

Female Physiology Before Pregnancy and Female Hormones

Female reproductive functions can be divided into two major phases: (1) preparation of the female body for conception and pregnancy and (2) the period of pregnancy itself. This chapter is concerned with preparation of the female body for pregnancy, and [Chapter 83](#) presents the physiology of pregnancy and childbirth.

PHYSIOLOGIC ANATOMY OF THE FEMALE SEXUAL ORGANS

[Figures 82-1](#) and [82-2](#) show the principal organs of the human female reproductive tract, including the *ovaries*, *fallopian tubes* (also called *uterine tubes*), *uterus*, and *vagina*. Reproduction begins with the development of ova in the ovaries. In the middle of each monthly sexual cycle, a single ovum is expelled from an ovarian follicle into the abdominal cavity near the open fimbriated ends of the two fallopian tubes. This ovum then passes through one of the fallopian tubes into the uterus; if it has been fertilized by a sperm, it implants in the uterus, where it develops into a fetus, a placenta, and fetal membranes—and eventually into a baby.

OOGENESIS AND FOLLICULAR DEVELOPMENT IN THE OVARIES

A developing egg (*oocyte*) differentiates into a mature egg (*ovum*) through a series of steps called *oogenesis* ([Figure 82-3](#)). During early embryonic development, *primordial germ cells* from the dorsal endoderm of the yolk sac migrate along the mesentery of the hindgut to the outer surface of the ovary, which is covered by a germinal epithelium, derived embryologically from the epithelium of the germinal ridges. During this migration, the germ cells divide repeatedly. Once these primordial germ cells reach the germinal epithelium, they migrate into the substance of the ovarian cortex and become *oogonia* or *primordial ova*.

Each primordial ovum then collects around it a layer of spindle cells from the ovarian *stroma* (the supporting tissue of the ovary) and causes them to take on epithelioid characteristics; these epithelioid-like cells are then called *granulosa cells*. The ovum surrounded by a single layer of granulosa cells is called a *primordial follicle*. At this stage, the ovum is still immature and is called a *primary oocyte*,

requiring two more cell divisions before it can be fertilized by a sperm.

The oogonia in the embryonic ovary complete mitotic replication, and the first stage of meiosis starts by the fifth month of fetal development. The germ cell mitosis then ceases and no additional oocytes are formed. At birth the ovary contains about 1 to 2 million primary oocytes.

The first stage of meiosis starts during fetal development but is arrested in the late stage of prophase I until puberty, which usually occurs between ages 10 and 14 in females. The first meiotic division of the oocyte is completed after puberty. Each oocyte divides into two cells, a large ovum (*secondary oocyte*) and a small first *polar body*. Each of these cells contains 23 duplicated chromosomes. The first polar body may or may not undergo a second meiotic division and then disintegrates. The ovum undergoes a second meiotic division, and after the sister chromatids separate, there is a pause in meiosis. If the ovum is fertilized, the final step in meiosis occurs and the sister chromatids in the ovum go to separate cells.

When the ovary releases the ovum (*ovulation*), and if the ovum is fertilized, the final meiosis occurs. Half of the sister chromatids remain in the fertilized ovum, and the other half are released in a second polar body, which then disintegrates.

At puberty, only about 300,000 oocytes remain in the ovaries, and only a small percentage of these oocytes become mature. The many thousands of oocytes that do not mature degenerate. During all the reproductive years of adult life, between about 13 and 46 years of age on average, only 400 to 500 of the primordial follicles develop enough to expel their ova, one each month; the remainder degenerate (i.e., become *atretic*). At the end of reproductive capability (at *menopause*), only a few primordial follicles remain in the ovaries, and even these follicles degenerate soon thereafter.

FEMALE HORMONAL SYSTEM

The female hormonal system, like that of the male hormonal system, consists of three hierarchies of hormones, as follows:

1. A hypothalamic releasing hormone, called *gonadotropin-releasing hormone* (GnRH)

2. The anterior pituitary sex hormones, *follicle-stimulating hormone* (FSH) and *luteinizing hormone* (LH), both of which are secreted in response to release of GnRH from the hypothalamus
3. The ovarian hormones, *estrogen* and *progesterone*, which are secreted by the ovaries in response to the two female sex hormones from the anterior pituitary gland

These various hormones are secreted at drastically differing rates during different parts of the female monthly sexual cycle. **Figure 82-4** shows the approximate changing concentrations of the anterior pituitary gonadotropic hormones FSH and LH (bottom two curves) and of the ovarian hormones estradiol (estrogen) and progesterone (top two curves).

The amount of GnRH released from the hypothalamus increases and decreases much less drastically during the monthly sexual cycle. It is secreted in short pulses averaging once every 90 minutes, as occurs in males.

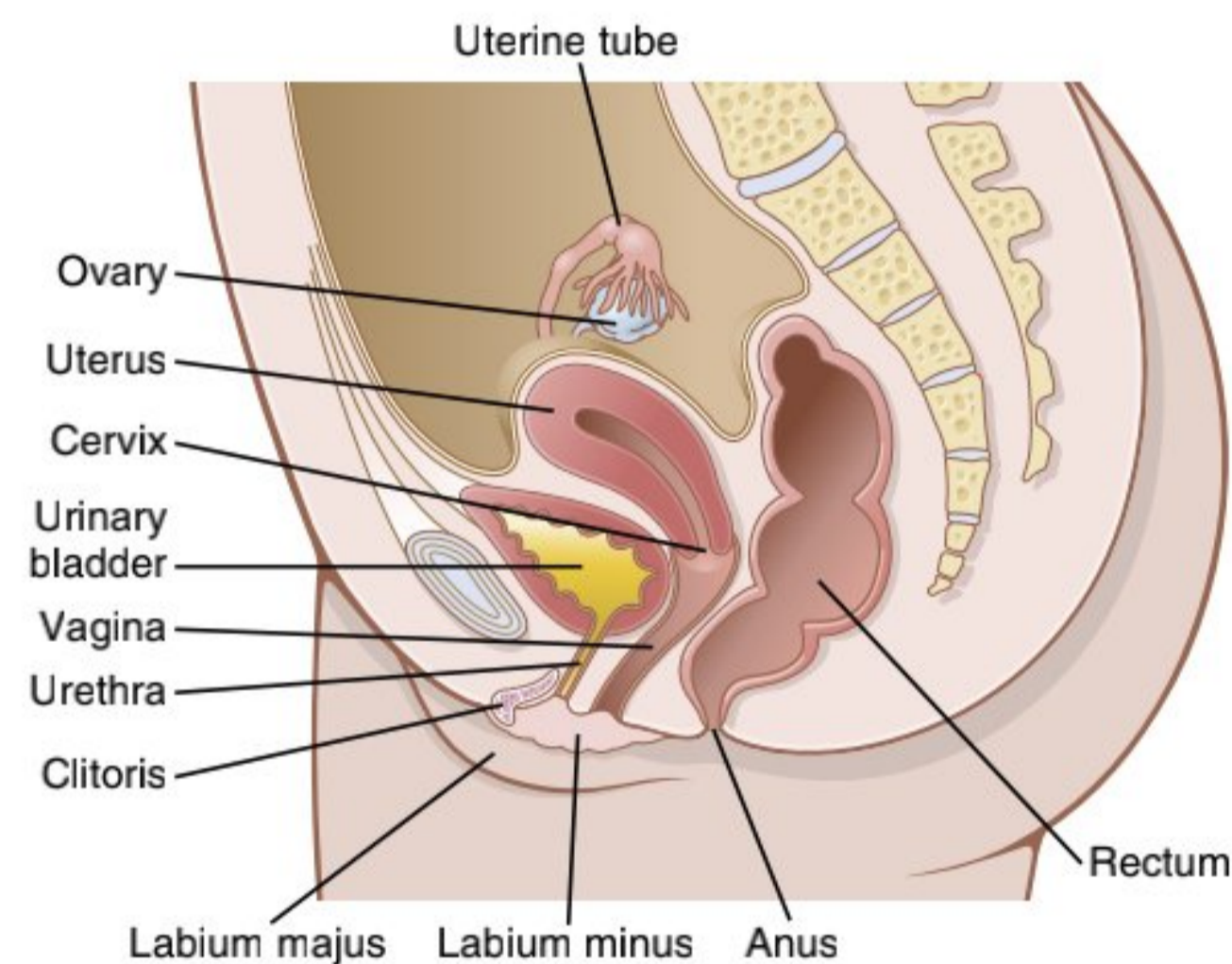


Figure 82-1. The female reproductive organs.

MONTHLY OVARIAN CYCLE AND FUNCTION OF GONADOTROPIC HORMONES

The normal reproductive years of the female are characterized by monthly rhythmic changes in the rates of secretion of the female hormones and corresponding physical changes in the ovaries and other sexual organs. This rhythmic pattern is called the *female monthly sexual cycle* (or, less accurately, the *menstrual cycle*). The duration of the cycle averages 28 days. It may be as short as 20 days or as long as 45 days in some women, although abnormal cycle length is frequently associated with decreased fertility.

The female sexual cycle has two significant results. First, only a *single* ovum is normally released from the ovaries each month, so normally only a single fetus will begin to grow at a time. Second, the uterine endometrium is prepared in advance for implantation of the fertilized ovum at the required time of the month.

GONADOTROPIC HORMONES AND THEIR EFFECTS ON THE OVARIES

The ovarian changes that occur during the sexual cycle depend completely on the gonadotropic hormones FSH and LH, which are secreted by the anterior pituitary gland. Both FSH and LH are small glycoproteins that have molecular weights of about 30,000. In the absence of these hormones, the ovaries remain inactive, which is the case throughout childhood, when almost no pituitary gonadotropic hormones are secreted. At age 9 to 12 years, the pituitary begins to secrete progressively more FSH and LH, which leads to the onset of normal monthly sexual cycles beginning between the ages of 11 and 15 years. This period of change is called *puberty*, and the time of the first menstrual cycle is called *menarche*. During each month of the female sexual cycle, there is a cyclical increase and decrease of FSH and LH, as shown in the bottom of **Figure 82-4**. These cyclical variations

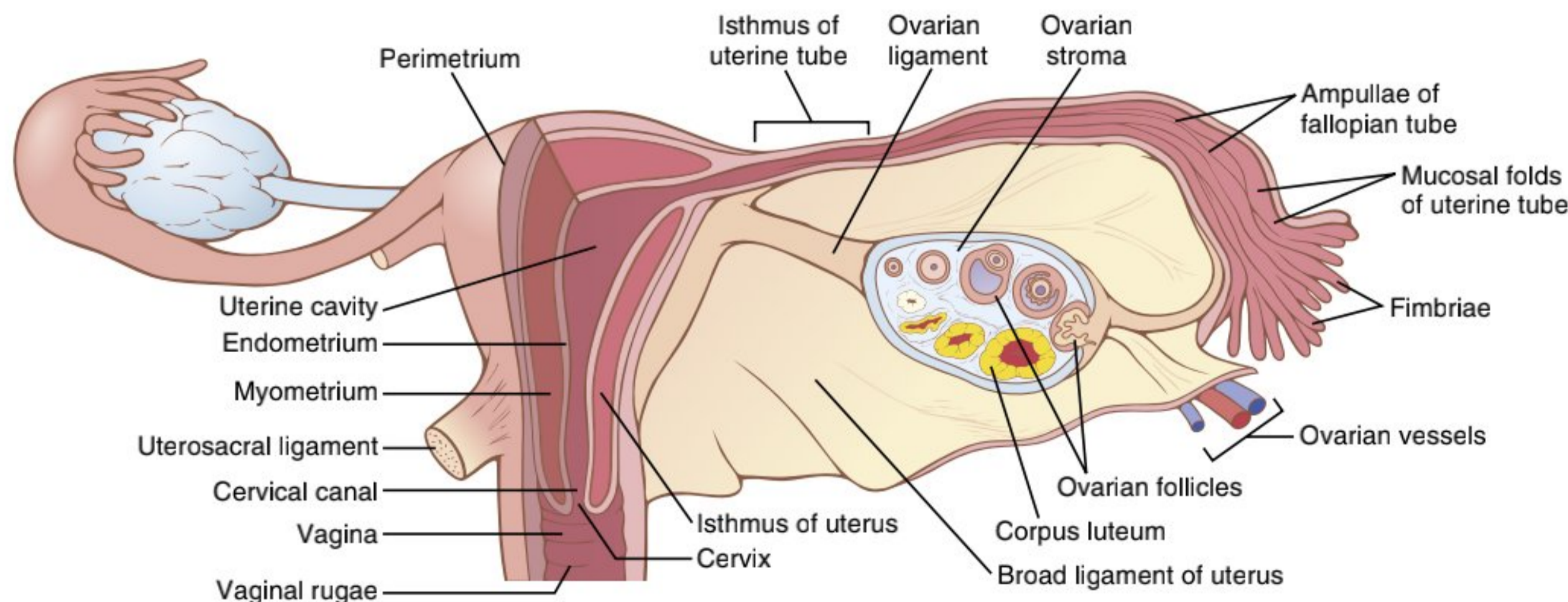


Figure 82-2. Internal structures of the uterus, ovary, and a uterine tube.

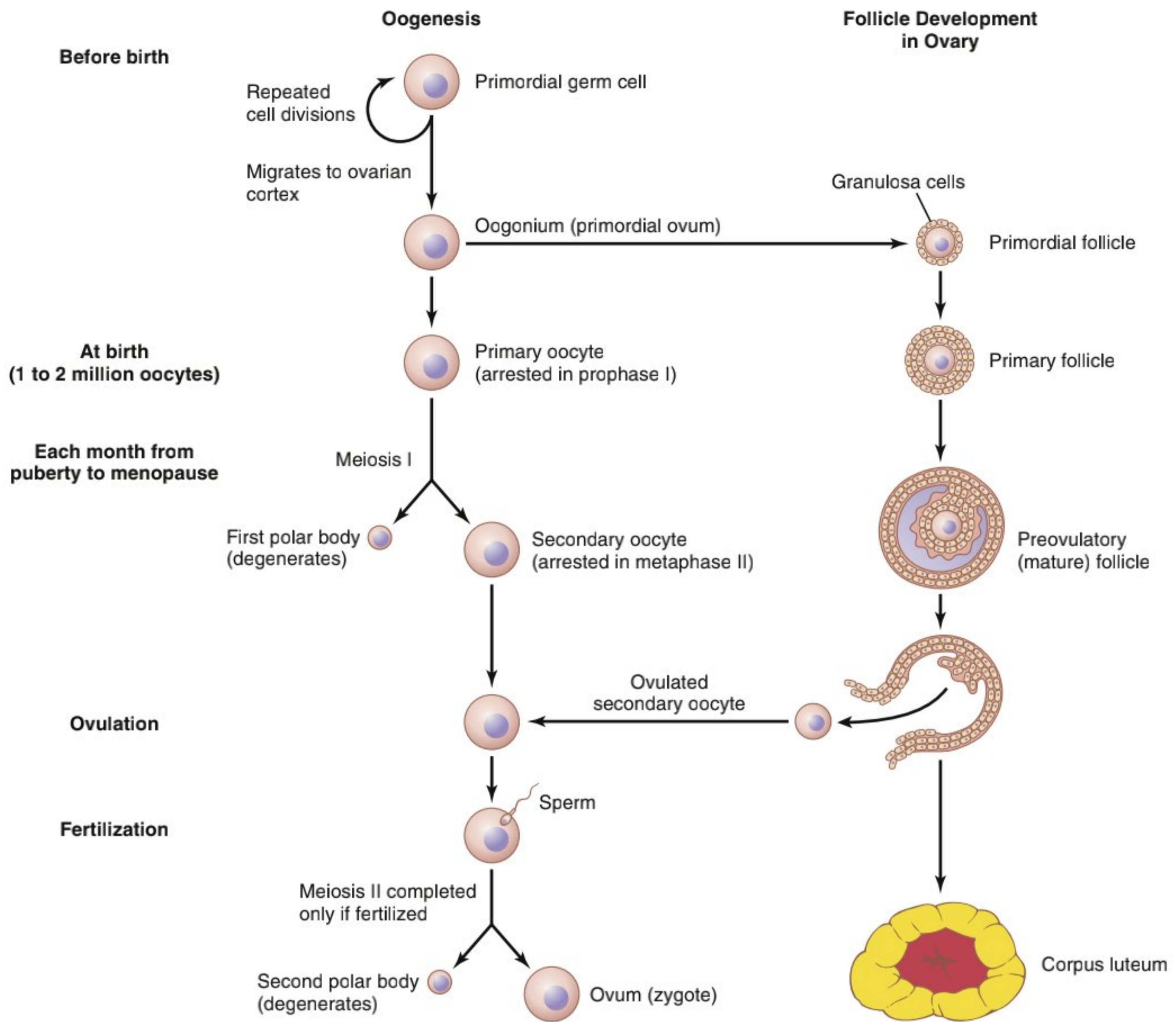


Figure 82-3. Oogenesis and follicle development.

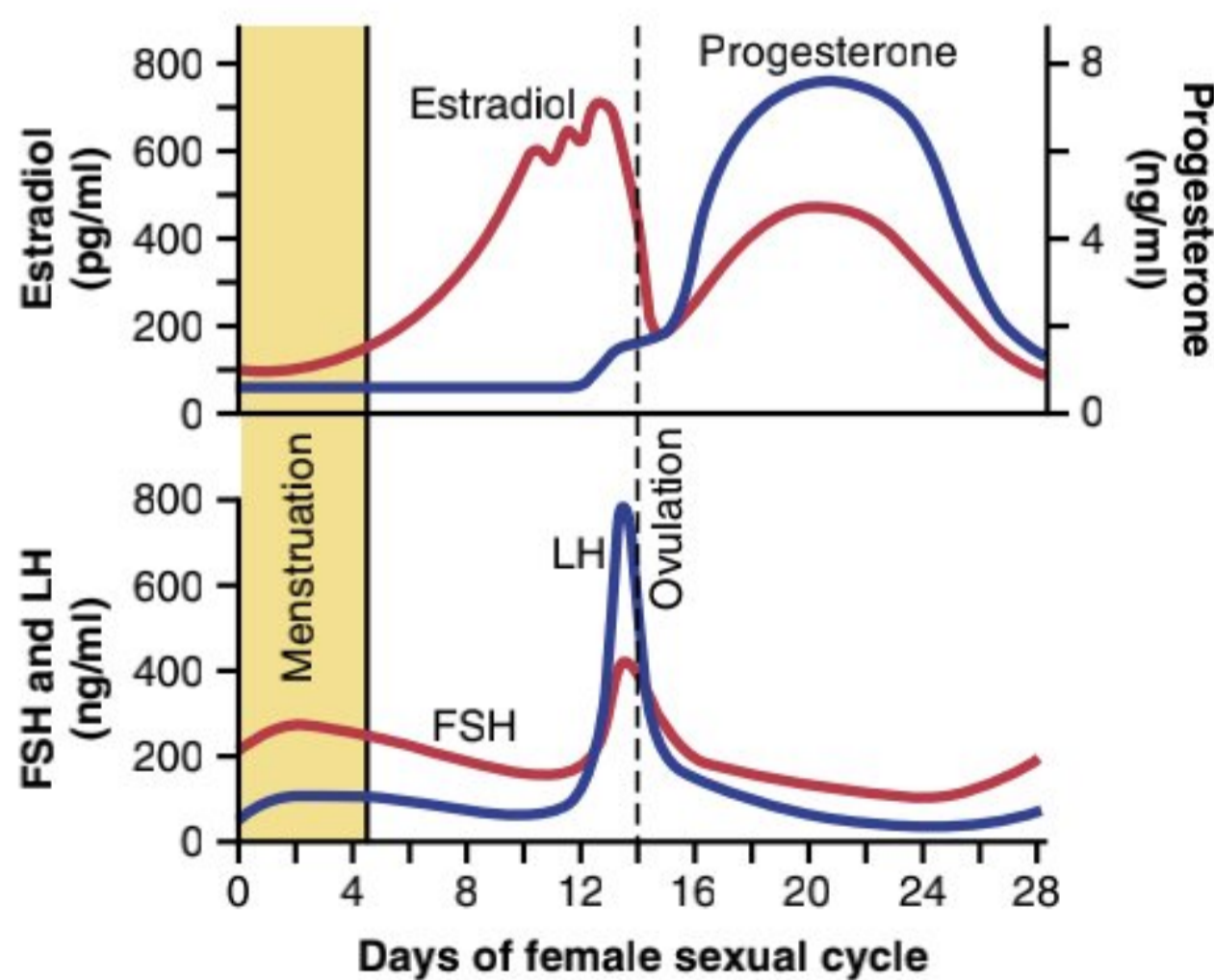


Figure 82-4. Approximate plasma concentrations of the gonadotropins and ovarian hormones during the normal female sexual cycle. FSH, Follicle-stimulating hormone; LH, luteinizing hormone.

cause cyclical ovarian changes, which are explained in the following sections.

Both FSH and LH stimulate their ovarian target cells by combining with highly specific FSH and LH receptors in the ovarian target cell membranes. In turn, the activated receptors increase the cells' secretion rates and usually the growth and proliferation of the cells as well. Almost all these stimulatory effects result from *activation of the cyclic adenosine monophosphate second messenger system* in the cell cytoplasm, which causes formation of *protein kinase* and multiple *phosphorylations of key enzymes* that stimulate sex hormone synthesis, as explained in [Chapter 75](#).

OVARIAN FOLLICLE GROWTH—THE FOLLICULAR PHASE OF THE OVARIAN CYCLE

Figure 82-5 shows the progressive stages of follicular growth in the ovaries. When a female child is born,

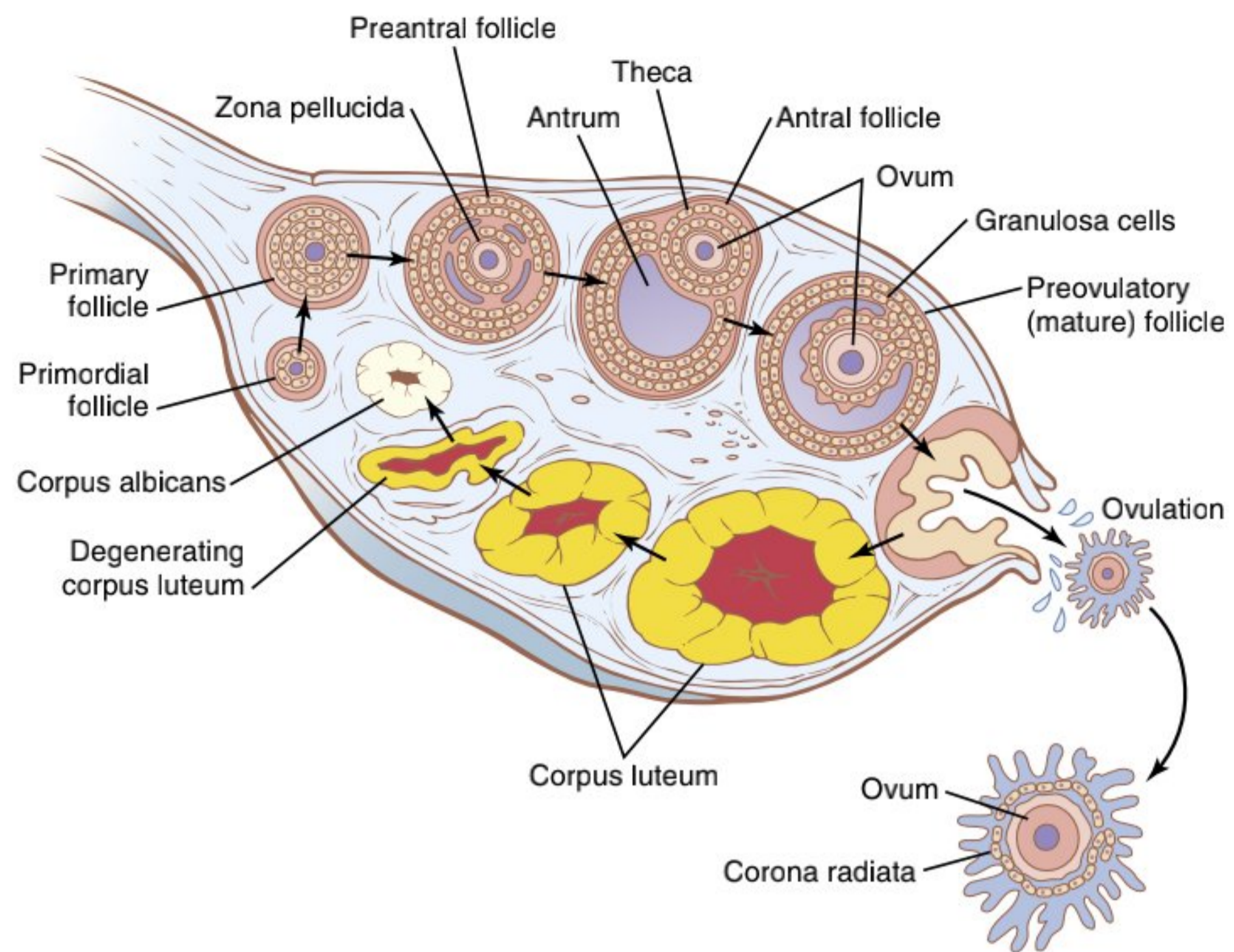


Figure 82-5. Stages of follicular growth in the ovary, also showing formation of the corpus luteum.

each ovum is surrounded by a single layer of granulosa cells; the ovum, with this granulosa cell sheath, is called a *primordial follicle*, as shown in the figure. Throughout childhood, the granulosa cells are believed to provide nourishment for the ovum and to secrete an *oocyte maturation inhibiting factor* that keeps the ovum suspended in its primordial state in the prophase stage of meiotic division. Then, after puberty, when FSH and LH from the anterior pituitary gland begin to be secreted in significant quantities, the ovaries (together with some of the follicles within them) begin to grow.

The first stage of follicular growth is moderate enlargement of the ovum, which increases in diameter 2-fold to 3-fold. That stage is followed by growth of additional layers of granulosa cells in some of the follicles. These follicles are known as *primary follicles*.

Development of Antral and Vesicular Follicles. During the first few days of each monthly female sexual cycle, the concentrations of FSH and LH secreted by the anterior pituitary gland increase slightly to moderately, with the increase in FSH slightly greater than that of LH and preceding it by a few days. These hormones, especially FSH, cause accelerated growth of 6 to 12 primary follicles each month. The initial effect is rapid proliferation of the granulosa cells, giving rise to many more layers of these cells. In addition, spindle cells derived from the ovary interstitium collect in several layers outside the granulosa cells, giving rise to a second mass of cells called the *theca*. The theca is divided into two layers. In the *theca interna*, the cells take on epithelioid characteristics similar to those of the granulosa cells and develop the ability to secrete additional steroid sex hormones (estrogen and progesterone). The outer layer, the *theca*

externa, develops into a highly vascular connective tissue capsule that becomes the capsule of the developing follicle.

After the early proliferative phase of growth, which lasts for a few days, the mass of granulosa cells secretes a *follicular fluid* that contains a high concentration of estrogen, one of the important female sex hormones (discussed later). Accumulation of this fluid causes an *antrum* to appear within the mass of granulosa cells, as shown in **Figure 82-5**.

The early growth of the primary follicle up to the antral stage is stimulated mainly by FSH alone. Greatly accelerated growth then occurs, leading to still larger follicles called *vesicular follicles*. This accelerated growth is caused by the following mechanisms:

1. Estrogen is secreted into the follicle and causes the granulosa cells to form increasing numbers of FSH receptors, which causes a positive feedback effect because it makes the granulosa cells even more sensitive to FSH.
2. The pituitary FSH and the estrogens combine to promote LH receptors on the original granulosa cells, thus allowing LH stimulation to occur in addition to FSH stimulation and creating an even more rapid increase in follicular secretion.
3. The increasing estrogens from the follicle plus the increasing LH from the anterior pituitary gland act together to cause proliferation of the follicular thecal cells and increase their secretion.

Once the antral follicles begin to grow, their growth occurs almost explosively. The ovum also enlarges in diameter another 3-fold to 4-fold, giving a total ovum diameter increase up to 10-fold, or a mass increase of 1000-fold. As the follicle enlarges, the ovum remains

embedded in a mass of granulosa cells located at one pole of the follicle.

Only One Follicle Fully Matures Each Month, and the Remainder Undergo Atresia. After a week or more of growth—but before ovulation occurs—one of the follicles begins to outgrow all the others, and the remaining 5 to 11 developing follicles involute (a process called *atresia*).

The cause of the atresia is unclear, but it has been postulated to be the following: The large amounts of estrogen from the most rapidly growing follicle act on the hypothalamus to depress further enhancement of FSH secretion by the anterior pituitary gland, in this way blocking further growth of the less well-developed follicles. Therefore, the largest follicle continues to grow because of its intrinsic positive feedback effects, while all the other follicles stop growing and actually involute.

This process of atresia is important because it normally allows only one of the follicles to grow large enough each month to ovulate, which usually prevents more than one child from developing with each pregnancy. The single follicle reaches a diameter of 1 to 1.5 centimeters at the time of ovulation and is called the *mature follicle*.

Ovulation

Ovulation in a woman who has a normal 28-day female sexual cycle occurs 14 days after the onset of menstruation. Shortly before ovulation, the protruding outer wall of the follicle swells rapidly, and a small area in the center of the follicular capsule, called the *stigma*, protrudes like a nipple. In another 30 minutes or so, fluid begins to ooze from the follicle through the stigma, and about 2 minutes later, the stigma ruptures widely, allowing a more viscous fluid, which has occupied the central portion of the follicle, to evaginate outward. This viscous fluid carries with it the ovum surrounded by a mass of several thousand small granulosa cells, called the *corona radiata*.

A Surge of Luteinizing Hormone Is Necessary for Ovulation. LH is necessary for final follicular growth and ovulation. Without this hormone, even when large quantities of FSH are available, the follicle will not progress to the ovulation stage.

About 2 days before ovulation, the rate of secretion of LH by the anterior pituitary gland increases markedly, rising 6- to 10-fold and peaking about 16 hours before ovulation. FSH also increases about 2-fold to 3-fold at the same time, and the FSH and LH act synergistically to cause rapid swelling of the follicle during the last few days before ovulation. The LH also has a specific effect on the granulosa and theca cells, converting them mainly to progesterone-secreting cells. Therefore, the rate of estrogen secretion begins to fall about 1 day before ovulation, while increasing amounts of progesterone begin to be secreted.

It is in this environment of (1) rapid growth of the follicle, (2) diminishing estrogen secretion after a prolonged

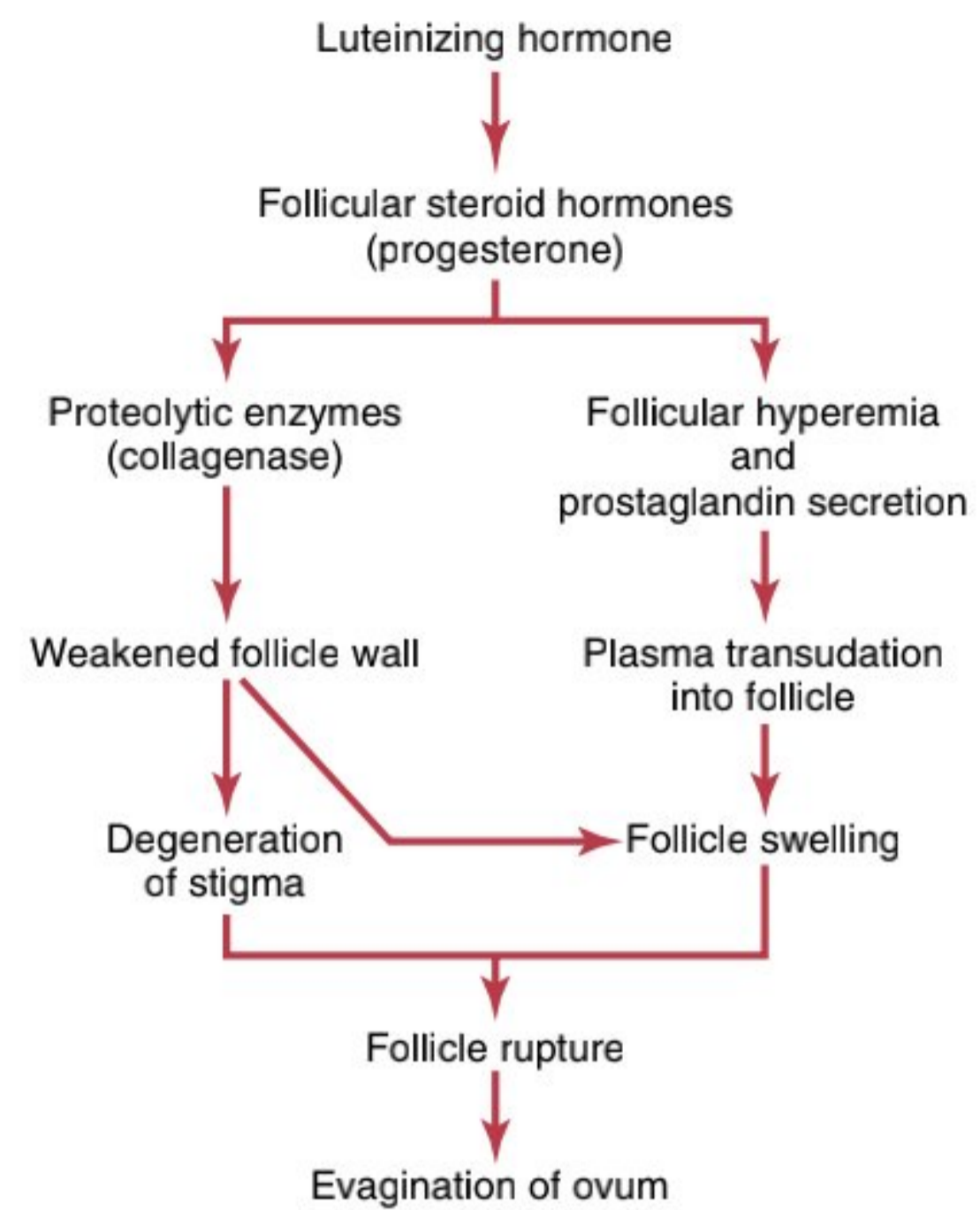


Figure 82-6. The postulated mechanism of ovulation.

phase of excessive estrogen secretion, and (3) initiation of secretion of progesterone that ovulation occurs. Without the initial preovulatory surge of LH, ovulation will not take place.

Initiation of Ovulation. Figure 82-6 provides a schema for the initiation of ovulation, showing the role of the large quantity of LH secreted by the anterior pituitary gland. This LH causes rapid secretion of follicular steroid hormones that contain progesterone. Within a few hours, two events occur, both of which are necessary for ovulation:

1. The *theca externa* (i.e., the capsule of the follicle) begins to release proteolytic enzymes from lysosomes. These enzymes cause dissolution of the follicular capsular wall and consequent weakening of the wall, resulting in further swelling of the entire follicle and degeneration of the stigma.
2. Simultaneously there is rapid growth of new blood vessels into the follicle wall. At the same time, prostaglandins (local hormones that cause vasodilation) are secreted into the follicular tissues.

These two effects cause plasma transudation into the follicle, which contributes to follicle swelling. Finally, the combination of follicle swelling and simultaneous degeneration of the stigma causes follicle rupture, with discharge of the ovum.

CORPUS LUTEUM—THE LUTEAL PHASE OF THE OVARIAN CYCLE

During the first few hours after expulsion of the ovum from the follicle, the remaining granulosa and theca interna cells change rapidly into *lutein cells*. They enlarge

in diameter two or more times and become filled with lipid inclusions that give them a yellowish appearance. This process is called *luteinization*, and the total mass of cells together is called the *corpus luteum*, which is shown in [Figure 82-5](#). A well-developed vascular supply also grows into the corpus luteum.

The *granulosa cells* in the corpus luteum develop extensive intracellular smooth endoplasmic reticula that form large amounts of the female sex hormones *progesterone* and *estrogen* (with more progesterone than estrogen during the luteal phase). The *theca cells* form mainly the androgens *androstenedione* and *testosterone* rather than female sex hormones. However, most of these hormones are also converted by the enzyme *aromatase* in the granulosa cells into estrogens.

The corpus luteum normally grows to about 1.5 centimeters in diameter, reaching this stage of development 7 to 8 days after ovulation. Then the corpus luteum begins to involute and eventually loses its secretory function and its yellowish, lipid characteristic about 12 days after ovulation, becoming the *corpus albicans*; during the ensuing few weeks, the corpus albicans is replaced by connective tissue and over months is absorbed.

Luteinizing Function of Luteinizing Hormone. The change of granulosa and theca interna cells into lutein cells depends mainly on LH secreted by the anterior pituitary gland. In fact, this function gives LH its name—“luteinizing,” for “yellowing.” Luteinization also depends on extrusion of the ovum from the follicle. A yet uncharacterized factor in the follicular fluid, called *luteinization-inhibiting factor*, seems to hold the luteinization process in check until after ovulation.

Secretion by the Corpus Luteum: An Additional Function of Luteinizing Hormone. The corpus luteum is a highly secretory organ, secreting large amounts of *progesterone* and *estrogen*. Once LH (mainly that secreted during the ovulatory surge) has acted on the granulosa and theca cells to cause luteinization, the newly formed lutein cells go through a sequence of (1) proliferation, (2) enlargement, and (3) secretion, followed by (4) degeneration. All this occurs in about 12 days. As discussed in [Chapter 83](#), another hormone with almost exactly the same properties as LH, *chorionic gonadotropin*, which is secreted by the placenta, can act on the corpus luteum to prolong its life—usually maintaining it for at least the first 2 to 4 months of pregnancy.

Involution of the Corpus Luteum and Onset of the Next Ovarian Cycle. Estrogen in particular and progesterone to a lesser extent, secreted by the corpus luteum during the luteal phase of the ovarian cycle, have strong feedback effects on the anterior pituitary gland to maintain low secretory rates of FSH and LH.

In addition, the lutein cells secrete small amounts of the hormone *inhibin*, the same as the inhibin secreted by

the Sertoli cells of the male testes. This hormone inhibits FSH secretion by the anterior pituitary gland. Low blood concentrations of FSH and LH result, and loss of these hormones finally causes the corpus luteum to degenerate completely, a process called *involution* of the corpus luteum.

Final involution normally occurs at the end of almost exactly 12 days of corpus luteum life, which is around the 26th day of the normal female sexual cycle, 2 days before menstruation begins. At this time, the sudden cessation of estrogen, progesterone, and inhibin secretion by the corpus luteum removes the feedback inhibition of the anterior pituitary gland, allowing it to begin secreting increasing amounts of FSH and LH again. FSH and LH initiate the growth of new follicles, beginning a new ovarian cycle. The paucity of progesterone and estrogen secretion at this time also leads to menstruation by the uterus, which will be explained later.

SUMMARY

About every 28 days, gonadotropic hormones from the anterior pituitary gland cause 8 to 12 new follicles to begin to grow in the ovaries. One of these follicles finally becomes “mature” and ovulates on the 14th day of the cycle. During growth of the follicles, estrogen is mainly secreted.

After ovulation, the secretory cells of the ovulating follicle develop into a corpus luteum that secretes large quantities of progesterone and estrogen. After another 2 weeks, the corpus luteum degenerates, whereupon the ovarian hormones estrogen and progesterone decrease greatly, and menstruation begins. A new ovarian cycle then follows.

FUNCTIONS OF OVARIAN HORMONES—ESTRADIOL AND PROGESTERONE

The two types of ovarian sex hormones are the *estrogens* and the *progestins*. By far the most important of the estrogens is *estradiol*, and by far the most important progestin is *progesterone*. The estrogens mainly promote proliferation and growth of specific cells in the body that are responsible for development of most secondary sexual characteristics of females. The progestins function mainly to prepare the uterus for pregnancy and the breasts for lactation.

CHEMISTRY OF THE SEX HORMONES

Estrogens. In the normal *nonpregnant* female, estrogens are secreted in significant quantities only by the ovaries, although minute amounts are also secreted by the adrenal cortices. During *pregnancy*, large quantities of estrogens are also secreted by the placenta, as discussed in [Chapter 83](#).

Only three estrogens are present in significant quantities in the plasma of the human female— β -estradiol, estrone, and *estriol*, the formulas for which are shown in **Figure 82-7**. The principal estrogen secreted by the ovaries is β -estradiol. Small amounts of estrone are also secreted, but most of this is formed in peripheral tissues from androgens secreted by the adrenal cortices and by ovarian thecal cells. Estriol is a weak estrogen; it is an oxidative product derived from both estradiol and estrone, with the conversion occurring mainly in the liver.

The estrogenic potency of β -estradiol is 12 times that of estrone and 80 times that of estriol. Considering these relative potencies, one can see that the total estrogenic effect of β -estradiol is usually many times that of the other two together. For this reason, β -estradiol is considered the major estrogen, although the estrogenic effects of estrone are not negligible.

Progestins. By far the most important of the progestins is progesterone. However, small amounts of another progestin, 17α -hydroxyprogesterone, are secreted along with progesterone and have essentially the same effects. Yet, for practical purposes, progesterone is usually considered to be the only important progestin.

In nonpregnant females, progesterone is usually secreted in significant amounts only during the latter half

of each ovarian cycle, when it is secreted by the corpus luteum.

As discussed in **Chapter 83**, large amounts of progesterone are also secreted by the placenta during pregnancy, especially after the fourth month of gestation.

Synthesis of the Estrogens and Progestins. Note from the chemical formulas of the estrogens and progesterone in **Figure 82-7** that they are all steroids. They are synthesized in the ovaries mainly from cholesterol derived from the blood but also to a slight extent from acetyl coenzyme A, multiple molecules of which can combine to form the appropriate steroid nucleus.

During synthesis, mainly progesterone and androgens (testosterone and androstenedione) are synthesized first; then, during the follicular phase of the ovarian cycle, before these two initial hormones can leave the ovaries, almost all the androgens and much of the progesterone are converted into estrogens by the enzyme *aromatase* in the granulosa cells. Because the theca cells lack aromatase, they cannot convert androgens to estrogens. However, androgens diffuse out of the theca cells into the adjacent granulosa cells, where they are converted to estrogens by aromatase, the activity of which is stimulated by FSH (**Figure 82-8**).

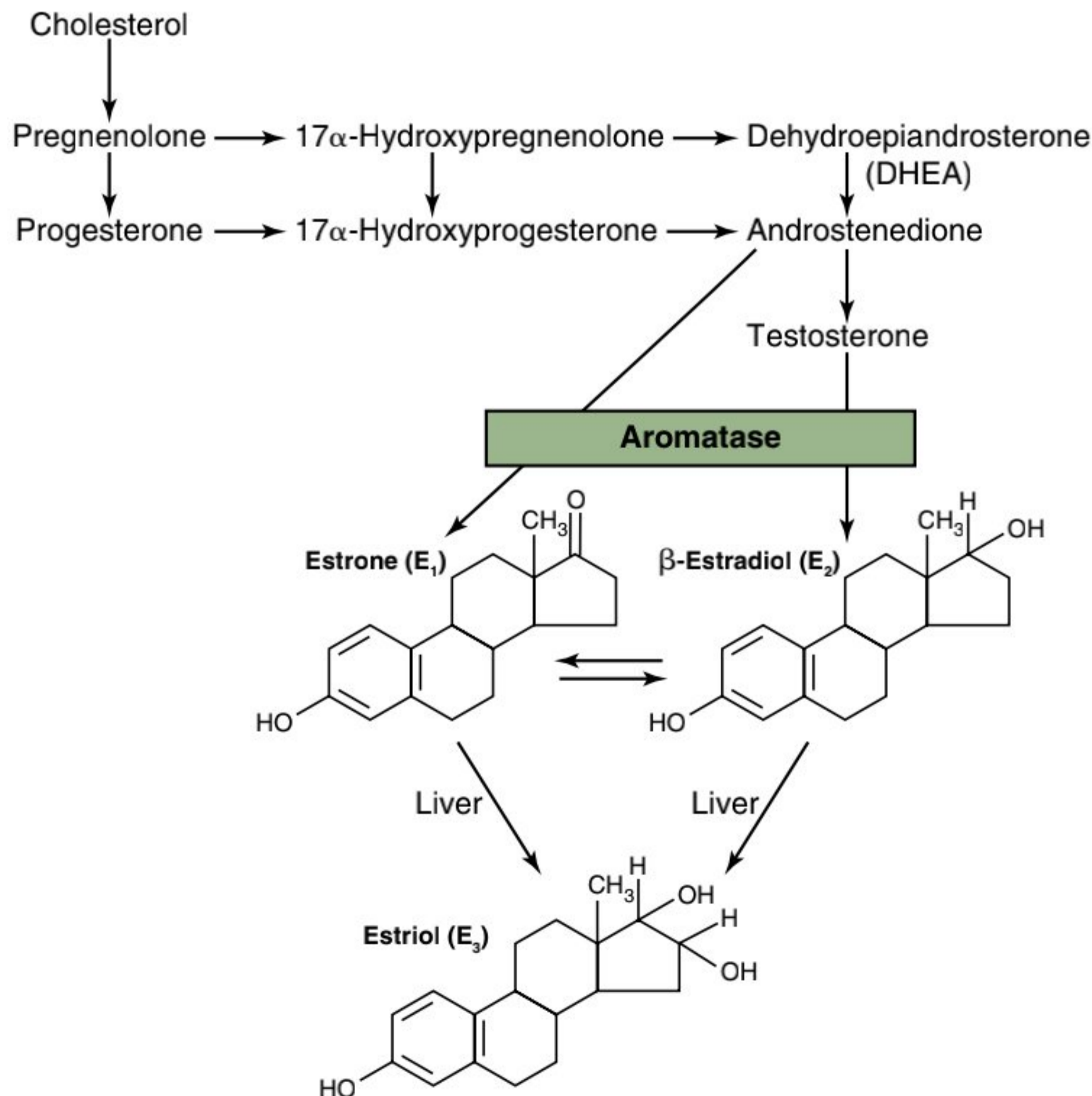
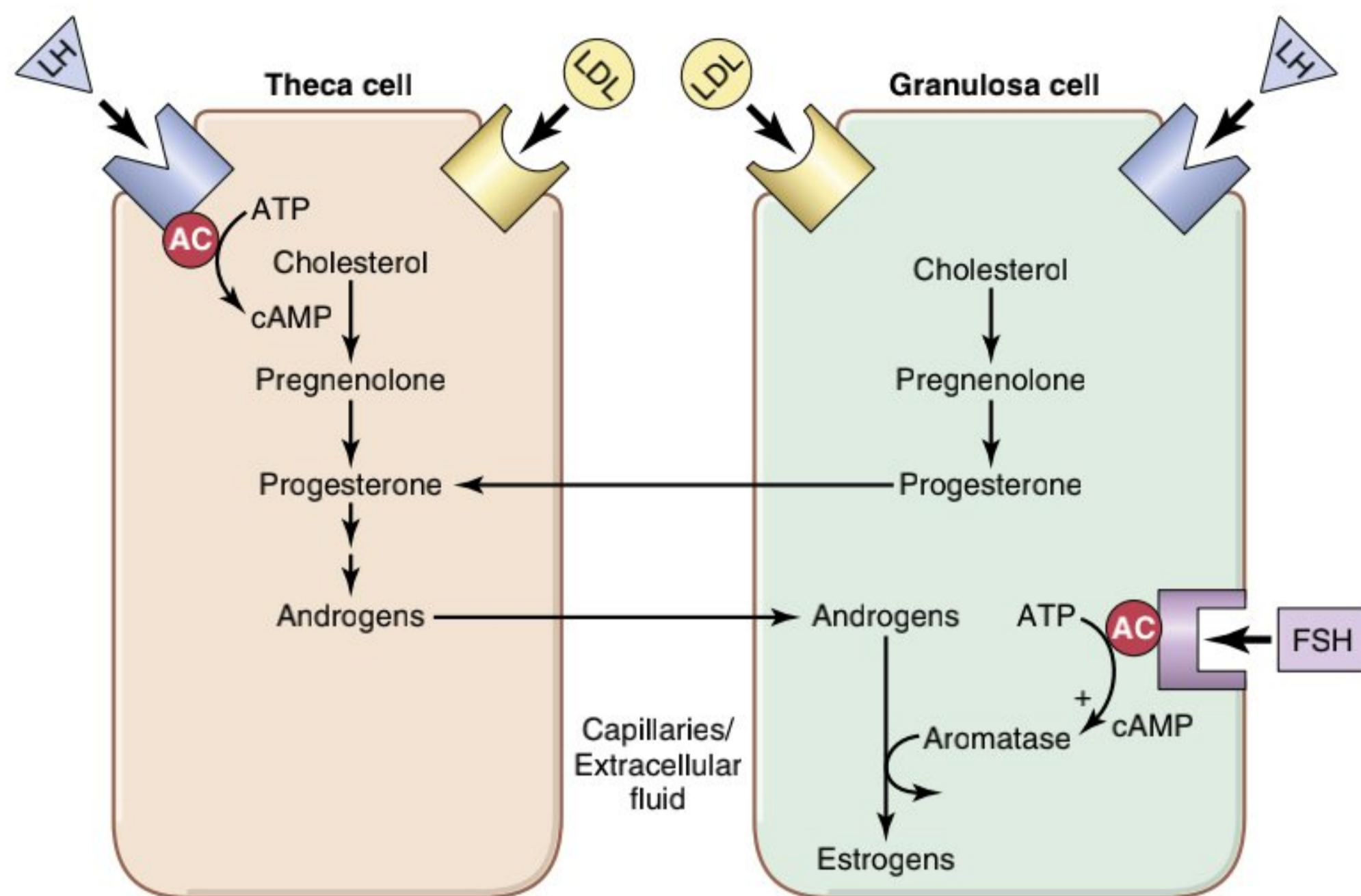


Figure 82-7. Synthesis of the principal female hormones. The chemical structures of the precursor hormones, including progesterone, are shown in Figure 78-2.

Figure 82-8. Interaction of follicular theca and granulosa cells for production of estrogens. The theca cells, under the control of luteinizing hormone (LH), produce androgens that diffuse into the granulosa cells. In mature follicles, follicle-stimulating hormone (FSH) acts on granulosa cells to stimulate aromatase activity, which converts the androgens to estrogens. AC, Adenylate cyclase; ATP, adenosine triphosphate; cAMP, cyclic adenosine monophosphate; LDL, low-density lipoproteins.



During the luteal phase of the cycle, far too much progesterone is formed for all of it to be converted, which accounts for the large secretion of progesterone into the circulating blood at this time. Also, about one-fifteenth as much testosterone is secreted into the plasma of the female by the ovaries as is secreted into the plasma of the male by the testes.

Estrogens and Progesterone Are Transported in the Blood Bound to Plasma Proteins. Both estrogens and progesterone are transported in the blood bound mainly with plasma albumin and with specific estrogen- and progesterone-binding globulins. The binding between these hormones and the plasma proteins is loose enough that they are rapidly released to the tissues over a period of 30 minutes or so.

Functions of the Liver in Estrogen Degradation. The liver conjugates estrogens to form glucuronides and sulfates, and about one-fifth of these conjugated products is excreted in the bile; most of the remainder is excreted in the urine. Also, the liver converts the potent estrogens estradiol and estrone into the almost totally impotent estrogen estriol. Therefore, diminished liver function actually *increases* the activity of estrogens in the body, sometimes causing *hyperestrinism*.

Fate of Progesterone. Within a few minutes after secretion, almost all the progesterone is degraded to other steroids that have no progestational effect. As with the estrogens, the liver is especially important for this metabolic degradation.

The major end product of progesterone degradation is *pregnanediol*. About 10% of the original progesterone is excreted in the urine in this form. Therefore, one can estimate the rate of progesterone formation in the body from the rate of this excretion.

FUNCTIONS OF THE ESTROGENS—THEIR EFFECTS ON THE PRIMARY AND SECONDARY FEMALE SEX CHARACTERISTICS

A primary function of the estrogens is to cause cellular proliferation and growth of the tissues of the sex organs and other tissues related to reproduction.

Effect of Estrogens on the Uterus and External Female Sex Organs. During childhood, estrogens are secreted only in minute quantities, but at puberty, the quantity secreted in the female under the influence of the pituitary gonadotropic hormones increases 20-fold or more. At this time, the female sex organs change from those of a child to those of an adult. The ovaries, fallopian tubes, uterus, and vagina all increase several times in size. Also, the external genitalia enlarge, with deposition of fat in the mons pubis and labia majora and enlargement of the labia minora.

In addition, estrogens change the vaginal epithelium from a cuboidal into a stratified type, which is considerably more resistant to trauma and infection than is the prepubertal cuboidal cell epithelium. Vaginal infections in children can often be cured by the administration of estrogens simply because of the resulting increased resistance of the vaginal epithelium.

During the first few years after puberty, the size of the uterus increases 2-fold to 3-fold, but more important than the increase in uterus size are the changes that take place in the uterine endometrium under the influence of estrogens. Estrogens cause marked proliferation of the endometrial stroma and greatly increased development of the endometrial glands, which will later aid in providing nutrition to the implanted ovum. These effects are discussed later in the chapter in connection with the endometrial cycle.

Effect of Estrogens on the Fallopian Tubes. The estrogens' effects on the mucosal lining of the fallopian tubes are similar to their effects on the uterine endometrium. They cause the glandular tissues of this lining to proliferate, and especially important, they cause the number of ciliated epithelial cells that line the fallopian tubes to increase. Also, activity of the cilia is considerably enhanced. These cilia always beat toward the uterus, which helps propel the fertilized ovum in that direction.

Effect of Estrogens on the Breasts. The primordial breasts of females and males are exactly alike. In fact, under the influence of appropriate hormones, the masculine breast during the first 2 decades of life can develop sufficiently to produce milk in the same manner as the female breast.

Estrogens cause (1) development of the stromal tissues of the breasts, (2) growth of an extensive ductile system, and (3) deposition of fat in the breasts. The lobules and alveoli of the breast develop to a slight extent under the influence of estrogens alone, but it is progesterone and prolactin that ultimately complete the growth and function of these structures.

In summary, the estrogens initiate growth of the breasts and of the milk-producing apparatus. They are also responsible for the characteristic growth and external appearance of the mature female breast. However, they do not complete the job of converting the breasts into milk-producing organs.

Effect of Estrogens on the Skeleton. Estrogens inhibit osteoclastic activity in the bones and therefore stimulate bone growth. As discussed in [Chapter 80](#), at least part of this effect is due to stimulation of *osteoprotegerin*, which is also called *osteoclastogenesis inhibitory factor*, a cytokine that inhibits bone resorption.

At puberty, when the female enters her reproductive years, her growth in height becomes rapid for several years. However, estrogens also cause uniting of the epiphyses with the shafts of the long bones. This effect of estrogen in the female is much stronger than the similar effect of testosterone in the male. As a result, growth of the female usually ceases several years earlier than growth of the male. A female eunuch who is devoid of estrogen production usually grows several inches taller than a normal mature female because her epiphyses do not unite at the normal time.

Osteoporosis of the Bones Caused by Estrogen Deficiency in Old Age. After menopause, almost no estrogens are secreted by the ovaries. This estrogen deficiency leads to (1) increased osteoclastic activity in the bones, (2) decreased bone matrix, and (3) decreased deposition of bone calcium and phosphate. In some women this effect is extremely severe, and the resulting condition is called *osteoporosis*, described in [Chapter 80](#). Because osteoporosis can greatly weaken the bones and lead to

bone fracture, especially fracture of the vertebrae, many postmenopausal women are treated prophylactically with estrogen replacement to prevent the osteoporotic effects.

Estrogens Slightly Increase Protein Deposition. Estrogens cause a slight increase in total body protein, which is evidenced by a slight positive nitrogen balance when estrogens are administered. This effect mainly results from the growth-promoting effect of estrogen on the sexual organs, the bones, and a few other tissues of the body. The enhanced protein deposition caused by testosterone is much more general and much more powerful than that caused by estrogens.

Estrogens Increase Body Metabolism and Fat Deposition. Estrogens increase the whole-body metabolic rate slightly, but only about one-third as much as the increase caused by testosterone. Estrogens also cause deposition of increased quantities of fat in the subcutaneous tissues. As a result, the percentage of body fat in females is considerably greater than that in the males whose bodies contain more protein. In addition to deposition of fat in the breasts and subcutaneous tissues, estrogens cause deposition of fat in the buttocks and thighs, which is characteristic of the feminine figure.

Estrogens Have Little Effect on Hair Distribution. Estrogens do not greatly affect hair distribution. However, hair does develop in the pubic region and in the axillae after puberty. Androgens formed in increased quantities by the female adrenal glands after puberty are mainly responsible for this development of hair.

Effect of Estrogens on the Skin. Estrogens cause the skin to develop a texture that is soft and usually smooth, but even so, the skin of a woman is thicker than that of a child or a castrated female. Estrogens also cause the skin to become more vascular, which is often associated with increased warmth of the skin and greater bleeding of cut surfaces than is observed in men.

Effect of Estrogens on Electrolyte Balance. The chemical similarity of estrogenic hormones to adrenocortical hormones has been discussed previously. Estrogens, like aldosterone and some other adrenocortical hormones, cause sodium and water retention by the kidney tubules. This effect of estrogens is normally slight and rarely of significance, but during pregnancy the tremendous formation of estrogens by the placenta may contribute to body fluid retention, as discussed in [Chapter 83](#).

FUNCTIONS OF PROGESTERONE

Progesterone Promotes Secretory Changes in the Uterus. A major function of progesterone is to *promote secretory changes in the uterine endometrium* during the latter half of the monthly female sexual cycle, thus preparing the uterus for implantation of the fertilized ovum.

This function is discussed later in connection with the endometrial cycle of the uterus.

In addition to this effect on the endometrium, progesterone decreases the frequency and intensity of uterine contractions, thereby helping to prevent expulsion of the implanted ovum.

Progesterone Promotes Secretion by the Fallopian Tubes. Progesterone also promotes increased secretion by the mucosal lining of the fallopian tubes. These secretions are necessary for nutrition of the fertilized, dividing ovum as it traverses the fallopian tube before implantation.

Progesterone Promotes Development of the Breasts. Progesterone promotes development of the lobules and alveoli of the breasts, causing the alveolar cells to proliferate, enlarge, and become secretory. However, progesterone does not cause the alveoli to secrete milk; as discussed in Chapter 83, milk is secreted only after the prepared breast is further stimulated by prolactin from the anterior pituitary gland.

Progesterone also causes the breasts to swell. Part of this swelling is due to the secretory development in the lobules and alveoli, but part also results from increased fluid in the tissue.

MONTHLY ENDOMETRIAL CYCLE AND MENSTRUATION

Associated with the monthly cyclical production of estrogens and progesterone by the ovaries is an endometrial cycle in the lining of the uterus that operates through the following stages: (1) proliferation of the uterine endometrium; (2) development of secretory changes in the endometrium; and (3) desquamation of the endometrium, which is known as *menstruation*. The various phases of this endometrial cycle are shown in Figure 82-9. See Video 82-1.

Proliferative Phase (Estrogen Phase) of the Endometrial Cycle Occurs Before Ovulation. At the beginning of each monthly cycle, most of the endometrium has been desquamated by menstruation. After menstruation, only a thin layer of endometrial stroma remains, and the only epithelial cells that are left are those located in the remaining deeper portions of the glands and crypts of the endometrium. Under the influence of estrogens, secreted in increasing quantities by the ovary during the first part of the monthly ovarian cycle, the stromal cells and the epithelial cells proliferate rapidly. The endometrial surface is re-epithelialized within 4 to 7 days after the beginning of menstruation.

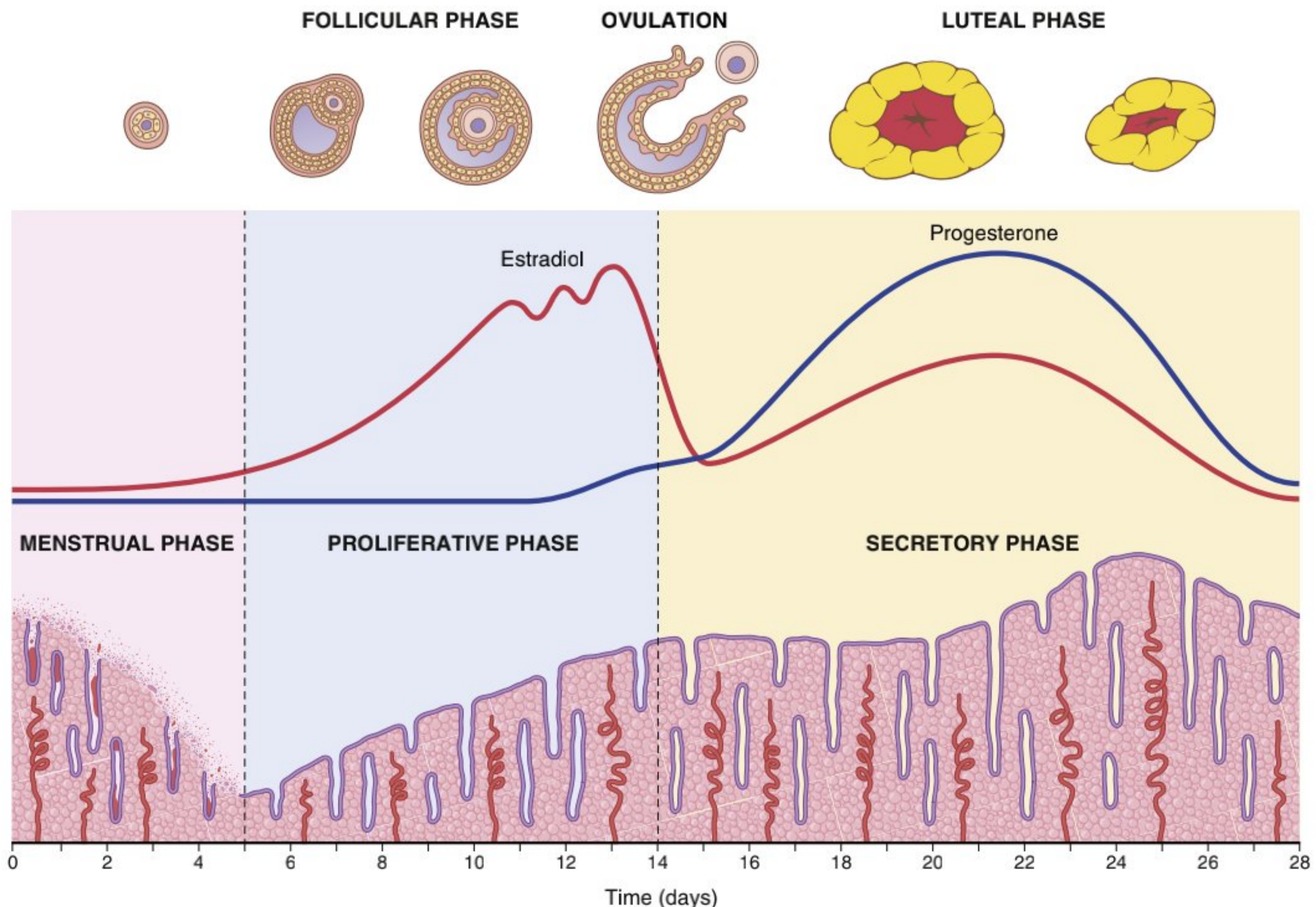


Figure 82-9. Phases of endometrial growth and menstruation during each monthly female sexual cycle.

Then, during the next week and a half, before ovulation occurs, the endometrium increases greatly in thickness, owing to increasing numbers of stromal cells and to progressive growth of the endometrial glands and new blood vessels into the endometrium. At the time of ovulation, the endometrium is 3 to 5 millimeters thick.

The endometrial glands, especially those of the cervical region, secrete thin, stringy mucus. The mucus strings actually align themselves along the length of the cervical canal, forming channels that help guide sperm in the proper direction from the vagina into the uterus.

Secretory Phase (Progestational Phase) of the Endometrial Cycle Occurs After Ovulation. During most of the latter half of the monthly cycle, after ovulation has occurred, progesterone and estrogen together are secreted in large quantities by the corpus luteum. The estrogens cause slight additional cellular proliferation in the endometrium during this phase of the cycle, whereas progesterone causes marked swelling and secretory development of the endometrium. The glands increase in tortuosity, and excess secretory substances accumulate in the glandular epithelial cells. In addition, the cytoplasm of the stromal cells increases, lipid and glycogen deposits increase greatly in the stromal cells, and the blood supply to the endometrium further increases in proportion to the developing secretory activity, with the blood vessels becoming highly tortuous. At the peak of the secretory phase, about 1 week after ovulation, the endometrium has a thickness of 5 to 6 millimeters.

The purpose of all these endometrial changes is to produce a highly secretory endometrium that contains large amounts of stored nutrients to provide appropriate conditions for implantation of a *fertilized* ovum during the latter half of the monthly cycle. From the time a fertilized ovum enters the uterine cavity from the fallopian tube (which occurs 3 to 4 days after ovulation) until the time the ovum implants (7 to 9 days after ovulation), the uterine secretions, called “uterine milk,” provide nutrition for the early dividing ovum. Then, once the ovum implants in the endometrium, the trophoblastic cells on the surface of the implanting ovum (in the blastocyst stage) begin to digest the endometrium and absorb the endometrial stored substances, thus making great quantities of nutrients available to the early implanting embryo.

Menstruation. If the ovum is not fertilized, about 2 days before the end of the monthly cycle, the corpus luteum in the ovary involutes, and the ovarian hormones (estrogens and progesterone) decrease to low levels of secretion, as shown in [Figure 82-9](#). Menstruation follows.

Menstruation is caused by the reduction of estrogens and progesterone, especially progesterone, at the end of the monthly ovarian cycle. The first effect is decreased stimulation of the endometrial cells by these two hormones, followed rapidly by involution of the endometrium to about 65% of its previous thickness. Then, during

the 24 hours preceding the onset of menstruation, the tortuous blood vessels leading to the mucosal layers of the endometrium become vasospastic, presumably because of some effect of involution, such as release of a vasoconstrictor material—possibly one of the vasoconstrictor types of prostaglandins that are present in abundance at this time.

The vasospasm, the decrease in nutrients to the endometrium, and the loss of hormonal stimulation initiate necrosis in the endometrium, especially of the blood vessels. As a result, blood at first seeps into the vascular layer of the endometrium and the hemorrhagic areas grow rapidly over a period of 24 to 36 hours. Gradually, the necrotic outer layers of the endometrium separate from the uterus at the sites of the hemorrhages until, about 48 hours after the onset of menstruation, all the superficial layers of the endometrium have desquamated. The mass of desquamated tissue and blood in the uterine cavity, plus contractile effects of prostaglandins or other substances in the decaying desquamate, all acting together, initiate uterine contractions that expel the uterine contents.

During normal menstruation, approximately 40 milliliters of blood and an additional 35 milliliters of serous fluid are lost. The menstrual fluid is normally nonclotting because a *fibrinolysin* is released along with the necrotic endometrial material. If heavy bleeding occurs from the uterine surface, the quantity of fibrinolysin may be insufficient to prevent clotting, resulting in the passage of blood clots. Menstrual blood clots are not uncommon and usually occur during the first couple of days of menstruation, when bleeding is greatest; however, excessive bleeding and large clots during menstruation can be clinical evidence of uterine disease.

Within 4 to 7 days after menstruation starts, the loss of blood ceases because, by this time, the endometrium has become re-epithelialized.

Leukorrhea During Menstruation. During menstruation, large numbers of leukocytes are released, along with the necrotic material and blood. A substance liberated by the endometrial necrosis likely causes this outflow of leukocytes. As a result of the presence of these leukocytes and possibly other factors, the uterus is highly resistant to infection during menstruation, even though the endometrial surfaces are denuded. This resistance to infection is of extreme protective value.

REGULATION OF FEMALE MONTHLY RHYTHM—INTERPLAY BETWEEN OVARIAN AND HYPOTHALAMIC-PITUITARY HORMONES

Now that we have presented the major cyclical changes that occur during the monthly female sexual cycle, we can explain the basic rhythmic mechanism that causes the cyclical variations.

THE HYPOTHALAMUS SECRETES GNRH, WHICH STIMULATES THE ANTERIOR PITUITARY GLAND TO SECRETE LH AND FSH

As discussed in [Chapter 75](#), secretion of most of the anterior pituitary hormones is controlled by “releasing hormones” formed in the hypothalamus and then transported to the anterior pituitary gland by way of the hypothalamic-hypophysial portal system. In the case of the gonadotropins, one releasing hormone, *GnRH*, is important. This hormone has been purified and has been found to be a decapeptide with the following formula:



Intermittent, Pulsatile Secretion of GnRH by the Hypothalamus Stimulates Pulsatile Release of LH From the Anterior Pituitary Gland. The hypothalamus does not secrete GnRH continuously but instead secretes it in pulses lasting 5 to 25 minutes that occur every 1 to 2 hours. The lower curve in [Figure 82-10](#) shows the electrical pulsatile signals in the hypothalamus that cause the hypothalamic pulsatile output of GnRH.

It is intriguing that when GnRH is infused continuously so that it is available all the time rather than in pulses, its ability to cause release of LH and FSH by the anterior pituitary gland is lost. Therefore, the pulsatile nature of GnRH release is essential to its function.

The pulsatile release of GnRH also causes intermittent output of LH secretion about every 90 minutes, which is shown by the upper curve in [Figure 82-10](#).

Hypothalamic Centers for Release of Gonadotropin-Releasing Hormone. The neuronal activity that causes pulsatile release of GnRH in humans occurs primarily in the mediobasal hypothalamus, especially in the arcuate nuclei of this area. Neurons located in the preoptic area of the anterior hypothalamus also secrete GnRH in

moderate amounts. Multiple neuronal centers in the higher brain’s “limbic” system (the system for psychic control) transmit signals into the hypothalamus to modify the intensity of GnRH release and the frequency of the pulses, thus providing a partial explanation of why psychic factors often modify female sexual function.

NEGATIVE FEEDBACK EFFECTS OF ESTROGEN AND PROGESTERONE TO DECREASE LH AND FSH SECRETION

Estrogen in small amounts has a strong inhibitory effect on production of LH and FSH. Also, when progesterone is available, the inhibitory effect of estrogen is multiplied, even though progesterone by itself has little effect ([Figure 82-11](#)).

These feedback effects seem to operate mainly on the anterior pituitary gland directly, but they also operate to a lesser extent on the hypothalamus to decrease secretion of GnRH, especially by altering the frequency of the GnRH pulses.

Inhibin From the Corpus Luteum Inhibits FSH and LH Secretion. In addition to the feedback effects of estrogen and progesterone, other hormones are involved, especially *inhibin*, which is secreted along with the steroid sex hormones by the granulosa cells of the ovarian corpus luteum in the same way that Sertoli cells secrete inhibin in the male testes (see [Figure 82-11](#)). This hormone has the same effect in the female as in the male—it inhibits secretion of FSH and, to a lesser extent, LH by the anterior pituitary gland. Therefore, inhibin may be especially important in causing the decrease in secretion of FSH and LH at the end of the monthly female sexual cycle.

POSITIVE FEEDBACK EFFECT OF ESTROGEN BEFORE OVULATION—THE PREOVULATORY LUTEINIZING HORMONE SURGE

The anterior pituitary gland secretes greatly increased amounts of LH for 1 to 2 days beginning 24 to 48 hours

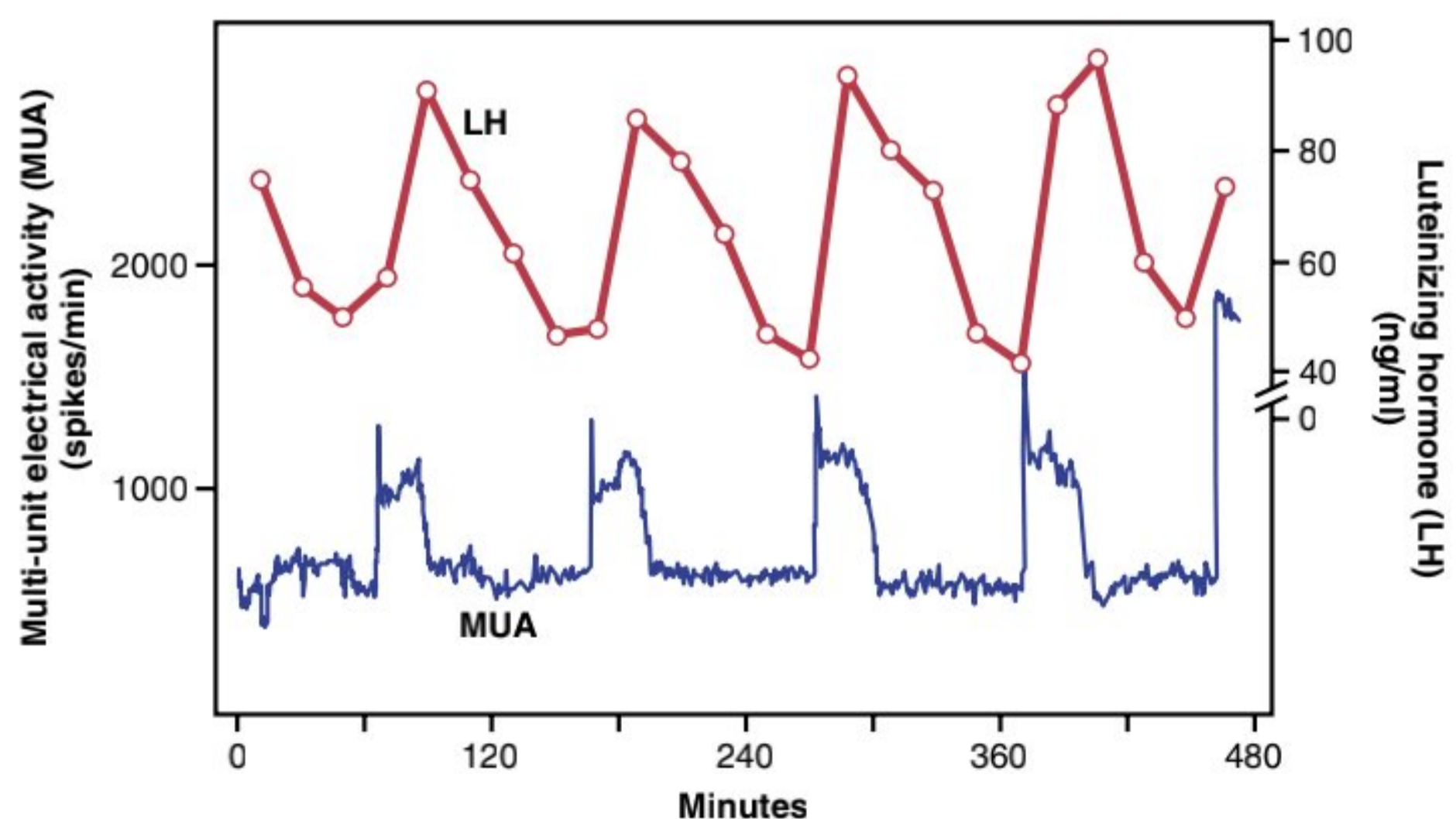


Figure 82-10. Shown is a pulsatile change in luteinizing hormone (LH) in the peripheral circulation of a pentobarbital-anesthetized ovariectomized rhesus monkey (red line) and a minute by minute recording of multi-unit electrical activity (MUA) in the mediobasal hypothalamus (blue line). (Data from Wilson RC, Kesner JS, Kaufman JM, et al: Central electrophysiologic correlates of pulsatile luteinizing hormone secretion. *Neuroendocrinology* 39:256, 1984.)

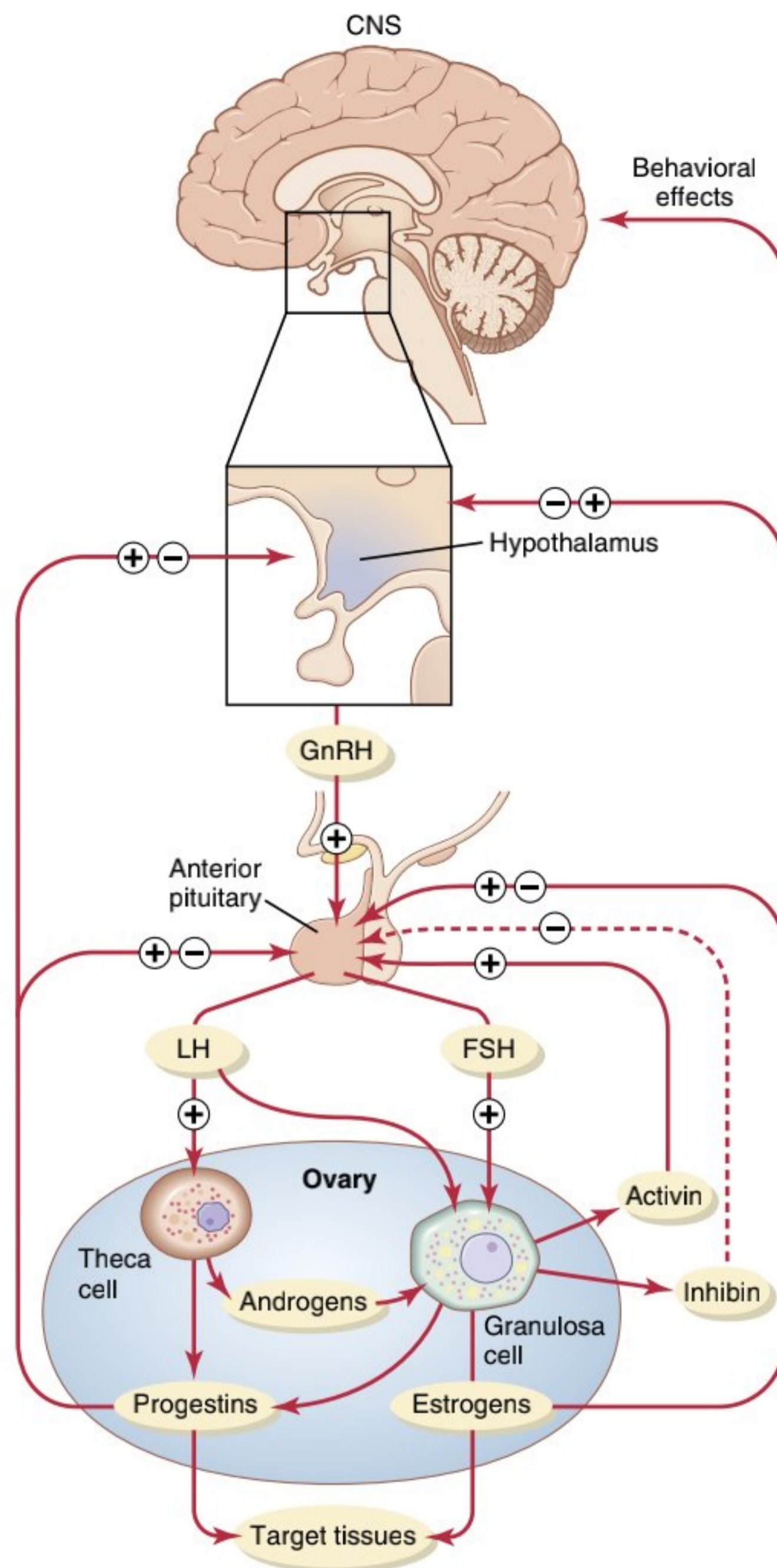


Figure 82-11. Feedback regulation of the hypothalamic-pituitary-ovarian axis in females. Stimulatory effects are shown by plus signs (+); negative feedback inhibitory effects are shown by minus signs (-). Estrogens and progesterins exert negative and positive feedback effects on the anterior pituitary and hypothalamus, depending on the stage of the ovarian cycle. Inhibin has a negative feedback effect on the anterior pituitary, whereas activin has the opposite effect, stimulating follicle-stimulating hormone (FSH) secretion by the anterior pituitary. CNS, Central nervous system; GnRH, gonadotropin-releasing hormone; LH, luteinizing hormone.

before ovulation. This effect is demonstrated in [Figure 82-4](#). The figure shows a much smaller preovulatory surge of FSH as well.

Experiments have shown that estrogen infusion into a female above a critical rate for 2 to 3 days during the latter part of the first half of the ovarian cycle will cause rapidly accelerating growth of the ovarian follicles, as well as

rapidly accelerating secretion of ovarian estrogens. During this period, secretions of FSH and LH by the anterior pituitary gland are at first slightly suppressed. Secretion of LH then increases abruptly 6-fold to 8-fold, and secretion of FSH increases about 2-fold. The greatly increased LH secretion causes ovulation to occur.

The cause of this abrupt surge in LH secretion is not known. However, the following explanations are possible:

1. It has been suggested that at this point in the cycle, estrogen has a peculiar *positive feedback effect* of stimulating pituitary secretion of LH and, to a lesser extent, FSH (see [Figure 82-11](#)), which is in sharp contrast to the normal negative feedback effect of estrogen that occurs during the remainder of the female monthly cycle.
2. The granulosa cells of the follicles begin to secrete small but increasing quantities of progesterone a day or so before the preovulatory LH surge, and it has been suggested that this secretion might be the factor that stimulates the excess LH secretion.

Without this normal preovulatory surge of LH, ovulation will not occur.

FEEDBACK OSCILLATION OF THE HYPOTHALAMIC-PITUITARY-OVARIAN SYSTEM

Now that we have discussed the interrelations of the different components of the female hormonal system, we can explain the feedback oscillation that controls the rhythm of the female sexual cycle. It seems to operate in approximately the following sequence of three events.

1. *Postovulatory secretion of the ovarian hormones and depression of the pituitary gonadotropins.* Between ovulation and the beginning of menstruation, the corpus luteum secretes large quantities of progesterone and estrogen, as well as inhibin. All these hormones together have a combined negative feedback effect on the anterior pituitary gland and hypothalamus, causing suppression of FSH and LH secretion and decreasing them to their lowest levels about 3 to 4 days before the onset of menstruation. These effects are shown in [Figure 82-4](#).
2. *Follicular growth phase.* Two to 3 days before menstruation, the corpus luteum has regressed to almost total involution and secretion of estrogen, progesterone, and inhibin from the corpus luteum decreases to a low ebb, which releases the hypothalamus and anterior pituitary from the negative feedback effect of these hormones. Therefore, a day or so later, at about the time that menstruation begins, pituitary secretion of FSH begins to increase again, as much as 2-fold; then, several days after menstruation begins, LH secretion increases slightly as well. These hormones initiate new ovarian follicle growth and a progressive increase in the secretion of estrogen, reaching a peak estrogen

secretion at about 12.5 to 13 days after the onset of the new female monthly sexual cycle. During the first 11 to 12 days of this follicle growth, the rates of pituitary secretion of the gonadotropins FSH and LH decrease slightly because of the negative feedback effect, mainly of estrogen, on the anterior pituitary gland. Then there is a sudden, marked increase in the secretion of LH and, to a lesser extent, FSH. This increased secretion is the preovulatory surge of LH and FSH, which is followed by ovulation.

3. *The preovulatory surge of LH and FSH causes ovulation.* About 11.5 to 12 days after the onset of the monthly cycle, the decline in FSH and LH secretion comes to an abrupt halt. The high level of estrogens at this time (or the beginning of progesterone secretion by the follicles) is believed to cause a positive feedback stimulatory effect on the anterior pituitary, as explained earlier, which leads to a large surge in the secretion of LH and, to a lesser extent, FSH. Whatever the cause of this preovulatory LH and FSH surge, the great excess of LH leads to both ovulation and subsequent development of and secretion by the corpus luteum. Thus, the hormonal system begins its new round of secretions until the next instance of ovulation.

Anovulatory Cycles—Sexual Cycles at Puberty

If the preovulatory surge of LH is not of sufficient magnitude, ovulation will not occur, and the cycle is said to be “anovulatory.” The phases of the sexual cycle continue, but they are altered in the following ways:

1. Lack of ovulation causes failure of development of the corpus luteum, so there is almost no secretion of progesterone during the latter portion of the cycle.
2. The cycle is shortened by several days, but the rhythm continues.

Therefore, it is likely that progesterone is not required for maintenance of the cycle, although it can alter the cycle's rhythm.

The first few cycles after the onset of puberty are usually anovulatory, as are the cycles occurring several months to years before menopause, presumably because the LH surge is not potent enough at these times to cause ovulation.

PUBERTY AND MENARCHE

Puberty means the onset of adult sexual life, and *menarche* means the beginning of the cycle of menstruation. The period of puberty is caused by a gradual increase in gonadotropic hormone secretion by the pituitary, beginning in about the eighth year of life, as shown in [Figure 82-12](#), and usually culminating in the onset of puberty and menstruation between ages 10 and 14 years in girls (average, 12 years).

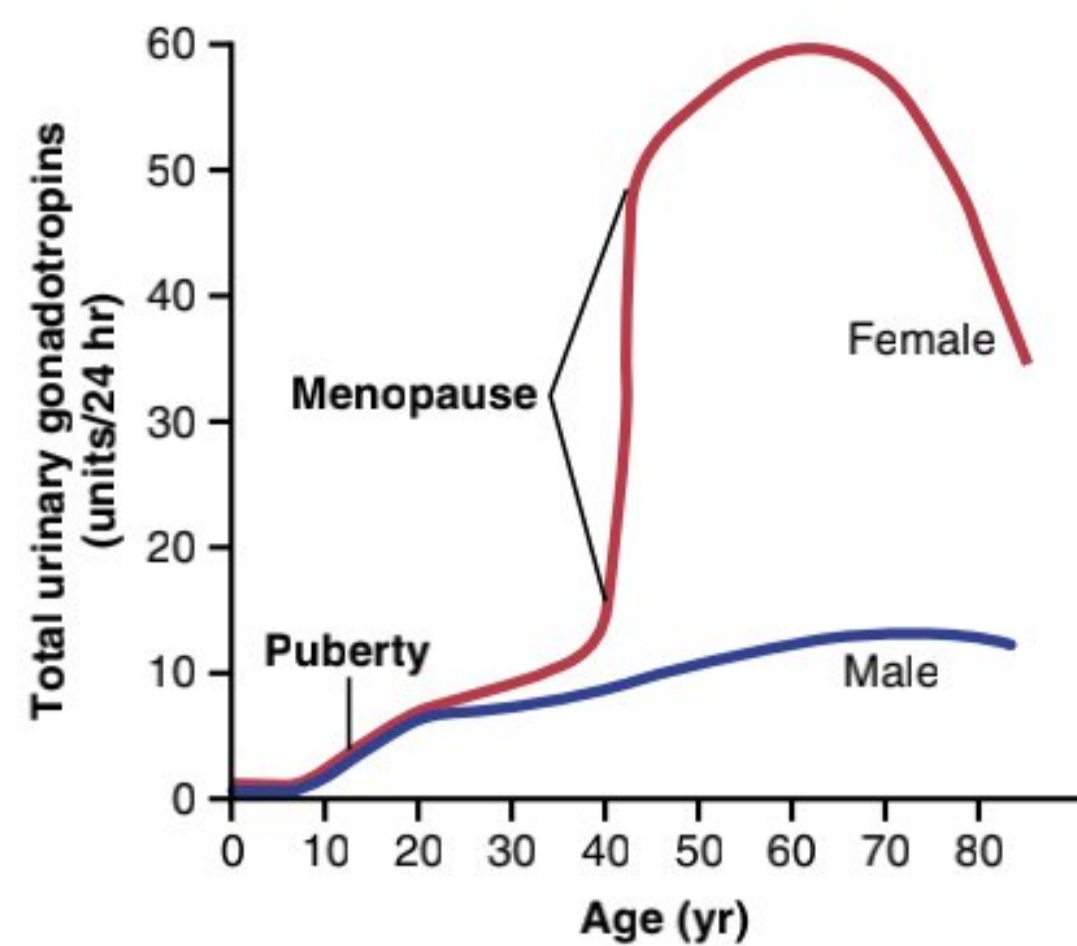


Figure 82-12. Total rates of secretion of gonadotropic hormones throughout the sexual lives of female and male human beings, showing an especially abrupt increase in gonadotropic hormones at menopause in the female.

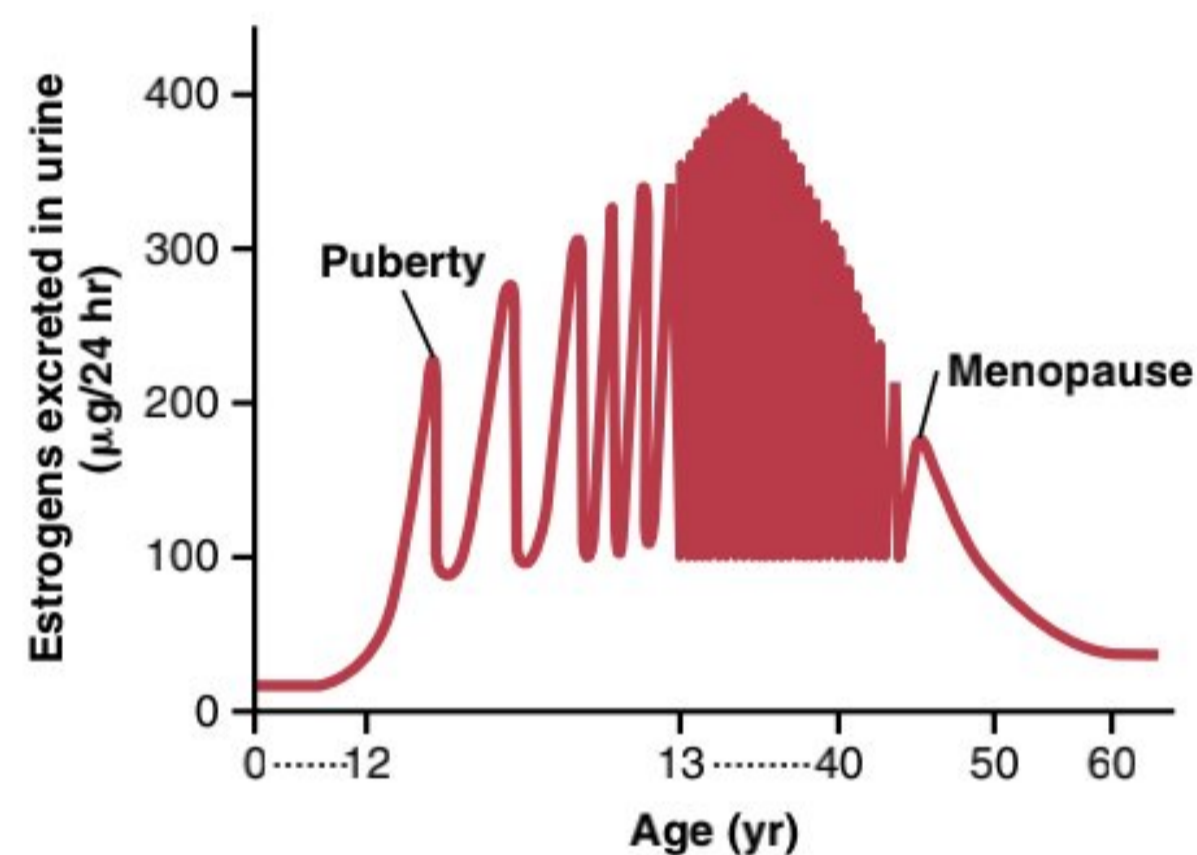


Figure 82-13. Estrogen secretion throughout the sexual life of the female human being.

In the female, as in the male, the infantile pituitary gland and ovaries are capable of full function if they are appropriately stimulated. However, as is also true in the male, and for reasons that are not understood, the hypothalamus does not secrete significant quantities of GnRH during childhood. Experiments have shown that the hypothalamus is capable of secreting this hormone, but the appropriate signal from some other area of the brain to cause secretion is lacking. Therefore, it is now believed that the onset of puberty is initiated by some maturation process that occurs elsewhere in the brain, perhaps somewhere in the limbic system.

[Figure 82-13](#) shows (1) the increasing levels of estrogen secretion at puberty, (2) the cyclical variation during the monthly sexual cycle, (3) the further increase in estrogen secretion during the first few years of reproductive life, (4) the progressive decrease in estrogen secretion toward the end of reproductive life, and, finally, (5) almost no estrogen or progesterone secretion beyond menopause.

MENOPAUSE

At age 40 to 50 years, the sexual cycle usually becomes irregular, and ovulation often fails to occur. After a few

months to a few years, the cycle ceases altogether, as shown in **Figure 82-13**. The period during which the cycle ceases and the female sex hormones diminish to almost none is called *menopause*.

The cause of menopause is “burning out” of the ovaries. Throughout a woman’s reproductive life, about 400 of the primordial follicles grow into mature follicles and ovulate, and hundreds of thousands of ova degenerate. At about age 45 years, only a few primordial follicles remain to be stimulated by FSH and LH and, as shown in **Figure 82-13**, the production of estrogens by the ovaries decreases as the number of primordial follicles approaches zero. When estrogen production falls below a critical value, the estrogens can no longer inhibit the production of FSH and LH. Instead, as shown in **Figure 82-12**, the gonadotropins FSH and LH (mainly FSH) are produced after menopause in large and continuous quantities, but as the remaining primordial follicles become atretic, production of estrogens by the ovaries falls virtually to zero.

At the time of menopause, a woman must readjust her life from one that has been physiologically stimulated by estrogen and progesterone production to one devoid of these hormones. The loss of estrogens often causes marked physiological changes in the function of the body, including (1) “hot flushes” characterized by extreme flushing of the skin, (2) psychic sensations of dyspnea, (3) irritability, (4) fatigue, (5) anxiety, and (6) decreased strength and calcification of bones throughout the body. These symptoms are of sufficient magnitude in about 15% of women to warrant treatment. Daily administration of estrogen in small quantities usually reverses the symptoms, and by gradually decreasing the dose, postmenopausal women may avoid severe symptoms.

Large clinical trials have provided evidence that administration of estrogen after menopause, although ameliorating many of the symptoms of menopause, may increase the risk for cardiovascular disease. As a result, hormone replacement therapy with estrogen is no longer routinely prescribed for postmenopausal women. Some studies, however, suggest that estrogen therapy may actually reduce the risk for cardiovascular disease if it is begun early in the postmenopausal years. Therefore, it is currently recommended that postmenopausal women who are considering hormone replacement therapy should discuss with their physicians whether the benefits outweigh the risks.

Abnormalities of Secretion by the Ovaries

Hypogonadism—Reduced Secretion by the Ovaries.

Less than normal secretion by the ovaries can result from poorly formed ovaries, lack of ovaries, or genetically abnormal ovaries that secrete the wrong hormones because of missing enzymes in the secretory cells. When ovaries are absent from birth or when they become nonfunctional before puberty, *female eunuchism* occurs. In this condition the usual secondary sexual characteristics do not appear, and the sexual organs remain infantile. Especially characteristic of this condition is prolonged growth of the long bones

because the epiphyses do not unite with the shafts as early as they do in a normal woman. Consequently, the female eunuch is essentially as tall as or perhaps even slightly taller than her male counterpart of similar genetic background.

When the ovaries of a fully developed woman are removed, the sexual organs regress to some extent so that the uterus becomes almost infantile in size, the vagina becomes smaller, and the vaginal epithelium becomes thin and easily damaged. The breasts atrophy and become pendulous, and the pubic hair becomes thinner. The same changes occur in women after menopause.

Irregularity of Menses, and Amenorrhea Caused by Hypogonadism. As pointed out in the preceding discussion of menopause, the quantity of estrogens produced by the ovaries must rise above a critical value to cause rhythmic sexual cycles. Consequently, in hypogonadism or when the gonads are secreting small quantities of estrogens as a result of other factors, such as *hypothyroidism*, the ovarian cycle often does not occur normally. Instead, several months may elapse between menstrual periods, or menstruation may cease altogether (amenorrhea). Prolonged ovarian cycles are frequently associated with failure of ovulation, presumably because of insufficient secretion of LH at the time of the preovulatory surge of LH, which is necessary for ovulation.

Hypersecretion by the Ovaries. Extreme hypersecretion of ovarian hormones by the ovaries is a rare clinical entity because excessive secretion of estrogens automatically decreases production of gonadotropins by the pituitary, which limits production of ovarian hormones. Consequently, hypersecretion of feminizing hormones is usually recognized clinically only when a feminizing tumor develops.

A rare *granulosa cell tumor* can develop in an ovary; development of this tumor occurs more often after menopause than before menopause. These tumors secrete large quantities of estrogens, which exert the usual estrogenic effects, including hypertrophy of the uterine endometrium and irregular bleeding from this endometrium. In fact, bleeding is often the first and only indication that such a tumor exists.

FEMALE SEXUAL ACT

Stimulation of the Female Sexual Act. As is true in the male sexual act, successful performance of the female sexual act depends on both psychic stimulation and local sexual stimulation.

Thinking sexual thoughts can lead to female sexual desire, and this aids greatly in the performance of the female sexual act. Such desire is based on psychological and physiological drive, although sexual desire does increase in proportion to the level of sex hormones secreted. Desire also changes during the monthly sexual cycle, reaching a peak near the time of ovulation, probably because of the high levels of estrogen secretion during the preovulatory period.

Local sexual stimulation in women occurs in more or less the same manner as in men because massage and other types of stimulation of the vulva, vagina, and other perineal regions can create sexual sensations. The glans of the *clitoris* is especially sensitive for initiating sexual sensations.

As in the male, the sexual sensory signals are transmitted to the sacral segments of the spinal cord through the pudendal nerve and sacral plexus. Once these signals have entered the spinal cord, they are transmitted to the cerebrum. Also, local reflexes integrated in the sacral and lumbar spinal cord are at least partly responsible for some of the reactions in the female sexual organs.

Female Erection and Lubrication. Located around the introitus and extending into the clitoris is erectile tissue almost identical to the erectile tissue of the penis. This erectile tissue, like that of the penis, is controlled by the parasympathetic nerves that pass through the *nervi erigentes* from the sacral plexus to the external genitalia. In the early phases of sexual stimulation, parasympathetic signals dilate the arteries of the erectile tissue, probably resulting from release of acetylcholine, nitric oxide, and vasoactive intestinal polypeptide at the nerve endings. This allows rapid accumulation of blood in the erectile tissue so that the introitus tightens around the penis, which aids the male in his attainment of sufficient sexual stimulation for ejaculation to occur.

Parasympathetic signals also pass to the bilateral Bartholin glands located beneath the labia minora and cause them to secrete mucus immediately inside the introitus. This mucus is responsible for much of the lubrication during sexual intercourse, although much lubrication is also provided by mucus secreted by the vaginal epithelium, and a small amount is provided from the male urethral glands. This lubrication is necessary during intercourse to establish a satisfactory massaging sensation rather than an irritative sensation, which may be provoked by a dry vagina. A massaging sensation constitutes the optimal stimulus for evoking the appropriate reflexes that culminate in both the male and female climaxes.

Female Orgasm. When local sexual stimulation reaches maximum intensity, and especially when the local sensations are supported by appropriate psychic conditioning signals from the cerebrum, reflexes are initiated that cause the female orgasm, also called the *female climax*. The female orgasm is analogous to emission and ejaculation in the male, and it may help promote fertilization of the ovum. Indeed, the human female is known to be somewhat more fertile when inseminated by normal sexual intercourse rather than by artificial methods, thus indicating an important function of the female orgasm. Possible reasons for this phenomenon are as follows.

First, during the orgasm, the perineal muscles of the female contract rhythmically, which results from spinal cord reflexes similar to those that cause ejaculation in the male. It is possible that these reflexes increase uterine and fallopian tube motility during the orgasm, thus helping to transport the sperm upward through the uterus toward the ovum; information on this subject is scanty, however. Also, the orgasm seems to cause dilation of the cervical canal for up to 30 minutes, thus allowing easy transport of the sperm.

Second, in many animals, copulation causes the posterior pituitary gland to secrete oxytocin; this effect is probably mediated through the brain amygdaloid nuclei and then through the hypothalamus to the pituitary. The oxytocin causes increased rhythmic contractions of the uterus, which may increase transport of the sperm. A few sperm have been shown to traverse the entire length of the fallopian tube in the cow in about 5 minutes, a rate at least 10 times as fast as that which the swimming motions of the sperm could possibly achieve. Whether this effect occurs in the human female is unknown.

In addition to possible effects of the orgasm on fertilization, the intense sexual sensations that develop during the orgasm also pass to the cerebrum and cause intense muscle tension throughout the body. After culmination of the sexual act, this tension gives way during the succeeding minutes to a sense of satisfaction characterized by relaxed peacefulness, an effect called *resolution*.

Female Fertility

Fertile Period of Each Sexual Cycle. The ovum remains viable and capable of being fertilized probably no longer than 24 hours after it is expelled from the ovary. Therefore, sperm must be available soon after ovulation if fertilization is to take place. A few sperm can remain fertile in the female reproductive tract for up to 5 days. Therefore, for fertilization to take place, intercourse must occur sometime between 4 and 5 days before ovulation up to a few hours after ovulation. Thus, the period of female fertility during each month is short, about 4 to 5 days.

Rhythm Method of Contraception. One commonly practiced method of contraception is to avoid intercourse near the time of ovulation. The difficulty with this method of contraception is predicting the exact time of ovulation. Yet, the interval from ovulation until the next succeeding onset of menstruation is almost always between 13 and 15 days. Therefore, if the menstrual cycle is regular, with an exact periodicity of 28 days, ovulation usually occurs within 1 day of the 14th day of the cycle. If, in contrast, the periodicity of the cycle is 40 days, ovulation usually occurs within 1 day of the 26th day of the cycle. Finally, if the periodicity of the cycle is 21 days, ovulation usually occurs within 1 day of the seventh day of the cycle. Therefore, it is usually stated that avoidance of intercourse for 4 days before the calculated day of ovulation and 3 days afterward prevents conception. However, such a method of contraception can be used only when the periodicity of the menstrual cycle is regular. The failure rate of this method of contraception, resulting in an unintentional pregnancy, may be as high as 20% to 25% per year.

Hormonal Suppression of Fertility—"The Pill"

Administration of either estrogen or progesterone, if given in appropriate quantities during the first half of the monthly cycle, can inhibit ovulation. The reason for this is that appropriate administration of either of these hormones can prevent the preovulatory surge of LH secretion by the pituitary gland, which is essential in causing ovulation.

It is not fully understood why administration of estrogen or progesterone prevents the preovulatory surge of LH

secretion. However, experimental work has suggested that immediately before the surge occurs, a sudden depression of estrogen secretion by the ovarian follicles probably occurs, which might be the necessary signal that causes the subsequent feedback effect on the anterior pituitary that leads to the LH surge. The administration of sex hormones (estrogens or progesterone) could prevent the initial ovarian hormonal depression that might be the initiating signal for ovulation.

The challenge in devising methods for the hormonal suppression of ovulation has been in developing appropriate combinations of estrogens and progestins that suppress ovulation but do not cause other, unwanted effects. For example, too much of either hormone can cause abnormal menstrual bleeding patterns. However, use of certain synthetic progestins in place of progesterone, especially the 19-norsteroids, along with small amounts of estrogens, usually prevents ovulation yet allows an almost normal pattern of menstruation. Therefore, almost all “pills” used for the control of fertility consist of some combination of synthetic estrogens and synthetic progestins. The main reason for using synthetic estrogens and progestins is that the *natural* hormones are almost entirely destroyed by the liver within a short time after they are absorbed from the gastrointestinal tract into the portal circulation. However, many of the *synthetic* hormones can resist this destructive propensity of the liver, thus allowing oral administration.

Two of the most commonly used synthetic estrogens are *ethinyl estradiol* and *mestranol*. Among the most commonly used progestins are *norethindrone*, *norethynodrel*, *ethynodiol*, and *norgestrel*. The drug is usually begun in the early stages of the monthly cycle and continued beyond the time that ovulation would normally occur. Then the drug is stopped, allowing menstruation to occur and a new cycle to begin.

The failure rate, resulting in an unintentional pregnancy, for hormonal suppression of fertility using various forms of the “pill” is about 8% to 9% per year.

Abnormal Conditions That Cause Female Sterility

About 5% to 10% of women are infertile. Occasionally, no abnormality can be discovered in the female genital organs, in which case the infertility is assumed to be due to either abnormal physiological function of the genital system or abnormal genetic development of the ova.

The most common cause of female sterility is failure to ovulate. This failure can result from hyposecretion of gonadotropic hormones, in which case the intensity of the hormonal stimuli is simply insufficient to cause ovulation, or it can result from abnormal ovaries that do not allow ovulation. For example, thick ovarian capsules occasionally exist on the outsides of the ovaries, making ovulation difficult.

Because of the high incidence of anovulation in sterile women, special methods are often used to determine whether ovulation occurs. These methods are based mainly on the effects of progesterone on the body because the normal increase in progesterone secretion usually does not occur during the latter half of anovulatory cycles. In the absence of progestational effects, the cycle can be assumed to be anovulatory.

One of these tests is simply to analyze the urine for a surge in pregnanediol, the end product of progesterone metabolism, during the latter half of the sexual cycle; the lack of this substance indicates failure of ovulation.

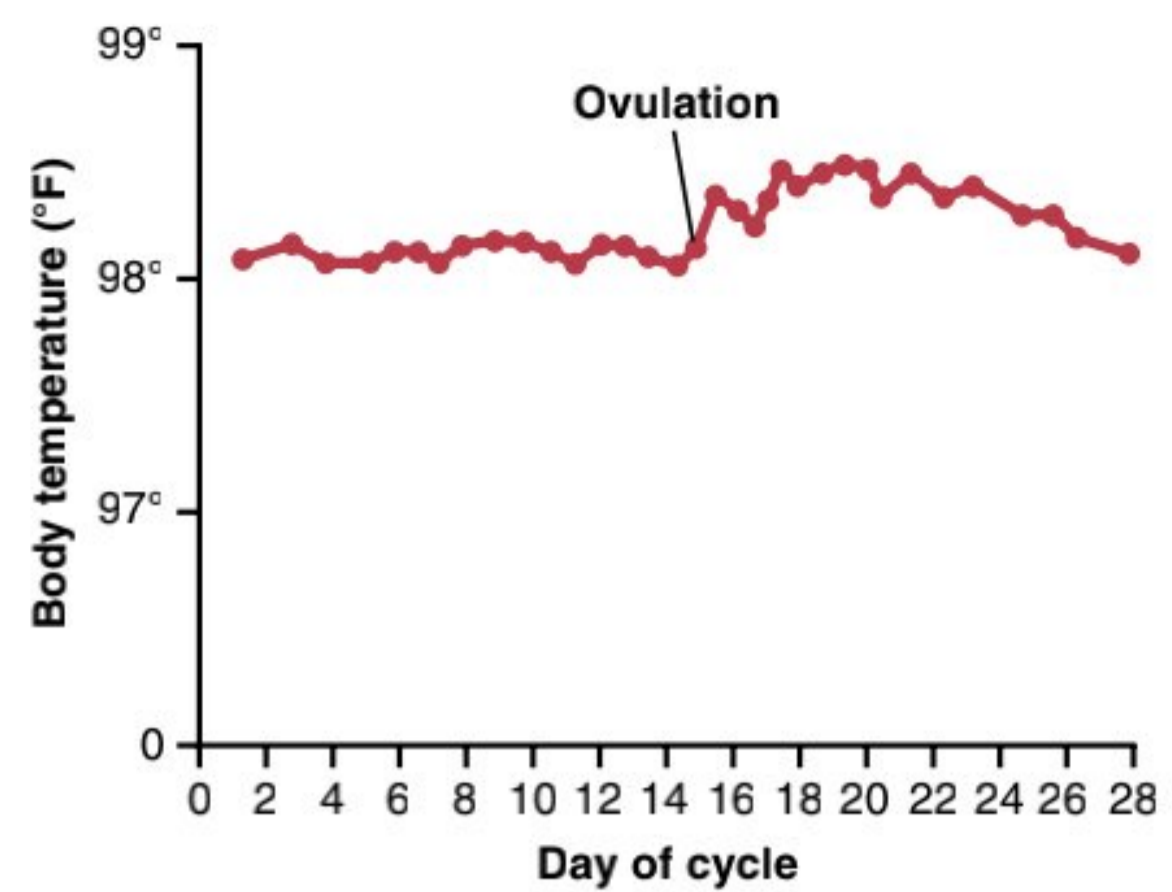


Figure 82-14. Elevation in body temperature shortly after ovulation.

Another common test is for the woman to chart her body temperature throughout the cycle. Secretion of progesterone during the latter half of the cycle raises the body temperature about 0.5°F, with the temperature rise coming abruptly at the time of ovulation. Such a temperature chart, showing the point of ovulation, is illustrated in [Figure 82-14](#).

Lack of ovulation caused by hyposecretion of the pituitary gonadotropic hormones can sometimes be treated by appropriately timed administration of *human chorionic gonadotropin*, a hormone (discussed in [Chapter 83](#)) that is extracted from the human placenta. This hormone, although secreted by the placenta, has almost the same effects as LH and is therefore a powerful stimulator of ovulation. However, excess use of this hormone can cause ovulation from many follicles simultaneously, which results in multiple births, an effect that has caused as many as eight babies (stillborn in many cases) to be born to mothers treated for infertility with this hormone.

One of the most common causes of female sterility is *endometriosis*, a common condition in which endometrial tissue almost identical to that of the normal uterine endometrium grows and even menstruates in the pelvic cavity surrounding the uterus, fallopian tubes, and ovaries. Endometriosis causes fibrosis throughout the pelvis, and this fibrosis sometimes so enshrouds the ovaries that an ovum cannot be released into the abdominal cavity. Often, endometriosis occludes the fallopian tubes, either at the fimbriated ends or elsewhere along their extent.

Another common cause of female infertility is *salpingitis*, that is, *inflammation of the fallopian tubes*; this inflammation causes fibrosis in the tubes, thereby occluding them. In the past, such inflammation occurred mainly as a result of gonococcal infection. However, with modern therapy, salpingitis is becoming a less prevalent cause of female infertility.

Still another cause of infertility is secretion of abnormal mucus by the uterine cervix. Ordinarily, at the time of ovulation, the hormonal environment of estrogen causes secretion of mucus with special characteristics that allow rapid mobility of sperm into the uterus and actually guide the sperm up along mucous “threads.” Abnormalities of the cervix, such as low-grade infection or inflammation, or abnormal hormonal stimulation of the cervix, can lead to a viscous mucous plug that prevents fertilization.

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