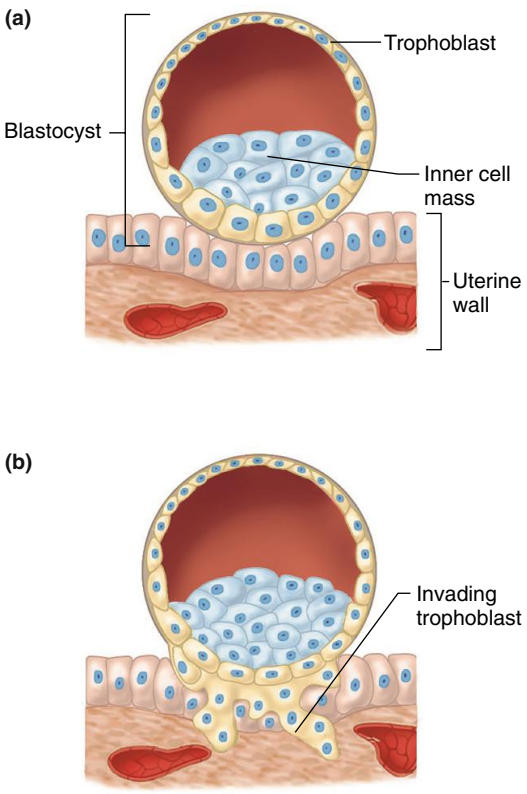
Implantation

The period during which the zygote develops into a blastocyst corresponds with days 14 to 21 of the typical menstrual cycle. During this period, the uterine lining is being prepared by progesterone (secreted by the corpus luteum) to receive the blastocyst. By approximately the twenty-first day of the cycle (that is, 7 days after ovulation), **implantation**—the embedding of the blastocyst into the endometrium—begins (see Figure 17.31). The trophoblast cells are sticky, particularly in the region overlying the inner cell mass, and it is this portion of the blastocyst that adheres to the endometrium and initiates implantation.

The initial contact between blastocyst and endometrium induces rapid proliferation of the trophoblast, the cells of which penetrate between endometrial cells. Proteolytic enzymes secreted by the trophoblast allow the blastocyst to bury itself in the endometrial layer. The endometrium, too, is undergoing changes at the site of contact. Implantation requires communication—via several paracrine signals—between the blastocyst and the cells of the



AP|R **Figure 17.30** Events from ovulation to implantation. Only one ovary and one fallopian tube are shown (right side of patient).



endometrium. Implantation is soon completed, and the nutrient-rich endometrial cells provide the metabolic fuel and raw materials required for early growth of the embryo.

Placentation This simple nutritive system, however, is only adequate to provide for the embryo during the first few weeks, when it is very small. The structure that takes over this function is the **placenta,** a combination of interlocking fetal and maternal tissues, which serves as the organ of exchange between mother and fetus for the remainder of the pregnancy.

The embryonic portion of the placenta is supplied by the outermost layers of trophoblast cells, the **chorion,** and the maternal portion by the endometrium underlying the chorion. Fingerlike projections of the trophoblast cells, called **chorionic villi,** extend from the chorion into the endometrium (**Figure 17.32**). The villi contain a rich network of capillaries that are part of the embryo's circulatory system. The endometrium around the villi is altered by enzymes and other paracrine molecules secreted from the cells of the invading villi so that each villus becomes completely surrounded by a pool, or **sinus,** of maternal blood supplied by maternal arterioles.

The maternal blood enters these placental sinuses via the uterine artery; the blood flows through the sinuses and then

AP|R **Figure 17.31** (a) Contact and (b) implantation of the blastocyst into the uterine wall at about 6–7 days after the previous LH peak. The trophoblast cells secrete hCG into the maternal circulation, which rescues the corpus luteum and maintains pregnancy. The trophoblast eventually develops into a component of the placenta.

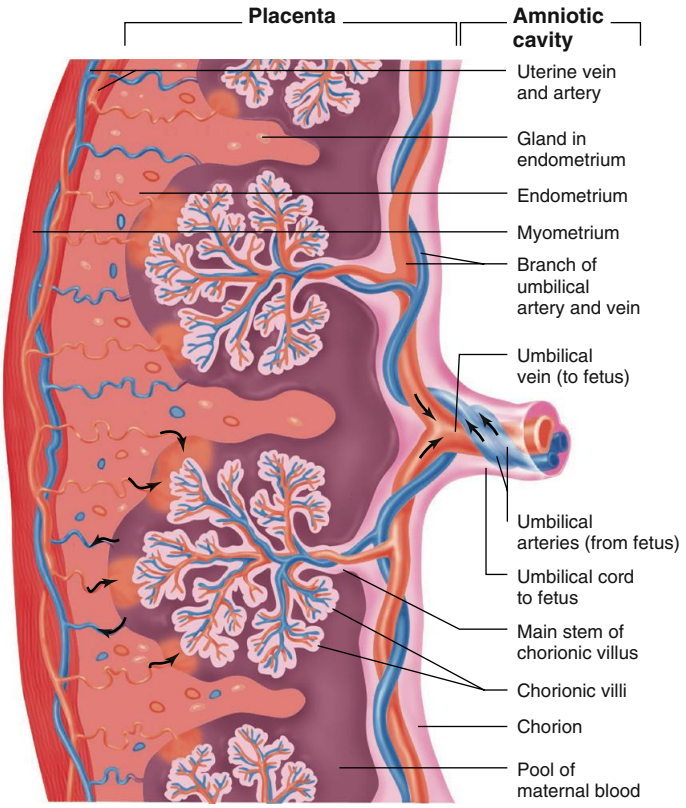


Figure 17.32 Interrelations of fetal and maternal tissues in the formation of the placenta. See Figure 17.33 for the orientation of the placenta.

PHYSIOLOGICAL INQUIRY

- How does this figure exemplify the general principle of physiology described in Chapter 1 that controlled exchange of materials occurs between compartments and across cellular membranes?

Answer can be found at end of chapter.

exits via the uterine veins. Simultaneously, blood flows from the fetus into the capillaries of the chorionic villi via the **umbilical arteries** and out of the capillaries back to the fetus via the **umbilical vein.** All of these umbilical vessels are contained in the **umbilical cord,** a long, ropelike structure that connects the fetus to the placenta.

Five weeks after implantation, the placenta has become well established; the fetal heart has begun to pump blood; the entire mechanism for nutrition of the embryo and, subsequently, fetus and the excretion of waste products is in operation. A layer of epithelial cells in the villi and of endothelial cells in the fetal capillaries separates the maternal and fetal blood. Waste products move from blood in the fetal capillaries across these layers into the maternal blood; nutrients, hormones, and growth factors move in the opposite direction. Some substances, such as oxygen and carbon dioxide, move by diffusion. Others, such as glucose, use transport proteins in the plasma membranes of the epithelial cells. Still other substances (e.g., several amino acids and hormones) are produced by the trophoblast layers of the placenta itself and added to the fetal and maternal blood. Note that there is an exchange of materials between the two bloodstreams but no mixing of the fetal and maternal blood. Umbilical veins carry oxygen and nutrient-rich blood from the placenta to the fetus, whereas umbilical arteries carry blood with waste products and a low oxygen content to the placenta.

Amniotic Cavity

Meanwhile, a space called the **amniotic cavity** has formed between the inner cell mass and the chorion (**Figure 17.33**). The epithelial layer lining the cavity is derived from the inner cell mass and is called the **amnion,** or **amniotic sac.** It eventually fuses with the inner surface of the chorion so that only a single combined membrane surrounds the fetus. The fluid in the amniotic cavity, the **amniotic fluid,** resembles the fetal extracellular fluid, and it buffers mechanical disturbances and temperature variations. The fetus, floating in the amniotic cavity and attached by the umbilical cord to the placenta, develops into a viable infant during the next 8 months.

Amniotic fluid can be sampled by ***amniocentesis*** as early as the sixteenth week of pregnancy. This is done by inserting a needle into the amniotic cavity. Some genetic diseases can be diagnosed by the finding of certain chemicals either in the fluid or in sloughed fetal cells suspended in the fluid. The chromosomes of these fetal cells can also be examined for diagnosis of certain disorders as well as to determine the sex of the fetus. Another technique for fetal diagnosis is ***chorionic villus sampling.*** This technique, which can be performed as early as 9 to 12 weeks of pregnancy, involves obtaining tissue from a chorionic villus of the placenta. This technique, however, carries a higher risk of inducing the loss of the fetus (***miscarriage***) than does amniocentesis. A third technique for fetal diagnosis is ultrasound, which provides a "picture" of the fetus without the use of x-rays. A fourth technique for screening for fetal abnormalities involves obtaining only *maternal* blood and analyzing it for several normally occurring substances whose concentrations change in the presence of these abnormalities. For example, particular changes in the concentrations of two hormones produced during pregnancy—human chorionic gonadotropin and estriol—and alpha-fetoprotein (a major fetal plasma protein that crosses the placenta into the maternal blood) can identify many cases of ***Down syndrome,*** a genetic form of intellectual and developmental disability associated with distinct facial and body features.

Maternal-Fetal Unit

Maternal nutrition is crucial for the fetus. Malnutrition early in pregnancy can cause specific abnormalities that are **congenital,** that is, existing at birth. Malnutrition retards fetal growth and results in infants with higher-than-normal death rates, reduced growth after birth, and an increased incidence of learning disabilities and other medical problems. Specific nutrients, not just total calories, are also very important. For example, there is an increased incidence of neural defects in the offspring of mothers who are deficient in the B-vitamin folate (also called folic acid and folacin). Recall from Chapter 11 that normal maternal and fetal thyroid hormone concentrations are necessary for normal fetal development.

The developing embryo and fetus are also subject to considerable influences by a host of nonnutrient factors, such as noise, radiation, chemicals, and viruses, to which the mother may be exposed. For example, drugs taken by the mother can reach the fetus via transport across the placenta and can impair fetal growth

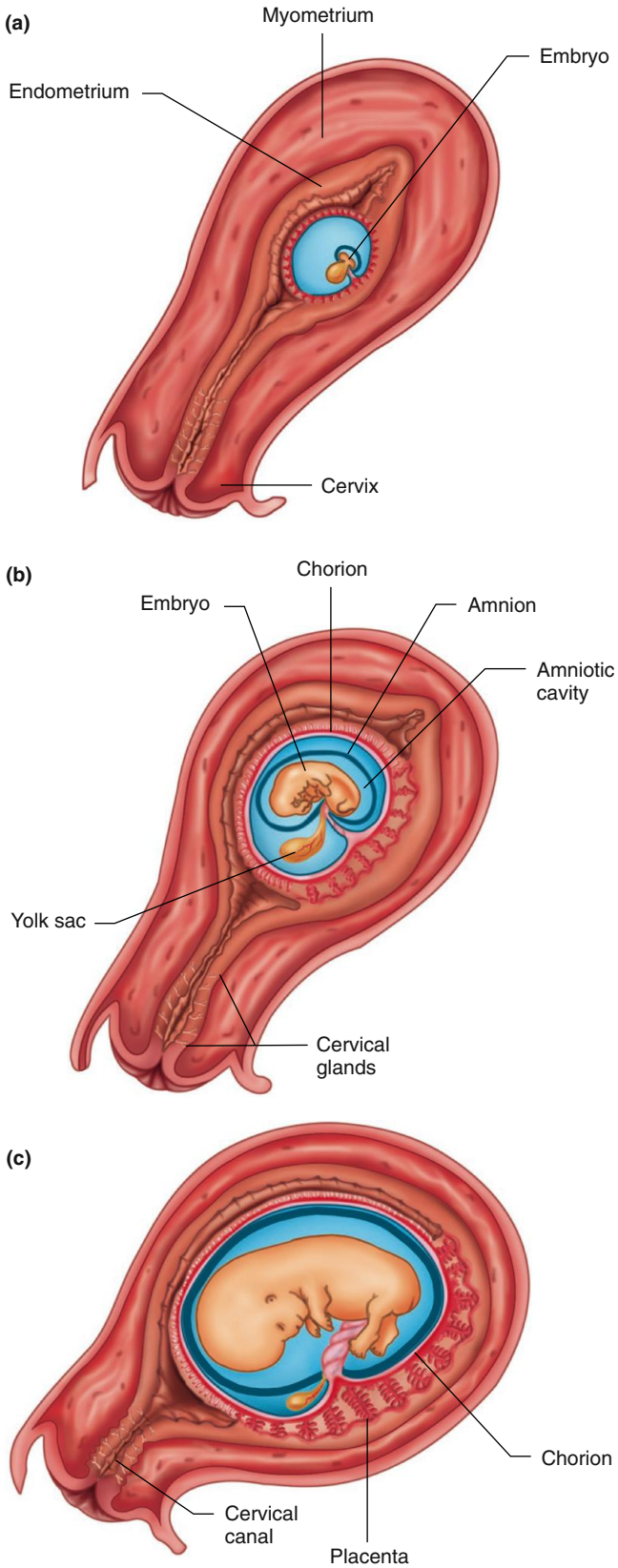


Figure 17.33 The uterus at (a) 3, (b) 5, and (c) 8 weeks after fertilization. Embryos and their membranes are drawn to actual size. Uterus is within actual size range. The yolk sac is formed from the trophoblast. It has no nutritional function in humans but is important in embryonic development.

and development. In this regard, it must be emphasized that aspirin, alcohol, and the chemicals in cigarette smoke are very potent agents, as are illicit drugs such as cocaine. Any agent that can cause birth defects in the fetus is known as a ***teratogen.***

Because half of the fetal genes—those from the father—differ from those of the mother, the fetus is in essence a foreign transplant in the mother. The integrity of the fetal–maternal blood barrier also protects the fetus from attack by the immune system of mother.

Hormonal and Other Changes During Pregnancy

Throughout pregnancy, plasma concentrations of estrogen and progesterone continually increase (**Figure 17.34**). Estrogen stimulates the growth of the uterine muscle mass, which will eventually supply the contractile force needed to deliver the fetus. Progesterone inhibits uterine contractility so that the fetus is not expelled prematurely. During approximately the first 2 months of pregnancy, almost all the estrogen and progesterone is supplied by the corpus luteum.

Recall that if pregnancy had not occurred, the corpus luteum would have degenerated within 2 weeks after its formation. The persistence of the corpus luteum during pregnancy is due to a hormone called **human chorionic gonadotropin** (**hCG**), which the trophoblast cells start to secrete around the time they start their endometrial invasion. Human chorionic gonadotropin

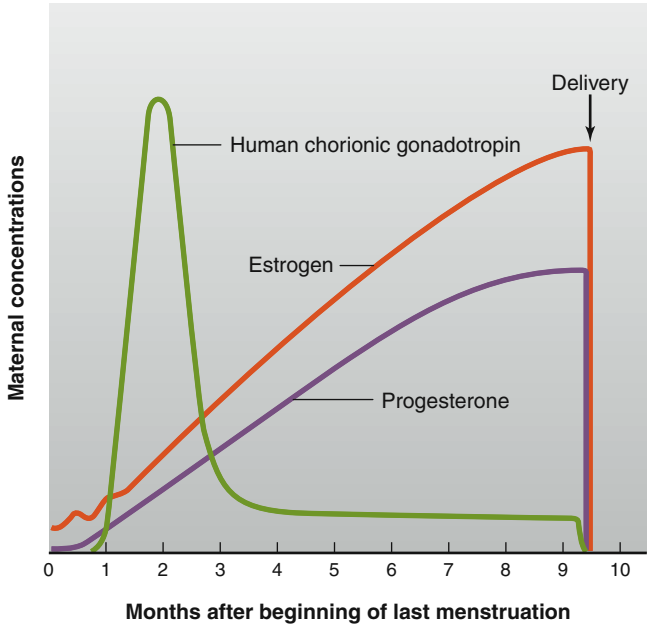


Figure 17.34 Maternal concentrations of estrogen, progesterone, and human chorionic gonadotropin during pregnancy. Curves depicting hormone concentrations are not drawn to scale. Note that the concentrations of estrogen and progesterone achieved in the maternal blood during pregnancy are much higher than during a typical menstrual cycle shown in Figure 17.22.

PHYSIOLOGICAL INQUIRY

- Why do progesterone and estrogen concentrations continue to increase during pregnancy even though human chorionic gonadotropin (hCG) concentration decreases?

Answer can be found at end of chapter.

gains entry to the maternal circulation, and the detection of this hormone in the mother's plasma and/or urine is used as a test for pregnancy. This glycoprotein is very similar to LH, and it not only prevents the corpus luteum from degenerating but strongly stimulates its steroid secretion. Therefore, the signal that preserves the corpus luteum comes from the conceptus, not the mother's tissues. The rescue of the corpus luteum by hCG is an example of the general principle of physiology that information flow between organs allows for integration of physiological processes. That is, hCG secreted into maternal blood from the developing trophoblasts of embryonic origin stimulates the maternal ovaries to continue to secrete gonadal steroids. This, via negative feedback on maternal gonadotropin secretion, prevents additional menstrual cycles that would otherwise result in the loss of the implanted embryo.

The secretion of hCG reaches a peak 60 to 80 days after the last menstruation (see Figure 17.34). It then decreases just as rapidly, so that by the end of the third month it has reached a low concentration that changes little for the duration of the pregnancy. Associated with this decrease in hCG secretion, the placenta begins to secrete large quantities of estrogen and progesterone. The very marked increases in plasma concentrations of estrogen and progesterone during the last 6 months of pregnancy are due to their secretion by the trophoblast cells of the placenta, and the corpus luteum regresses after 3 months.

An important aspect of placental steroid secretion is that the placenta has the enzymes required for the synthesis of progesterone but not those required for the formation of androgens, which are the precursors of estrogen. The placenta is supplied with androgens via the maternal ovaries and adrenal glands and by the *fetal* adrenal glands. The placenta converts the androgens into estrogen by expressing the enzyme aromatase.

The secretion of GnRH and, therefore, of LH and FSH is powerfully inhibited by high concentrations of progesterone in the presence of estrogen. Both of these gonadal steroids are secreted in high concentrations by the corpus luteum and then by the placenta throughout pregnancy, so the secretion of the pituitary gland gonadotropins remains extremely low. As a consequence, there are no ovarian or menstrual cycles during pregnancy.

The trophoblast cells of the placenta also produce inhibin and many other hormones that can influence the mother. One unique hormone that is secreted in very large amounts has effects similar to those of both prolactin and growth hormone. This protein hormone, **human placental lactogen,** mobilizes fats from maternal adipose tissue and stimulates glucose production in the liver (growth-hormone-like) in the mother. It also stimulates breast development (prolactin-like) in preparation for lactation. **Relaxin** is another hormone produced by the placenta; it has effects primarily on the maternal cardiovascular system. Among these are vasodilation and increased arteriolar compliance as well as increases in blood flow to the uterus. Finally, relaxin may facilitate the increase in maternal glomerular filtration rate characteristic of the normal renal adjustment to pregnancy. Some of the many other physiological changes, hormonal and nonhormonal, in the mother during pregnancy are summarized in **Table 17.9**.

Preeclampsia and Pregnancy Sickness Approximately 5% to 10% of pregnant women retain too much fluid (edema) and have protein in the urine and hypertension. These are the symptoms of ***preeclampsia;*** when convulsions also occur, the condition is termed ***eclampsia.*** These two syndromes are collectively called ***toxemia of pregnancy.*** This can result in decreased growth rate and death of the fetus. All of the factors responsible for eclampsia are not certain, but the evidence strongly implicates abnormal vasoconstriction of the maternal blood vessels and inadequate invasion of the endometrium by trophoblast cells, resulting in poor blood perfusion of the placenta.

Some women suffer from ***pregnancy sickness*** (popularly called morning sickness), which is characterized by nausea and vomiting during the first 3 months (first trimester) of pregnancy. The exact cause is unknown, but high concentrations of estrogen and other substances may be responsible. It may also be linked with increased sensitivity to odors, such as those of certain foods. It has been speculated that pregnancy sickness may have evolved to prevent ingestion of certain foods that may contain toxic alkaloid compounds or that carry parasites or other infectious organisms that could harm the developing fetus.

Parturition

A normal human pregnancy lasts approximately 40 weeks, counting from the first day of the last menstrual cycle, or approximately 38 weeks from the day of ovulation and conception. During the last few weeks of pregnancy, a variety of events occur in the uterus and the fetus, culminating in the birth (delivery) of the infant, followed by the placenta. All of these events, including delivery, are collectively called **parturition.** Throughout most of pregnancy, the smooth muscle cells of the myometrium are relatively disconnected from each other and the uterus is sealed at its outlet by the firm, inflexible collagen fibers that constitute the cervix. These features are maintained mainly by progesterone. During the last few weeks of pregnancy, as a result of ever-increasing concentrations of estrogen, the smooth muscle cells synthesize *connexins,* proteins that form gap junctions between the cells, which allow the myometrium to undergo coordinated contractions. Simultaneously, the cervix becomes soft and flexible due to an enzymatically mediated breakdown of its collagen fibers. The synthesis of the enzymes is mediated by a variety of messengers, including estrogen and placental prostaglandins, the synthesis of which is stimulated by estrogen. Estrogen also induces the expression of myometrial receptors for the posterior pituitary hormone oxytocin, which is a powerful stimulator of uterine smooth muscle contraction.

Delivery is produced by strong rhythmic contractions of the myometrium. Actually, weak and infrequent uterine contractions begin at approximately 30 weeks and gradually increase in both strength and frequency. During the last month, the entire uterine contents shift downward so that the near-term fetus is brought into contact with the cervix.

At the onset of labor and delivery or before, the amniotic sac ruptures, and the amniotic fluid flows through the vagina. When labor begins in earnest, the uterine contractions become strong and occur at approximately 10 to 15 min intervals. The contractions begin in the upper portion of the uterus and sweep downward.

As the contractions increase in intensity and frequency, the cervix is gradually forced open (dilation) to a maximum diameter of approximately 10 cm (4 in). Until this point, the contractions have not moved the fetus out of the uterus. Now the contractions move the fetus through the cervix and vagina. At this time, the mother—by bearing down to increase abdominal pressure—adds to the effect of uterine contractions to deliver the baby. The

TABLE 17.9 Maternal Responses to Pregnancy

Placenta	Secretion of estrogen, progesterone, human chorionic gonadotropin, inhibin, human placental lactogen, and other hormones
Anterior pituitary gland	Increased secretion of prolactin Secretes very little FSH and LH
Adrenal cortex	Increased secretion of aldosterone and cortisol
Posterior pituitary gland	Increased secretion of vasopressin
Parathyroids	Increased secretion of parathyroid hormone
Kidneys	Increased secretion of renin, erythropoietin, and 1,25-dihydroxyvitamin D Retention of salt and water *Cause:* Increased aldosterone, vasopressin, and estrogen
Breasts	Enlarge and develop mature glandular structure *Cause:* Estrogen, progesterone, prolactin, and human placental lactogen
Blood volume	Increased *Cause:* Total erythrocyte number increased by erythropoietin, and plasma volume by salt and water retention; however, plasma volume usually increases more than red cells, thereby leading to small decreases in hematocrit
Bone turnover	Increased *Cause:* Increased parathyroid hormone and 1,25-dihydroxyvitamin D
Body weight	Increased by average of 12.5 kg, 60% of which is water
Circulation	Cardiac output increases, total peripheral resistance decreases (vasodilation in uterus, skin, breasts, GI tract, and kidneys), and mean arterial pressure stays constant
Respiration	Hyperventilation occurs (arterial P_{CO_2} decreases) due to the effects of increased progesterone
Organic metabolism	Metabolic rate increases Plasma glucose, gluconeogenesis, and fatty acid mobilization all increase *Cause:* Hyporesponsiveness to insulin due to insulin antagonism by human placental lactogen and cortisol
Appetite and thirst	Increased (particularly after the first trimester)
Nutritional RDAs*	Increased

*RDA—Recommended daily allowance

umbilical vessels and placenta are still functioning so that the baby is not yet on its own; but within minutes of delivery, both the umbilical vessels and the placental vessels completely constrict, stopping blood flow to the placenta. The entire placenta becomes separated from the underlying uterine wall, and a wave of uterine contractions delivers the placenta.

Usually, parturition proceeds automatically from beginning to end and requires no significant medical intervention. In a small percentage of cases, however, the position of the baby or some maternal complication can interfere with normal delivery. In over 90% of births, the baby's head is downward and acts as the wedge to dilate the cervical canal when labor begins (**Figure 17.35**). Occasionally, a baby is oriented with some other part of the body downward (***breech presentation***). This may require the surgical delivery of the fetus and placenta through an abdominal and uterine incision (***cesarean section***). The headfirst position of the fetus is important for several reasons. (1) If the baby is not oriented headfirst, another portion of its body is in contact with the cervix and is generally a less effective wedge. (2) Because of the head's large diameter compared with the rest of the body, if the body were to go through the cervical canal first, the canal might obstruct the passage of the head, leading to problems when the partially delivered baby tries to breathe. (3) If the umbilical cord becomes caught between the canal wall and the baby's head or chest, mechanical compression of the umbilical vessels can result. Despite these potential problems, however, many babies who are not oriented headfirst are born without significant difficulties.

Mechanisms that Control the Events of Parturition

1. The smooth muscle cells of the myometrium have inherent rhythmicity and are capable of autonomous contractions, which are facilitated as the muscle is stretched by the growing fetus.
2. The pregnant uterus near term and during labor secretes several prostaglandins (PGE_2 and $PGF_{2\alpha}$) that are potent stimulators of uterine smooth muscle contraction.

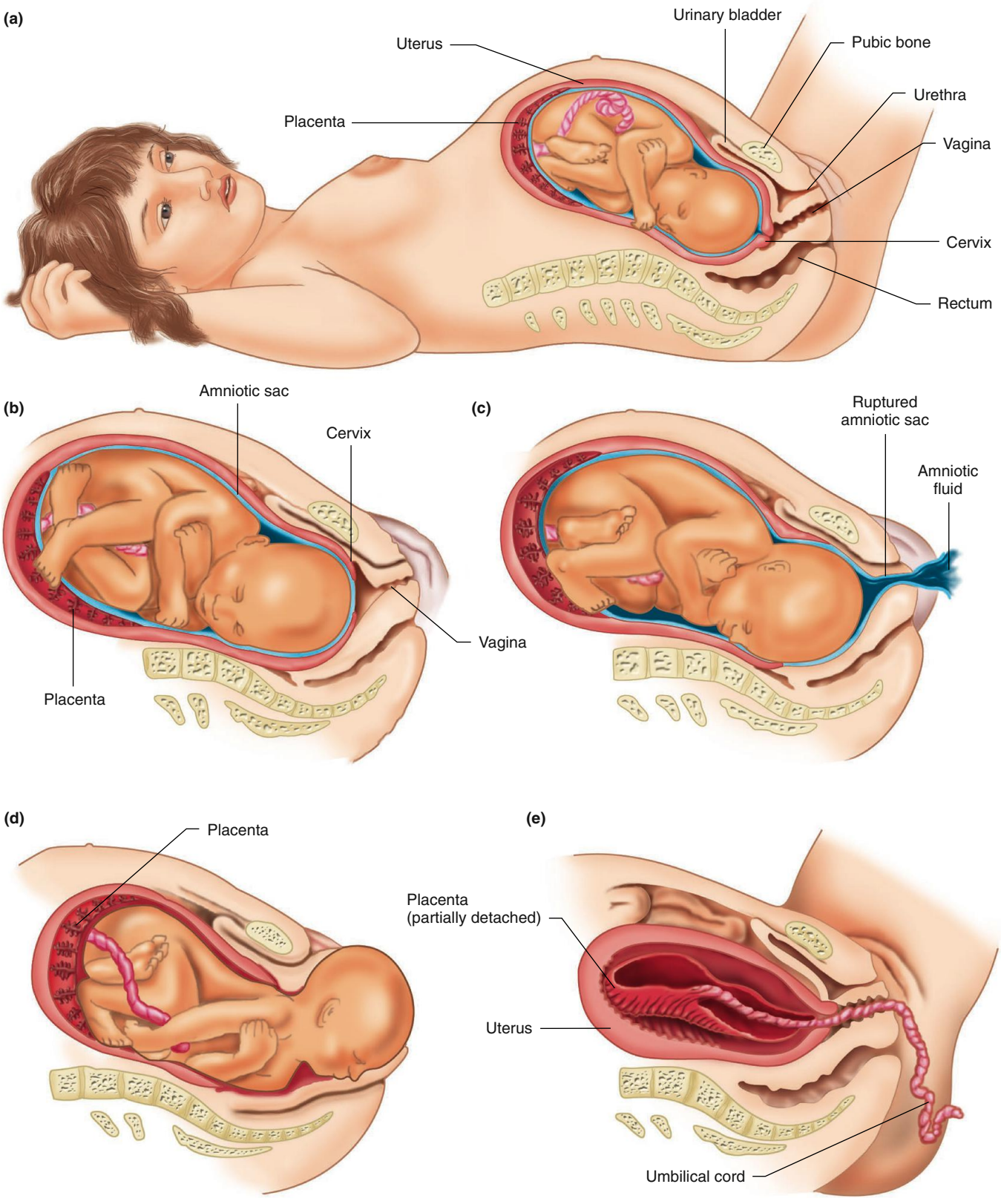


Figure 17.35 Stages of parturition. (a) Parturition has not yet begun. (b) The cervix is dilating. (c) The cervix is completely dilated, and the fetus's head is entering the cervical canal; the amniotic sac has ruptured and the amniotic fluid escapes. (d) The fetus is moving through the vagina. (e) The placenta is coming loose from the uterine wall in preparation for its expulsion.

3. **Oxytocin,** one of the hormones released from the posterior pituitary gland, is a potent uterine muscle stimulant. It not only acts directly on uterine smooth muscle but also stimulates it to synthesize the prostaglandins. Oxytocin is reflexively secreted from the posterior pituitary gland as a result of neural input to the hypothalamus, originating from receptors in the uterus, particularly the cervix. Also, as noted previously, the number of oxytocin receptors in the uterus increases during the last few weeks of pregnancy. Therefore, the contractile response to any given plasma concentration of oxytocin is greatly increased at parturition.
4. Throughout pregnancy, progesterone exerts an essential powerful inhibitory effect upon uterine contractions by decreasing the sensitivity of the myometrium to estrogen, oxytocin, and prostaglandins. Unlike the situation in many other species, however, the rate of progesterone secretion does not decrease before or during parturition in women (until after delivery of the placenta, the source of the progesterone); therefore, progesterone withdrawal is not important in human parturition.

These mechanisms are shown in **Figure 17.36**. Once started, the uterine contractions exert a positive feedback effect upon themselves via both local facilitation of inherent uterine contractions and reflexive stimulation of oxytocin secretion. Precisely what the relative importance of all these factors is in *initiating* parturition remains unclear. One hypothesis is that the fetoplacental unit, rather than the mother, is the source of the initiating signals to start parturition. That is, the fetus begins to outstrip the ability of the placenta to supply oxygen and nutrients and to remove waste products. This leads to the fetal production of hormonal signals like ACTH. Another theory is that a "placental clock," acting via placental production of CRH, signals the fetal production of ACTH. Either way, ACTH-mediated increases in fetal adrenal steroid production seem to be an important signal to the mother to begin parturition. Whether it is a signal from the fetus, the placenta, or both, the initiation of parturition is another excellent example of the general principle of physiology that information flow—in this case, from the fetoplacental unit to the maternal brain and pituitary gland—allows for integration of physiological processes.

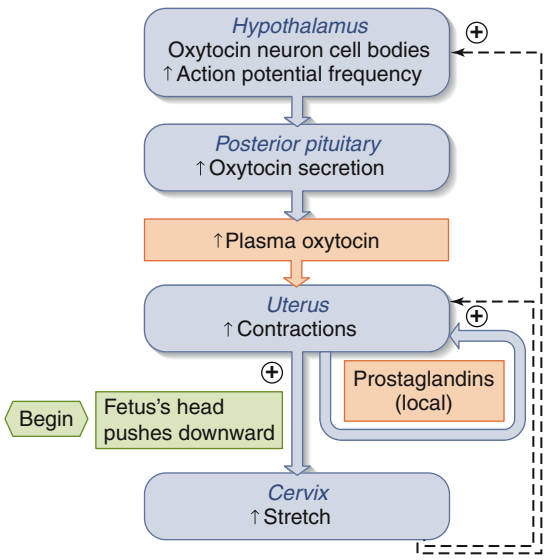


Figure 17.36 Factors stimulating uterine contractions during parturition. Note the positive feedback nature of several of the inputs.

PHYSIOLOGICAL INQUIRY

- If a full-term fetus is oriented feet-first in the uterus, parturition may not proceed in a timely manner. Why?

Answer can be found at end of chapter.

The actions of prostaglandins on parturition are the last in a series of prostaglandin effects on the female reproductive system. They are summarized in **Table 17.10**.

Lactation

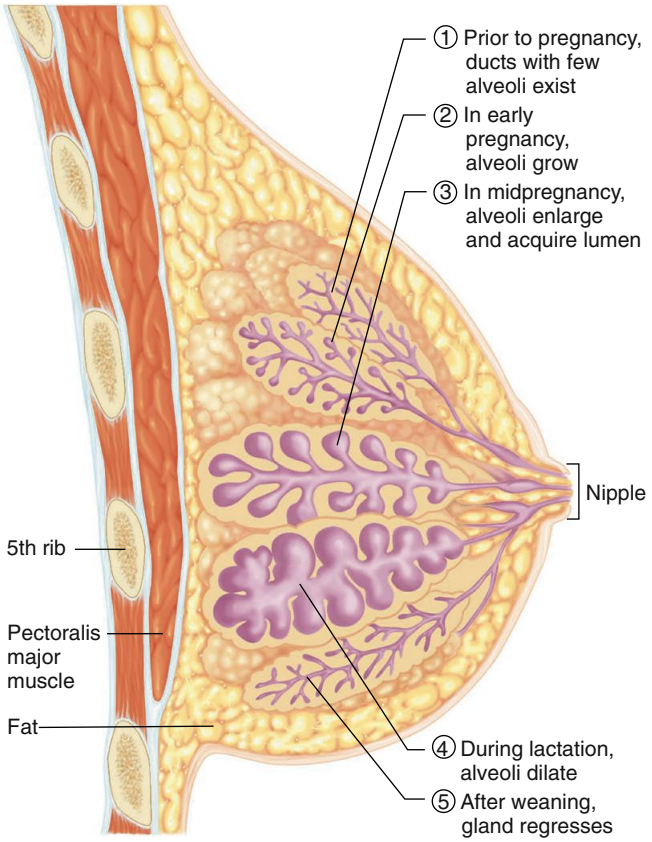
The production and secretion of milk by the **mammary glands,** which are located within the breasts, is called **lactogenesis.** The mammary glands undergo an increase in size and cell number during late pregnancy. After birth of the baby, milk is produced and secreted; this process is also known as **lactation** (or nursing). Each breast contains numerous mammary glands, each with ducts that branch all through the tissue and converge at the nipples (**Figure 17.37**). These ducts start in saclike structures called **alveoli** (the same term is used to denote the lung air sacs). The breast alveoli, which are the sites of milk secretion, look like bunches of grapes with stems terminating in the ducts. The alveoli and the ducts immediately adjacent to them are surrounded by specialized contractile cells called **myoepithelial cells.**

Before puberty, the breasts are small with little internal glandular structure. With the onset of puberty in females, the increased estrogen concentration stimulates duct growth and

TABLE 17.10 Some Effects of Prostaglandins* on the Female Reproductive System

Site of Production	Action of Prostaglandins	Result
Late antral follicle	Stimulate production of digestive enzymes	Rupture of follicle
Corpus luteum	May interfere with hormone secretion and function	Death of corpus luteum
Uterus	Constrict blood vessels in endometrium	Onset of menstruation
	Cause changes in endometrial blood vessels and cells early in pregnancy	Facilitates implantation
	Increase contraction of myometrium	Helps to initiate both menstruation and parturition
	Cause cervical ripening	Facilitates cervical dilation during parturition

*The term *prostaglandins* is used loosely here, as is customary in reproductive physiology, to include all the eicosanoids.



AP|R **Figure 17.37** Anatomy of the breast. The numbers refer to the sequential changes that occur over time.

branching but relatively little development of the alveoli; much of the breast enlargement at this time is due to fat deposition. Progesterone secretion also commences at puberty during the luteal phase of each cycle, and this hormone contributes to breast growth by stimulating the growth of alveoli.

During each menstrual cycle, the breasts undergo fluctuations in association with the changing blood concentrations of estrogen and progesterone. These changes are small compared with the breast enlargement that occurs during pregnancy as a result of the stimulatory effects of high plasma concentrations of estrogen, progesterone, prolactin, and human placental lactogen. Except for prolactin, which is secreted by the maternal anterior pituitary gland, these hormones are secreted by the placenta. Under the influence of these hormones, both the ductal and the alveolar structures become fully developed.

As described in Chapter 11, other factors influence the anterior pituitary gland cells that secrete prolactin. They are inhibited by **dopamine,** which is secreted by the hypothalamus. They are probably stimulated by at least one **prolactin-releasing factor (PRF),** also secreted by the hypothalamus (the chemical identity of PRF in humans is still uncertain). The dopamine and PRF secreted by the hypothalamus are hypophysiotropic hormones that reach the anterior pituitary gland by way of the hypothalamo–hypophyseal portal vessels. This positive and negative hypophysiotropic control of the secretion of prolactin is reminiscent of the dual hypophysiotropic control of growth hormone described in Figure 11.28 and is an example of the general principle of physiology that functions are controlled by multiple regulatory systems, often acting in opposition.

Under the dominant inhibitory influence of dopamine, prolactin secretion is low before puberty. It then increases considerably at puberty in girls but not in boys, stimulated by the increased plasma estrogen concentration that occurs at this time. During pregnancy, there is a further large increase in prolactin secretion due to stimulation by estrogen.

Prolactin is the major hormone stimulating the production of milk. However, despite the fact that prolactin concentrations are increased and the breasts are considerably enlarged and fully developed as pregnancy progresses, there is usually no secretion of milk. This is because estrogen and progesterone, in large concentrations, prevent milk production by inhibiting this action of prolactin on the breasts. Therefore, although estrogen causes an increase in the secretion of prolactin and acts with prolactin in promoting breast growth and differentiation, it—along with progesterone—inhibits the ability of prolactin to induce milk production. Delivery removes the source—the placenta—of the large amounts of estrogen and progesterone and thereby releases milk production from inhibition.

The decrease in estrogen following parturition also causes basal prolactin secretion to decrease from its peak, late-pregnancy concentrations. After several months, prolactin returns toward prepregnancy concentrations even if the mother continues to nurse. Superimposed upon these basal concentrations, however, are large secretory bursts of prolactin during each nursing period. The episodic pulses of prolactin are signals to the breasts to maintain milk production. These pulses usually cease several days after the mother completely stops nursing her infant but continue as long as nursing continues.

The reflexes mediating the surges of prolactin (**Figure 17.38**) are initiated by afferent input to the hypothalamus from nipple receptors stimulated by suckling. This input's major effect is to inhibit the hypothalamic neurons that release dopamine.

One other reflex process is important for lactation. Milk is secreted into the lumen of the alveoli, but the infant cannot suck the milk out of the breast. It must first be moved into the ducts, from which it can be suckled. This movement is called the **milk ejection reflex** (also called milk letdown) and is accomplished by contraction of the myoepithelial cells surrounding the alveoli. The contraction is under the control of oxytocin, which is reflexively released from posterior pituitary neurons in response to suckling (see Figure 17.38). Higher brain centers can also exert an important influence over oxytocin release; a nursing mother may actually leak milk when she hears her baby cry or even thinks about nursing.

Suckling also inhibits the hypothalamo–hypophyseal–ovarian axis at a variety of steps, with a resultant block of ovulation. This is probably due to increased prolactin, which directly inhibits gonadotropin secretion and the hypothalamic GnRH neurons. If suckling is continued at a high frequency, ovulation can be delayed for months to years. This "natural" birth control may help to space out pregnancies. When supplements are added to the baby's diet and the frequency of suckling is decreased, however, most women will resume ovulation even though they continue to nurse. However, ovulation may resume even without a decrease in nursing. Failure to use adequate birth control may result in an unplanned pregnancy in nursing women.

After delivery, the breasts initially secrete a watery, protein-rich fluid called **colostrum.** After about 24 to 48 hours, the secretion of milk itself begins. Milk contains six major nutrients: water,

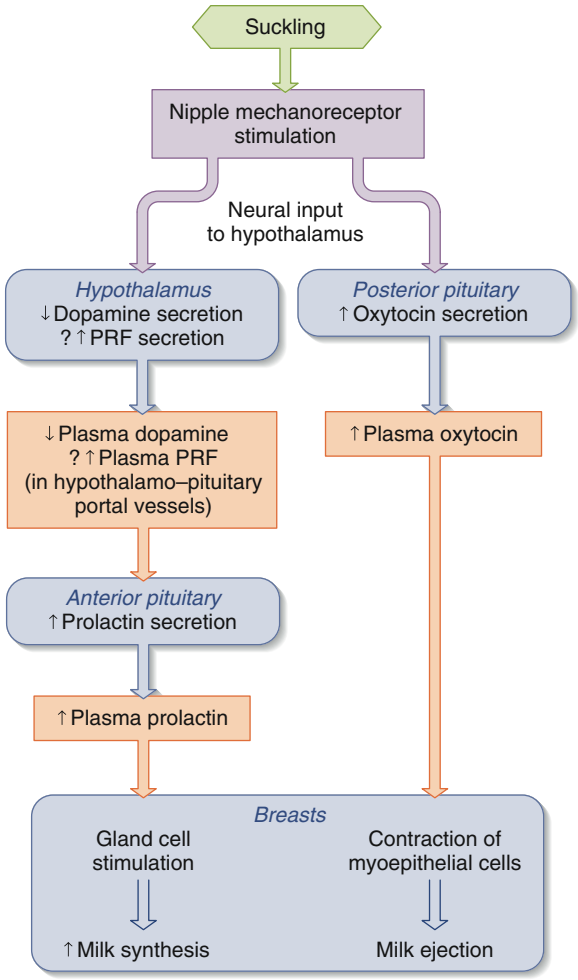


Figure 17.38 Major controls of the secretion of prolactin and oxytocin during nursing. The importance of PRF (prolactin-releasing factors) in humans is not known (indicated by ?).

proteins, lipids, the carbohydrate lactose (milk sugar), minerals, and vitamins.

Colostrum and milk also contain antibodies, leukocytes, and other messengers of the immune system, all of which are important for the protection of the newborn, as well as for longer-term activation of the child's own immune system. Milk also contains many growth factors and hormones thought to help in tissue development and maturation, as well as a large number of neuropeptides and endogenous opioids that may subtly shape the infant's brain and behavior. Some of these substances are synthesized by the breasts themselves, not just transported from blood to milk. The reasons the milk proteins can gain entry to the newborn's blood are that (1) the low gastric acidity of the newborn does not denature them, and (2) the newborn's intestinal epithelium is more permeable to proteins than is the adult epithelium.

Unfortunately, infectious agents, including the virus that causes AIDS, can also be transmitted through breast milk, as can some drugs. For example, the concentration of alcohol in breast milk is approximately the same as in maternal plasma.

Breast-feeding for at least the first 6 to 12 months is strongly advocated by health care professionals. In less-developed countries, where alternative formulas are often either contaminated or nutritionally inadequate because of improper dilution or inadequate refrigeration, breast-feeding significantly reduces infant sickness and mortality. In the United States, effects on infant survival are not usually apparent, but breast-feeding reduces the severity of gastrointestinal infections, has positive effects on mother–infant interaction, is economical, and has long-term health benefits. Cow's milk has many but not all of the constituents of mother's milk and often in very different concentrations; it is difficult to duplicate mother's milk in a commercial formula.

Contraception

Physiologically, pregnancy is said to begin not at fertilization but after implantation is complete, approximately one week *after* fertilization. Birth control methods that work prior to implantation are called ***contraceptives*** (**Table 17.11**). Procedures that cause the death of the embryo or fetus after implantation are called abortions; chemical substances used to induce abortions are called ***abortifacients.***

Some forms of contraception, such as vasectomy, tubal ligation, vaginal diaphragms, vaginal caps, spermicides, and condoms, prevent sperm from reaching the egg. In addition, condoms significantly reduce the risk of ***sexually transmitted diseases*** (***STDs***) such as AIDS, syphilis, gonorrhea, chlamydia, and herpes.

Oral contraceptives are based on the fact that estrogen and progesterone can inhibit pituitary gland gonadotropin release, thereby preventing ovulation. One type of oral contraceptive is a combination of a synthetic estrogen and a progesterone-like substance (a progestogen or progestin). Another type is the so-called minipill, which contains only the progesterone-like substance. In actuality, the oral contraceptives, particularly the minipill, do not always prevent ovulation, but they are still effective because they have other contraceptive effects. For example, progestogens affect the composition of the cervical mucus, reducing the ability of the sperm to pass through the cervix; they also inhibit the estrogen-induced proliferation of the endometrium, making it inhospitable for implantation. There are different formulations in both of these categories—more details can be found at www.fda.gov.

Delivery devices that use other than the oral route for contraception include subcutaneous implantables, intramuscular injections, skin patches, and vaginal rings. The ***intrauterine device*** (***IUD***) works beyond the point of fertilization but before implantation has begun or is complete. The IUD can be hormonal or elemental (e.g., copper) in nature. The mechanism of action includes thinning or disrupting the endometrial lining, preventing implantation.

In addition to the methods used before intercourse (precoital contraception), there are a variety of drugs used within 72 h *after* intercourse (postcoital or emergency contraception). These most commonly interfere with ovulation, transport of the conceptus to the uterus, or implantation. One approach is a high dose of estrogen, or two large doses (12 h apart) of a combined estrogen–progestin oral contraceptive. Another approach has used the drug ***mifepristone,*** which has antiprogesterone activity because it binds competitively to progesterone receptors in the uterus but does not activate them. Antagonism of progesterone's effects causes the endometrium to erode and the contractions of the fallopian tubes and myometrium to increase. Mifepristone can also be used later in pregnancy as an abortifacient.

TABLE 17.11 Some Forms of Contraception

Method	First-Year Failure Rate*	Physiological Mechanism of Effectiveness
Barrier methods	12%–23%	Prevent sperm from entering uterus
Condoms (♂ and ♀)		
Diaphragm/cervical cap (♀)		
Spermicides (♀)	20%–50%	Kill sperm in the vagina (after insemination)
Sterilization	<0.5%	
Vasectomy (♂)		Prevents sperm from becoming part of seminal fluid
Tubal ligation (♀)		Prevents sperm from reaching egg
Intrauterine device (IUD) (♀)	<3%	Prevents implantation of blastocyst
Estrogens and/or progestins		Prevent ovulation by suppressing LH surge (negative feedback); thicken cervical mucus (prevents sperm from entering uterus); alter endometrium to prevent implantation of blastocyst
Oral contraceptive pill (♀)	3%	
Emergency oral contraception (♀)	1%	
Injectable or implantable progestins (♀)	<0.5%	
Transdermal (skin patch) (♀)	1%–2%	
Vaginal ring (♀)	1%–2%	

***Failure rates assume consistent and proper use.**

From Hall, J. E., Infertility and Fertility Control, *Harrison's Principles of Internal Medicine,* McGraw-Hill, 2004; Rosen, M., and Cedars, M. I., Female Reproductive Endocrinology and Infertility, *Basic and Clinical Endocrinology,* 7th ed., McGraw-Hill, 2004; ACOG Practice Bulletin, Emergency Contraception, *Obstet. Gynecol.* 2005, 106:1443–52. See also www.fda.gov.

Notes:
Spermicides are often used in combination with diaphragm/cervical cap and condoms.
Only condoms are effective in preventing sexually transmitted diseases.
The cervical sponge was made available again in 2009.
Rhythm method (abstinence around time of ovulation) and coitus interruptus (withdrawal) are not listed because they are not reliable.
Only total abstinence is 100% effective in preventing pregnancy.

The ***rhythm method*** uses abstention from sexual intercourse near the time of ovulation. Unfortunately, it is difficult to time ovulation precisely, even with laboratory techniques. For example, the small increase in body temperature or change in vaginal epithelium, both of which are indicators of ovulation, occur only *after* ovulation. This, combined with the marked variability of the time of ovulation in many women—from day 5 to day 15 of the cycle, explains why the rhythm method has a high failure rate.

There are still no effective chemical agents for male contraception. Administration of low doses of testosterone has been proposed as a male contraceptive since it will decrease FSH and LH stimulation of the Leydig and Sertoli cells, respectively, but will maintain libido.

Infertility

With unprotected intercourse and no means to block conception, about 85% of couples will conceive during the first year. Approximately 12% of men and women of reproductive age in the United States are infertile. The numbers of infertile men and women are approximately equal until about age 30, after which infertility becomes more prevalent in women. In many cases, infertility can be successfully treated with drugs, artificial insemination, or corrective surgery.

When the cause of infertility cannot be treated, it can sometimes be circumvented in women by the technique of ***in vitro fertilization.*** First, the woman is injected with drugs that stimulate multiple egg production. Immediately before ovulation, at least one egg is then removed from the ovary via a needle inserted into the ovary through the top of the vagina or the lower abdominal wall. The egg is placed in a dish for several days with sperm. After the fertilized egg has developed into a cluster of two to eight cells, it is then transferred to the woman's uterus. The success rate of this procedure, when one egg is transferred, may be as high as 30%.

17.20 Menopause

When a woman is around the average age of 50 to 52, menstrual cycles become less regular. The phase of life during which menstrual irregularity begins is termed **perimenopause.** Ultimately, menstrual cycles cease entirely in all women; when this period exceeds 12 months, this cessation is known as **menopause.** The cessation of reproductive function involves many physical and sometimes psychological changes.

Menopause and the irregular function leading to it are caused primarily by ovarian failure. The ovaries lose their ability to respond to the gonadotropins, mainly because most, if not all, ovarian follicles and eggs have disappeared by this time through atresia. The hypothalamus and anterior pituitary gland continue to function relatively normally as demonstrated by the fact that the gonadotropins are secreted in greater amounts. The main reason for this is that the decrease in the plasma concentrations of estrogen and inhibin result in less negative feedback inhibition of gonadotropin secretion.

A small amount of estrogen usually persists in plasma beyond menopause, mainly from the peripheral conversion of adrenal androgens to estrogen by aromatase, but the concentration is inadequate to maintain estrogen-dependent tissues. The breasts and genital organs gradually atrophy. Thinning and dryness of the vaginal epithelium can cause sexual intercourse to be painful. Because estrogen is a potent bone-protective hormone, significant decreases in bone mass may occur (***osteoporosis***). This results in

an increased risk of bone fractures in postmenopausal women. The ***hot flashes*** so typical of menopause are periodic sudden feelings of warmth, dilation of the skin arterioles, and marked sweating. The effects of estrogen in the temperature-regulating regions of the hypothalamus are thought to be at least partially responsible for hot flashes. In addition, the incidence of cardiovascular disease increases after menopause.

Many of the symptoms associated with menopause, as well as the development of osteoporosis, can be reduced by the administration of estrogen. The desirability of administering estrogen to postmenopausal women is controversial, however, because estrogen administration increases the risk of developing uterine endometrial cancer and breast cancer. ■

SECTION C SUMMARY

Anatomy

I. The female internal genitalia are the ovaries, fallopian tubes, uterus, cervix, and vagina.
II. The female external genitalia include the mons pubis, labia, clitoris, and vestibule of the vagina. These are also called the vulva.

Ovarian Functions

I. The female gonads, the ovaries, produce eggs and secrete estrogen, progesterone, and inhibin.
II. The two meiotic divisions of oogenesis result in each ovum having 23 chromosomes, in contrast to the 46 of the original oogonia.
III. The follicle consists of the egg, inner layers of granulosa cells surrounding the egg, and outer layers of theca cells.
IV. At the beginning of each menstrual cycle, a group of preantral and early antral follicles continues to develop, but soon only the dominant follicle continues its development to full maturity and ovulation.
V. Following ovulation, the remaining cells of the dominant follicle differentiate into the corpus luteum, which lasts about 10 to 14 days if pregnancy does not occur.
VI. The menstrual cycle can be divided, according to ovarian events, into a follicular phase and a luteal phase, which each lasts approximately 14 days; they are separated by ovulation.

Control of Ovarian Function

I. The menstrual cycle results from a finely tuned interplay of hormones secreted by the ovaries, the anterior pituitary gland, and the hypothalamus.
II. During the early and middle follicular phases, FSH stimulates the granulosa cells to proliferate and secrete estrogen, and LH stimulates the theca cells to proliferate and produce the androgens that the granulosa cells use to make estrogen.
    a. During this time, estrogen exerts negative feedback on the anterior pituitary gland to inhibit the secretion of the gonadotropins. It also inhibits the secretion of GnRH by the hypothalamus.
    b. Inhibin preferentially inhibits FSH secretion.
III. During the late follicular phase, plasma estrogen increases to elicit a surge of LH, which then causes, via the granulosa cells, completion of the egg's first meiotic division and cytoplasmic maturation, ovulation, and formation of the corpus luteum.
IV. During the luteal phase, under the influence of small amounts of LH, the corpus luteum secretes progesterone and estrogen. Regression of the corpus luteum results in a cessation of the secretion of these hormones.
V. Secretion of GnRH and the gonadotropins is inhibited during the luteal phase by the combination of progesterone, estrogen, and inhibin.

Uterine Changes in the Menstrual Cycle

I. The ovarian follicular phase is equivalent to the uterine menstrual and proliferative phases, the first day of menstruation being the first day of the cycle. The ovarian luteal phase is equivalent to the uterine secretory phase.
    a. Menstruation occurs when the plasma estrogen and progesterone concentrations decrease as a result of regression of the corpus luteum.
    b. During the proliferative phase, estrogen stimulates growth of the endometrium and myometrium and causes the cervical mucus to be readily penetrable by sperm.
    c. During the secretory phase, progesterone converts the estrogen-primed endometrium to a secretory tissue and makes the cervical mucus relatively impenetrable to sperm. It also inhibits uterine contractions.

Additional Effects of Gonadal Steroids

I. The many effects of estrogen and progesterone are summarized in Table 17.8.
II. Androgens are produced in women and have several functions including growth of pubic and axillary hair.
III. Excess androgen can cause virilization.

Puberty

I. At puberty, the hypothalamo–pituitary–gonadal axis becomes active as a result of a change in brain function that permits increased secretion of GnRH.
II. The first sign of puberty is the appearance of pubic and axillary hair.

Female Sexual Response

I. Sexual intercourse results in increases in blood flow and muscular contractions throughout the body.
II. Androgens appear to be important in libido in women.

Pregnancy

I. After ovulation, the egg is swept into the fallopian tube, where a sperm, having undergone capacitation and the acrosome reaction, fertilizes it.
II. Following fertilization, the egg undergoes its second meiotic division and the nuclei of the egg and sperm fuse. Reactions in the ovum block penetration by other sperm and trigger cell division and embryogenesis.
III. The conceptus undergoes cleavage, eventually becoming a blastocyst, which implants in the endometrium on approximately day 7 after ovulation.
    a. The trophoblast gives rise to the fetal part of the placenta, whereas the inner cell mass develops into the embryo proper.
    b. Although they do not mix, fetal blood and maternal blood both flow through the placenta, exchanging gases, nutrients, hormones, waste products, and other substances.
    c. The fetus is surrounded by amniotic fluid in the amniotic sac.
IV. The progesterone and estrogen required to maintain the uterus during pregnancy come from the corpus luteum for the first 2 months of pregnancy, their secretion stimulated by human chorionic gonadotropin produced by the trophoblast.
V. During the last 7 months of pregnancy, the corpus luteum regresses and the placenta itself produces large amounts of progesterone and estrogen.
VI. The high concentrations of progesterone, in the presence of estrogen, inhibit the secretion of GnRH and thereby that of the gonadotropins, so that menstrual cycles do not occur.
VII. Delivery occurs by rhythmic contractions of the uterus, which first dilate the cervix and then move the infant, followed by the placenta, through the vagina. The contractions are stimulated in part by oxytocin, released from the posterior pituitary gland in a reflex triggered by uterine mechanoreceptors, and by uterine prostaglandins.

VIII. The breasts develop markedly during pregnancy as a result of the combined influences of estrogen, progesterone, prolactin, and human placental lactogen.
   a. Prolactin secretion is stimulated during pregnancy by estrogen acting on the anterior pituitary gland, but milk is not synthesized because high concentrations of estrogen and progesterone inhibit the milk-producing action of prolactin on the breasts.
   b. As a result of the suckling reflex, large bursts of prolactin and oxytocin are released during nursing. The prolactin stimulates milk production and the oxytocin causes milk ejection.

Menopause

I. When a woman is around the age of 50, her menstrual cycles become less regular and ultimately disappear—menopause.
   a. The cause of menopause is a decrease in the number of ovarian follicles and their hyporesponsiveness to the gonadotropins.
   b. The symptoms of menopause are largely due to the marked decrease in plasma estrogen concentration.

SECTION C REVIEW QUESTIONS

1. Draw the female reproductive tract.
2. Describe the various stages from oogonium to mature ovum.
3. Describe the progression from a primordial follicle to a dominant follicle.
4. Name three hormones produced by the ovaries and name the cells that produce them.
5. Diagram the changes in plasma concentrations of estrogen, progesterone, LH, and FSH during the menstrual cycle.
6. What are the analogies between the granulosa cells and the Sertoli cells and between the theca cells and the Leydig cells?
7. List the effects of FSH and LH on the follicle.
8. Describe the effects of estrogen and inhibin on gonadotropin secretion during the early, middle, and late follicular phases.
9. List the effects of the LH surge on the egg and the follicle.
10. What are the effects of the sex steroids and inhibin on gonadotropin secretion during the luteal phase?
11. Describe the hormonal control of the corpus luteum and the changes that occur in the corpus luteum in a nonpregnant cycle and in a cycle when pregnancy occurs.
12. What happens to the sex steroids and the gonadotropins as the corpus luteum degenerates?
13. Compare the phases of the menstrual cycle according to uterine and ovarian events.
14. Describe the effects of estrogen and progesterone on the endometrium, cervical mucus, and myometrium.
15. Describe the uterine events associated with menstruation.
16. List the effects of estrogen on the accessory sex organs and secondary sex characteristics.
17. List the effects of progesterone on the breasts, cervical mucus, vaginal epithelium, and body temperature.
18. What are the sources and effects of androgens in women?
19. How does the egg get from the ovary to a fallopian tube?
20. Where does fertilization normally occur?
21. Describe the events that occur during fertilization.
22. How many days after ovulation does implantation occur, and in what stage is the conceptus at that time?
23. Describe the structure of the placenta and the pathways for exchange between maternal and fetal blood.
24. State the sources of estrogen and progesterone during different stages of pregnancy. What is the dominant estrogen of pregnancy, and how is it produced?
25. What is the state of gonadotropin secretion during pregnancy, and what is the cause?
26. What anatomical feature permits coordinated contractions of the myometrium?
27. Describe the mechanisms and messengers that contribute to parturition.
28. List the effects of prostaglandins on the female reproductive system.
29. Describe the development of the breasts after puberty and during pregnancy, and list the major hormones responsible.
30. Describe the effects of estrogen on the secretion and actions of prolactin during pregnancy.
31. Diagram the suckling reflex for prolactin release.
32. Diagram the milk ejection reflex.
33. List two main types of amenorrhea and give examples of each.
34. What is the state of estrogen and gonadotropin secretion before puberty and after menopause?
35. List the hormonal and anatomical changes that occur after menopause.

SECTION C KEY TERMS

egg
menstrual cycles
menstruation
ovulation

17.12 Anatomy

cervix
clitoris
fallopian tubes
female external genitalia
female internal genitalia
fimbriae
hymen
uterus
vagina
vulva

17.13 Ovarian Functions

antrum
atresia
corpus luteum
cumulus oophorus
dominant follicle
follicles
follicular phase
fraternal (dizygotic) twins
graafian follicle
granulosa cells
luteal phase
oogenesis
oogonia (oogonium)
primordial follicles
theca
zona pellucida

17.14 Control of Ovarian Function

LH surge

17.15 Uterine Changes in the Menstrual Cycle

endometrium
menstrual phase
myometrium
proliferative phase
secretory phase

17.16 Additional Effects of Gonadal Steroids

estrogen priming

17.17 Puberty

menarche

17.19 Pregnancy

acrosome reaction
alveoli
amnion
amniotic cavity
amniotic fluid
amniotic sac
blastocyst
block to polyspermy
capacitation
chorion
chorionic villi
cleavage
colostrum
conceptus
congenital
cortical reaction
dopamine
embryo
fertilization
fetus
human chorionic gonadotropin (hCG)
human placental lactogen
implantation
inner cell mass
lactation
lactogenesis
mammary glands

milk ejection reflex
myoepithelial cells
oxytocin
parturition
placenta
prolactin-releasing factor (PRF)
relaxin
sinus
stem cells
totipotent
trophoblast
umbilical arteries
umbilical cord
umbilical vein

17.20 Menopause

menopause
perimenopause

SECTION C CLINICAL TERMS

17.15 Uterine Changes in the Menstrual Cycle

dysmenorrhea

17.16 Additional Effects of Gonadal Steroids

premenstrual dysphoric disorder (PMDD)
premenstrual syndrome (PMS)
premenstrual tension
virilization

17.17 Puberty

amenorrhea
anorexia nervosa
precocious puberty

17.19 Pregnancy

abortifacients
amniocentesis
breech presentation
cesarean section
chorionic villus sampling
contraceptives
Down syndrome
eclampsia
ectopic pregnancies
intrauterine device (IUD)
in vitro fertilization
mifepristone
miscarriage
oral contraceptives
preeclampsia
pregnancy sickness
rhythm method
sexually transmitted diseases (STDs)
teratogen
toxemia of pregnancy

17.20 Menopause

hot flashes
osteoporosis

CHAPTER 17

Clinical Case Study: Cessation of Menstrual Cycles in a 21-Year-Old College Student

A 21-year-old female college student underwent menarche at 13 years of age. After 5 years of normal menses, her menstrual periods became less frequent and finally stopped (***secondary amenorrhea***). She does not use oral contraception nor is she sexually active, and a urine pregnancy test is negative.

She also complains of headaches in the front of her head. During a physical examination by her family practitioner, a milky discharge can be expressed from both nipples. The clinician also finds that the patient has loss of temporal (peripheral) vision in both eyes. A pituitary gland tumor secreting prolactin is suspected. A magnetic resonance image (MRI) reveals the presence of a pituitary gland tumor, and when a blood test for prolactin concentration comes back very high, the diagnosis of *hyperprolactinemia* (excess prolactin in the blood) is confirmed.

Tumors of the lactotrophs of the anterior pituitary gland can hypersecrete prolactin, which in turn suppresses LH and FSH secretion (**Figure 17.39**). Thus, menstrual cycles cannot continue because gonadotropin concentrations are low. This is often accompanied by ***galactorrhea***—inappropriate milk production—because

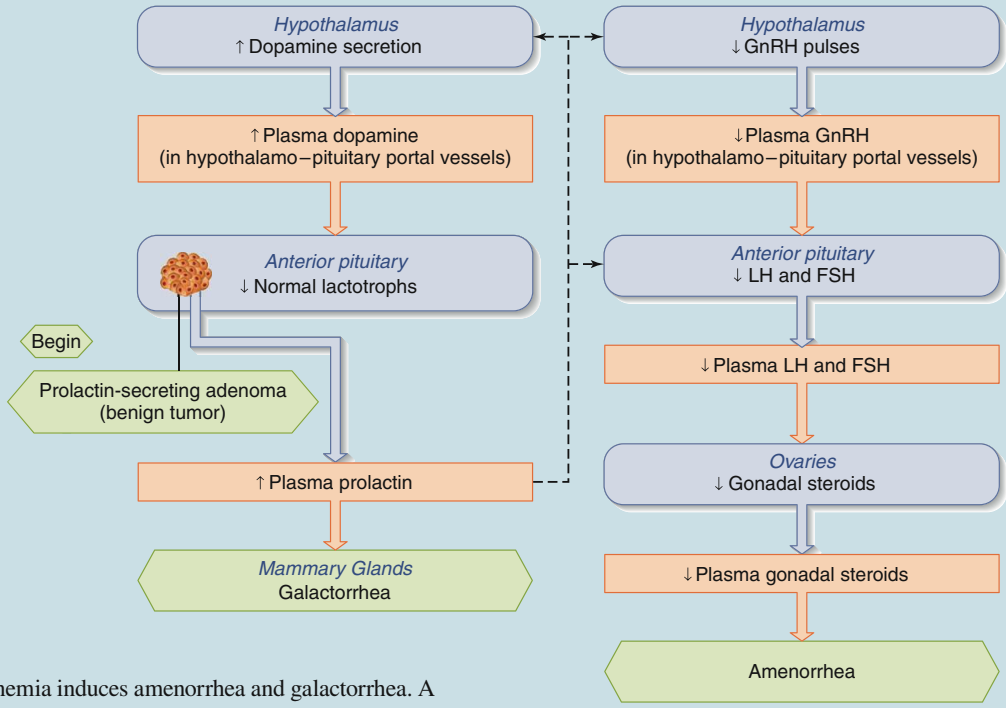


Figure 17.39 Mechanism of how hyperprolactinemia induces amenorrhea and galactorrhea. A benign prolactin-secreting pituitary tumor increases plasma prolactin. This stimulates lactogenesis in the mammary glands and inhibits GnRH pulses and pituitary gonadotropin secretion. This results in a marked decrease in ovarian estrogen secretion and the loss of menstrual cycles. The increase in prolactin can also stimulate dopamine release into the hypothalamo-pituitary-portal veins, thereby inhibiting the otherwise normal prolactin-secreting cells in the anterior pituitary (negative feedback loop).

(Continued)

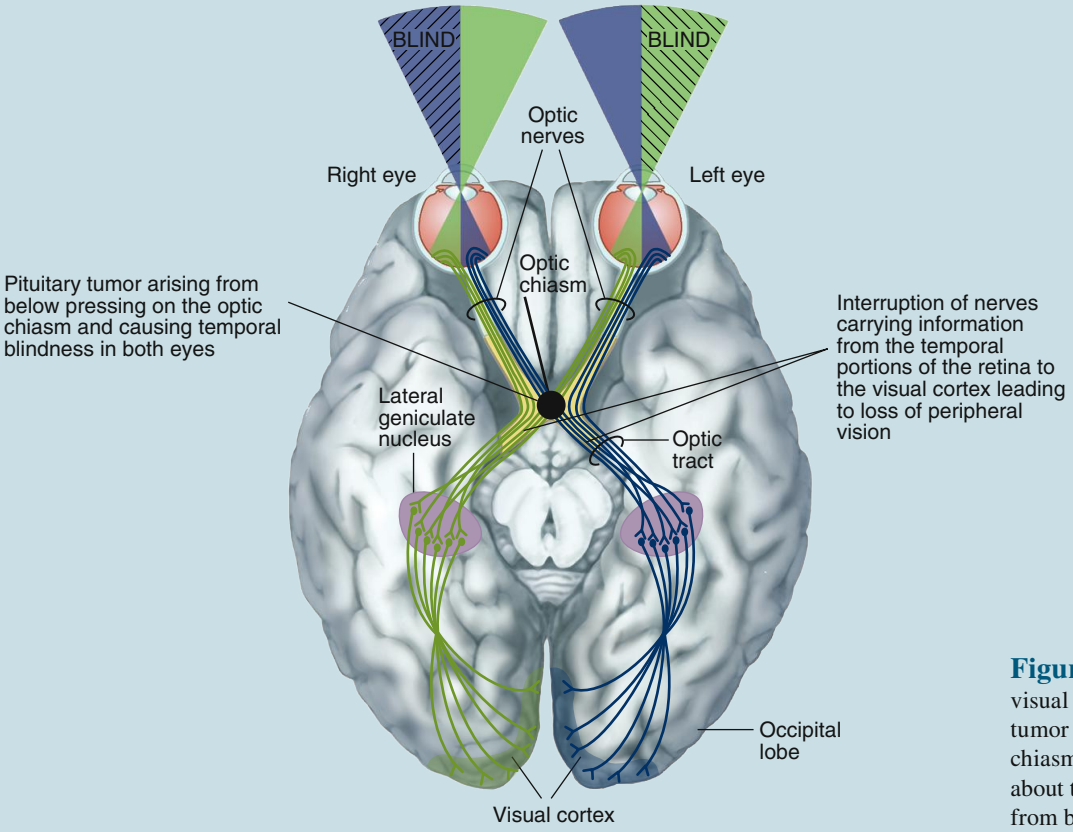


Figure 17.40 Mechanism of loss of lateral visual fields due to a large pituitary gland tumor pressing up from below on the optic chiasm. Refer back to Figure 7.31 for details about the optic tracts and chiasm. This view is from below the brain.

prolactin stimulates the mammary gland. Prolactin-secreting tumors (***prolactinomas***) are the most common of the functioning pituitary gland tumors. (Recall from Chapter 11 that pituitary gland tumors arising from different pituitary gland cell types can secrete other pituitary gland hormones—such as growth hormone, causing gigantism and acromegaly, and ACTH, causing Cushing's disease.)

Reflect and Review #1

- Why does pregnancy cause amenorrhea? *(Hint:* See Figures 17.26 and 17.34.)

If the tumor becomes large enough, it can cause headaches due to stretching of the dura mater near the pituitary gland. The mechanism of the loss of vision in our patient is shown in **Figure 17.40**. The pituitary gland is located just below the optic chiasm. As the tumor grows, it can press on the optic chiasm, interrupting afferent nerve transmission. Because the nerves from the medial parts of the retina cross just above the pituitary gland, they are usually most affected by compression from pituitary gland tumors. As illustrated in the figure, the loss of afferent input from the medial parts of the retina leads to a loss of lateral vision in both eyes. Hyperprolactinemia is usually treated with dopamine agonists such as bromocriptine or cabergoline, because prolactin is primarily under the inhibitory control of hypothalamic dopamine. Not only do dopamine agonists decrease the concentrations of prolactin in the blood, but they often lead to a shrinking of the pituitary gland tumor, thereby relieving the compression of the optic chiasm with the accompanying restoration of vision. If the pituitary gland tumor is very large or if it does not shrink adequately with medical therapy, pituitary gland surgery may be necessary to remove as much of the tumor as possible. Our patient was treated with cabergoline; fortunately, the tumor gradually got smaller over several months, her visual fields improved, her blood prolactin concentrations normalized, and her menstrual periods returned to normal. Her physician measures her plasma prolactin concentrations every 6 months to monitor for a recurrence of tumor growth.

Reflect and Review #2

- What might be the effect of a prolactinoma in a man? *(Hint:* See Figure 17.14.)

Clinical terms: galactorrhea, prolactinoma, secondary amenorrhea

See Chapter 19 for complete, integrative case studies.

CHAPTER 17 TEST QUESTIONS *Recall and Comprehend*

Answers appear in Appendix A.

These questions test your recall of important details covered in this chapter. They also help prepare you for the type of questions encountered in standardized exams. Many additional questions of this type are available on Connect and LearnSmart.

1. Development of normal female internal and external genitalia requires
   a. Müllerian-inhibiting substance.
   b. expression of the *SRY* gene.
   c. insensitivity to circulating testosterone.
   d. complete absence of testosterone.
   e. absence of a Y chromosome.

2. Which is *not* characteristic of a normal postpubertal male?
   a. Inhibin from the Sertoli cells decreases FSH secretion.
   b. Testosterone has paracrine effects on the Sertoli cells.
   c. Testosterone stimulates GnRH from the hypothalamus.
   d. Testosterone inhibits LH secretion.
   e. GnRH from the hypothalamus is released in pulses.

3–7. Match the day of the menstrual cycle (a–e) with the event (3–7; use each answer once).

Day of menstrual cycle:

a. day 1
b. day 7
c. day 13
d. day 23
e. day 26

Event:

3. Progesterone from the corpus luteum peaks.
4. Estrogen positive feedback is peaking.
5. One follicle becomes dominant.
6. Estrogen and progesterone are both decreasing.
7. Increase in FSH stimulates antral follicles to begin to secrete estrogen.

8. The Leydig cell is primarily characterized by
   a. aromatization of testosterone.
   b. secretion of inhibin.
   c. secretion of testosterone.
   d. expression of receptors only to FSH.
   e. transformation into the corpus luteum.

9. During the third trimester of pregnancy, the placenta is *not* the primary source of which hormone in maternal blood?
   a. estrogen
   b. prolactin
   c. progesterone
   d. inhibin
   e. hCG

10. Menopause is characterized primarily by
   a. primary ovarian failure.
   b. loss of estrogen secretion from the ovary due to a decrease in LH.
   c. loss of estrogen secretion from the ovary due to a decrease in FSH.
   d. a decrease in FSH and LH due to increased inhibin.
   e. a decrease in FSH and LH due to a decrease in GnRH pulses.

CHAPTER 17 TEST QUESTIONS *Apply, Analyze, and Evaluate*

Answers appear in Appendix A.

These questions, which are designed to be challenging, require you to integrate concepts covered in the chapter to draw your own conclusions. See if you can first answer the questions without using the hints that are provided; then, if you are having difficulty, refer back to the figures or sections indicated in the hints.

1. What finding will be common to a person whose Leydig cells have been destroyed and to a person whose Sertoli cells have been destroyed? What finding will not be common? *Hint:* See Figure 17.14.
2. A male athlete taking large amounts of an androgenic steroid becomes sterile (unable to produce sperm capable of causing fertilization). Explain. *Hint:* See Figure 17.14.
3. A man who is sterile (infertile) is found to have the following: no evidence of demasculinization, an increased blood concentration of FSH, and a normal plasma concentration of LH. What is the most likely basis of his infertility? *Hint:* See Figure 17.14.
4. If you were a scientist trying to develop a male contraceptive acting on the anterior pituitary gland, would you try to block the secretion of FSH or LH? Explain the reason for your choice. *Hint:* See Figure 17.14 and recall that you want to decrease sperm count but not libido.
5. A 30-year-old man has very small muscles, a sparse beard, and a high-pitched voice. His plasma concentration of LH is elevated. Explain the likely cause of all these findings. *Hint:* See Table 17.3.
6. There are disorders of the adrenal cortex in which excessive amounts of androgens are produced. If any of these occur in a woman, what will happen to her menstrual cycles? *Hint:* Remember that androgens are converted to estrogens by aromatase in target tissue.
7. Women with inadequate secretion of GnRH are often treated for their infertility with drugs that mimic the action of this hormone. Can you suggest a possible reason that such treatment is often associated with multiple births? *Hint:* See Figure 17.24 and recall the hormone that induces the maturation of follicles.
8. Which of the following would be a signal that ovulation is soon to occur: the cervical mucus becoming thick and sticky, an increase in body temperature, or a marked rise in plasma LH? *Hint:* Consider the effect of estrogen versus that of progesterone. See Table 17.8.
9. The absence of what phenomenon would interfere with the ability of sperm obtained by masturbation to fertilize an egg in a test tube? *Hint:* See Section 17.19 and recall what happens to the sperm while in the vagina, uterus, and fallopian tubes.
10. If a woman 7 months pregnant is found to have a marked decrease in plasma estrogen, what would you conclude about the health of the fetoplacental unit? *Hint:* Remember that the placenta expresses the aromatase enzyme.
11. What types of drugs might you work on if you were trying to develop one to stop premature labor? *Hint:* See Figure 17.36.
12. If a genetic male failed to produce MIS during fetal life, what would the result be? *Hint:* See Figure 17.4.
13. Could the symptoms of menopause be treated by injections of FSH and LH? *Hint:* See Section 17.20 and recall the main cause of menopause.

CHAPTER 17 TEST QUESTIONS *General Principles Assessment*

Answers appear in Appendix A.

These questions reinforce the key theme first introduced in Chapter 1, that general principles of phyasiology can be applied across all levels of organization and across all organ systems.

1. What general principle of physiology is illustrated in Figures 17.2 and 17.3?
2. How does Figure 17.14 illustrate the general principle of physiology that *most physiological functions are controlled by multiple regulatory systems, often working in opposition*?
3. List several examples from Table 17.9 that demonstrate the general principle of physiology that *the functions of organ systems are coordinated with each other.*

CHAPTER 17 ANSWERS TO PHYSIOLOGICAL INQUIRY QUESTIONS

Figure 17.4 These drugs would be absorbed by the pregnant woman and cross the placenta to enter the fetal circulation. These drugs would block production of dihydrotestosterone in target tissues with 5-α-reductase activity, thereby interfering with the development of normal sexual differentiation of the penis, scrotum, and prostate in the male fetus.

Figure 17.5 A mutation in a gene encoding a single enzyme in the steroid-synthesis pathway can lead to congenital adrenal hyperplasia. If the mutation were to result in a complete (100%) loss of function, the lack of cortisol production in the developing fetus would be lethal as cortisol is required for the normal development of many organs. Typically, a mutation causing a partial loss of enzyme function may result in infertility in the affected female as an adult but does not otherwise affect survival of the individual.

Figure 17.7 In the short term, there would be a decrease in sex hormone secretion that, because of a reduction in negative feedback, would result in an increase in GnRH secretion from the hypothalamus and LH and FSH from the anterior pituitary gland. Because of the trophic effects of LH and FSH, in the long term, this would eventually increase the size and function of the remaining gonad. This results in a restoration of sex hormone concentrations in the blood to normal. (See Chapter 11 for a general description of the effects of tropic/trophic anterior pituitary gland hormones.)

Figure 17.13 A fundamental feature of the physics of fluids is that pressure and volume of fluids (such as blood and air) are related. As you learned in Chapter 12 (Section 12.8) and Chapter 13 (equation 13-4 and Figure 13.16), the pressure inside a closed system is determined by the volume of the fluid filling the compartment (inflow minus outflow) and the compliance of the compartment. By increasing blood flow into the penis by arterial dilation and preventing outflow by compression of the veins, the volume of blood in the penis increases and the compartment becomes engorged. As a result, the pressure inside the compartment increases and the penis becomes erect. After ejaculation, the arteries constrict and blood flow entering the compartment decreases, thus decreasing the pressure in the compartment. The veins are no longer compressed, the excess blood drains from the penis, and it again becomes flaccid.

Figure 17.14 Testosterone alone usually does not restore spermatogenesis to normal. FSH is necessary to stimulate spermatogenesis from the Sertoli cell independently of local testosterone production. Furthermore, giving testosterone as a drug is usually not sufficient to replace the local production of testosterone in the testes necessary to maintain spermatogenesis. Therefore, gonadotropins with a mixture of activity for receptors to LH (to stimulate local testosterone production) and FSH (to stimulate the Sertoli cells) usually must be given to restore spermatogenesis.

Figure 17.22 (1) Plasma FSH increases because the corpus luteum is degenerating. The loss of the negative feedback by progesterone and estrogen from the corpus luteum relieves the pituitary gland of this inhibitory effect and allows FSH to increase, thus stimulating a group of follicles for the next menstrual cycle. (2) If conception occurs and the developing blastocyst implants (pregnancy), the trophoblast cells of the implanted blastocyst release a gonadotropin—human chorionic gonadotropin (hCG)—into the maternal blood, thus rescuing the corpus luteum in very early pregnancy. Production of progesterone from the corpus luteum of pregnancy prevents menses and the loss of the implanted embryo. The measurement of hCG in maternal blood or urine is the basis of the pregnancy test.

Figure 17.24 The increased pituitary gland gonadotropins suggest a lack of estrogen and inhibin negative feedback, pointing to premature ovarian failure as a diagnosis. One cause of premature ovarian failure is autoimmune ovarian destruction. Like Graves' disease and Addison's disease (see Chapters 11 and 19), premature ovarian failure is a form of endocrine autoimmunity.

Figure 17.32 The main functions of the placenta are to provide the developing fetus with oxygen and nutrients and to remove waste products. Therefore, it functions in a manner similar to the lungs, providing a large surface area for transfer of oxygen from the maternal to the fetal circulation and for transfer of carbon dioxide from the fetal to the maternal circulation. Furthermore, it can also function like the adult kidneys by removing waste products like urea from the fetal circulation. Although the quantities of these substances exchanged across the placenta are not controlled as precisely as in the kidneys, for example, the distribution of maternal and fetal blood flow to the placenta can be changed to meet the requirements of the developing fetus. Any disruption of this exchange of materials in the placenta can result in severe negative health consequences for both the fetus and the mother.

Figure 17.34 Human chorionic gonadotropin stimulates progesterone and estrogen from the corpus luteum early in pregnancy. The placenta takes over this function during the second trimester of pregnancy such that most of the maternal estrogen and progesterone later in pregnancy is from the placenta. Placental production of these steroids does not require gonadotropin stimulation.

Figure 17.36 The feet may not provide sufficient cervical stretch to maintain the positive feedback stimulation of oxytocin and uterine contraction.

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